

Review

# Clinical Trials Targeting the Stroma in Pancreatic Cancer: A Systematic Review and Meta-Analysis

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**Abstract:** The tumor microenvironment plays an important role in the initiation and progression of pancreatic adenocarcinoma (PDAC). In this systematic review, we provide an overview of clinical trials with stroma-targeting agents. We systematically searched MEDLINE/PubMed and the EMBASE database, using the PRISMA guidelines, for eligible clinical trials. In total, 2330 records were screened, from which we have included 106 articles. A meta-analysis could be performed on 51 articles which describe the targeting of the vascular endothelial growth factor (VEGF) pathway, and three articles which describe the targeting of hyaluronic acid. Anti-VEGF therapies did not show an increase in median overall survival (OS) with combined hazard ratios (HRs) of 1.01 (95% confidence interval (CI) 0.90–1.13). Treatment with hyaluronidase PEGPH20 showed promising results, but, thus far, only in combination with gemcitabine and nab-paclitaxel in selected patients with hyaluronic acid (HA)<sup>high</sup> tumors: An increase in median progression free survival (PFS) of 2.9 months, as well as a HR of 0.51 (95% CI 0.26–1.00). In conclusion, we found that anti-angiogenic therapies did not show an increased benefit in median OS or PFS in contrast to promising results with anti-hyaluronic acid treatment in combination with gemcitabine and nab-paclitaxel. The PEGPH20 clinical trials used patient selection to determine eligibility based on tumor biology, which underlines the importance to personalize treatment for pancreatic cancer patients.

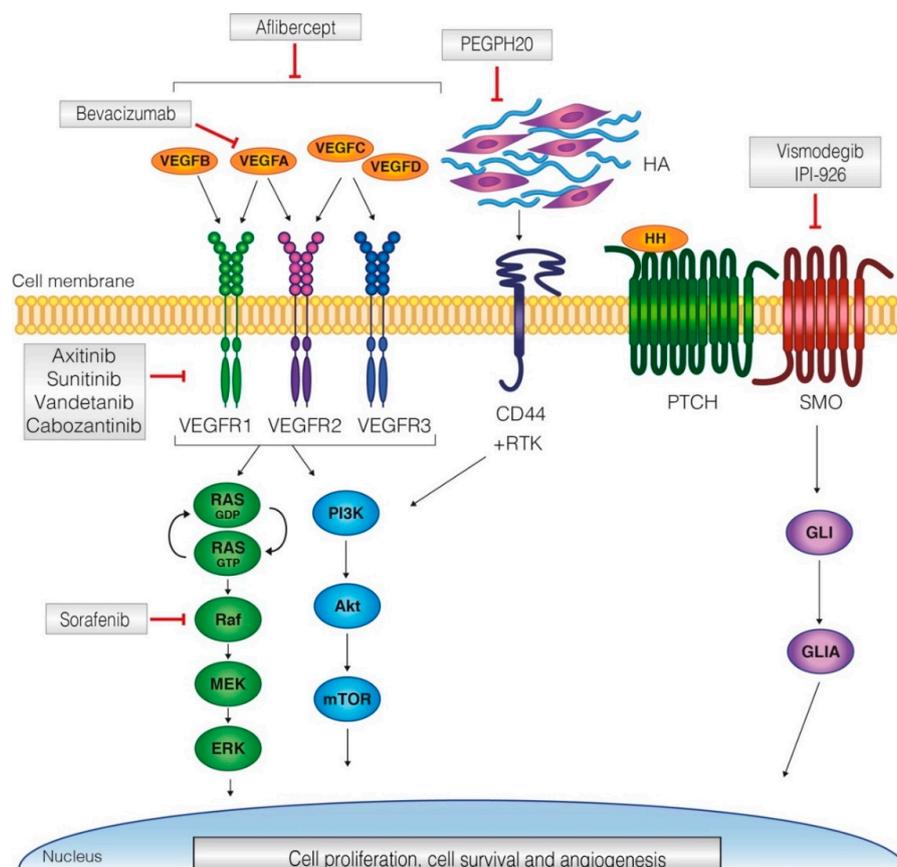
**Keywords:** PDAC; stroma; clinical trial; systematic review; targeted therapy

## 1. Introduction

Despite recent advances in our understanding of this disease, pancreatic adenocarcinoma remains one of the deadliest cancers, with a five-year survival rate of 8% [1]. The majority of patients present with locally advanced or metastatic diseases and are offered palliative care with chemotherapeutic treatment options [2]. Recent clinical trials showed that the addition of nab-paclitaxel to gemcitabine increased overall survival (OS) from 6.6 to 8.7 months (hazard ratio (HR) 0.72, 95% confidence interval (CI),

0.62 to 0.83) [3,4]. For patients with a good physical condition, treatment with FOLFIRINOX, consisting of 5-FU, oxaliplatin, and irinotecan, increased survival to 11.1 months compared to gemcitabine alone, but this treatment comes at the cost of potentially severe side-effects [5].

Based on recent advances in our understanding of the biology of pancreatic cancer, novel therapeutic strategies have focused on tumor-stromal interactions. The dense stroma is a characteristic of many solid tumors, but in particular of pancreatic cancer [6]. Several cell types such as fibroblasts, stellate cells, and immune cells are present in the (tumor) stroma, in addition to an abundance of fibrous proteins, glycoproteins, and polysaccharides [6]. These constituents are thought to prevent circulating drugs from reaching the tumor cells, to inhibit the immune system, and to provide the tumor cells with growth factors [7–9]. However, a strong desmoplastic reaction could also prevent tumor spread, as mechanical properties of the stroma are thought to encapsulate the tumor cells [10]. Most stroma-targeting treatments have targeted either angiogenesis, fibroblasts or aim to modify specific components of the extracellular matrix. In a pre-clinical setting, several tumor-stroma interactions have been targeted [10]. Human clinical trials were initiated in which the benefit of these agents was assessed in combination with the standard of care. With this systematic review of clinical trials targeting tumor-stroma interactions, we aimed to determine the value of these interactions for the treatment of pancreatic cancer. A meta-analysis could be performed on clinical trials investigating targeting hyaluronic acid (HA) or targeting the vascular endothelial growth factor (VEGF) pathway. These components together make up the bulk of the tumor micro-environment in pancreatic cancer (summarized in Figure 1). For other tumor stroma-targeting strategies, such as matrix-metalloproteinase inhibition, that have been assessed in human clinical trials, insufficient data was present to perform a meta-analysis, but these are discussed here.

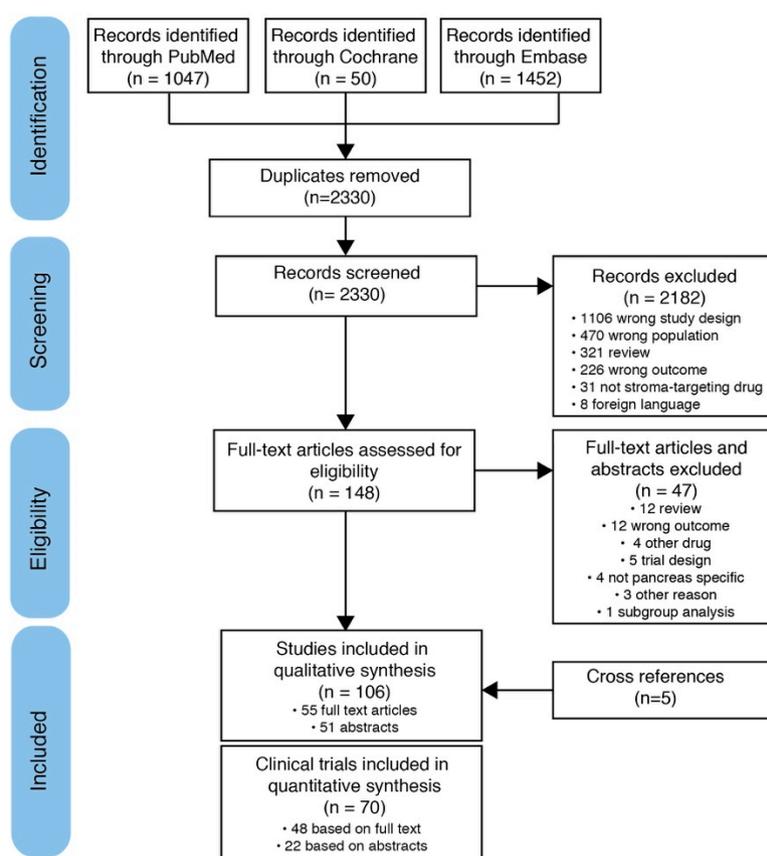


**Figure 1.** Schematic overview of pathways that are involved in desmoplasia in pancreatic cancer, including drugs and their targets. The vascular endothelial growth factor (VEGF) pathway is activated through ligand binding to any of the three receptors.

Downstream of these receptors are both the phosphoinositide 3 kinase (PI3K) and the Ras/Mek pathway. Anti-angiogenic treatment works through ligand binding or receptor blocking. Hyaluronic acid is a component of the extracellular matrix and is involved in cell proliferation through the cluster of differentiation 44 (CD44) receptor. Hedgehog is secreted by the stroma and binds to the Patched (PTCH) receptor, which activates the smoothened receptor and, through Glioma-Associated Oncogene (GLI) cell proliferation and survival, is activated.

## 2. Results

A total of 2330 studies were retrieved with our search strategy in the PubMed, Cochrane, and Embase databases. The search and selection process is shown in Figure 2. From the search results we have included 98 articles, of which 51 are congress abstracts, which describe anti-stromal therapies in pancreatic adenocarcinoma [11–107]. An additional five articles were found through cross-referencing [108–112]. These articles represent 70 individual clinical trials of which 51 used anti-vascular endothelial growth factor receptor (VEGFR) therapies, including 25 trials that investigated multi-tyrosine kinase inhibitors (TKIs) that are known to target additional receptors. Seven clinical trials investigated anti-Hedgehog therapies and three investigated anti-hyaluronic acid treatment. Nine trials could not be categorized in any of these categories. Twenty trials were randomized controlled trials, and most trials included patients with the advanced stage of disease (Table 1).



**Figure 2.** Flow chart of included articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [113].

Table 1. All clinical trials included in this review.

Author, Year	Phase	Type	Study Drug	Disease Stage	n	Treatment Backbone
<b>Anti-VEGFR</b>						
Kindler, 2005	II	Single arm	Bevacizumab	IV	52	Gemcitabine
Crane, 2006	I	Dose escalation	Bevacizumab	LAPC	4	Capecitabine + RT
Ko, 2008	II	Single arm	Bevacizumab	IV	52:60	Gemcitabine + cisplatin
Crane, 2009	II	Single arm	Bevacizumab	IV	82:63	Capecitabine + RT
Javle, 2009	III	Single arm	Bevacizumab	LAPC/IV	50:64	Gemcitabine + capecitabine
Starling, 2009	I	Dose escalation	Bevacizumab + erlotinib	LAPC/IV	20:60	Gemcitabine + capecitabine
Van Cutsem, 2009	III	RCT	Bevacizumab	IV	306:301	Gemcitabine + erlotinib
Picozzi, 2009	I/II	Single arm	Bevacizumab	IV	27	Gemcitabine + docetaxel
Isacoff, 2010	I	Single arm	Bevacizumab	LAPC/IV	28	5-FU + nab-paclitaxel + oxaliplatin
Kindler, 2010	III	RCT	Bevacizumab	LAPC/IV	302:300	Gemcitabine
Ko, 2010	II	Single arm	Bevacizumab + erlotinib	IV	36:60	-
Astsaturon, 2011	II	Dual arm	Bevacizumab	IV	16:16	Docetaxel
Czito, 2011	I	Dose escalation	Bevacizumab + erlotinib	Any	9	RT
Fogelman, 2011	II	Single arm	Bevacizumab	LAPC/IV	50:59	Gemcitabine + oxaliplatin
Small, 2011	II	Single arm	Bevacizumab	LAPC	29:62	Gemcitabine + RT
Isacoff, 2012	II	Single arm	Bevacizumab	LAPC/IV	40	5-FU + nab-paclitaxel + oxaliplatin
Ko, 2012	II	RCT	Bevacizumab + cetuximab	LAPC/IV	30:31	Gemcitabine
Martin, 2012	II	Single arm	Bevacizumab	LAPC/IV	42:60	Gemcitabine + 5-FU
Rougier, 2013	III	RCT	Aflibercept	IV	217:275	Gemcitabine
Sohal, 2013	II	Single arm	Bevacizumab	LAPC	19:60	Gemcitabine + oxaliplatin
Van Buren, 2013	II	Single arm	Bevacizumab	LAPC	59:60	Gemcitabine + RT
Sahora, 2014	II	Single arm	Bevacizumab	IV	30:65	Gemcitabine
Watkins, 2014	II	Single arm	Bevacizumab + erlotinib	LAPC/IV	44	Gemcitabine + capecitabine
Chadha, 2016	I	Dose escalation	Bevacizumab + erlotinib	LAPC	17:64	Capecitabine + RT
Berlin, 2018	II	Dual arm	Bevacizumab	Resected	62:65	Gemcitabine + RT
Sahai, 2018	I/II	Dose escalation	Bevacizumab	IV	12	5-FU + nab-paclitaxel + oxaliplatin
<b>Multi-TKI</b>						
Wallace, 2007	II	Single arm	Sorafenib	IV	17	Gemcitabine
Spano, 2008	II	RCT	Axitinib	LAPC/IV	103	Gemcitabine
Cohen, 2009	I	Single arm	Sorafenib	IV	19	Gemcitabine + erlotinib
Anderson, 2010	I	Dose escalation	Sorafenib	LAPC	27	Gemcitabine + RT
Lubner, 2010	II	Single arm	Sorafenib	Any	24	Oxaliplatin + capecitabine
O'Reilly, 2010	II	Single arm	Sunitinib	IV	77:65	-
Cohen, 2011	II	Single arm	Sorafenib	LAPC/IV	45	Gemcitabine + erlotinib
Kindler, 2011	III	RCT	Axitinib	III/IV	314:316	Gemcitabine
Saletti, 2011	I	Dose escalation	Vandetanib	LAPC/IV	15:67	Gemcitabine
El-Khoueiry, 2012	II	RCT	Sorafenib	IV	15:37	Gemcitabine
Goncalves, 2012	III	RCT	Sorafenib	IV	52:52	Gemcitabine
Kindler, 2012	II	Single arm	Sorafenib	LAPC/IV	17	Gemcitabine
Spano, 2012	I	Dose escalation	Axitinib	LAPC/IV	6:59	Gemcitabine
Reni, 2013	II	RCT	Sunitinib	IV	28:27	-
Aparicio, 2014	I	Dose escalation	Sorafenib	LAPC/	12	Gemcitabine + RT
Cardin, 2014	II	Single arm	Sorafenib + erlotinib	LAPC/IV	36:71	-

Table 1. Cont.

Author, Year	Phase	Type	Study Drug	Disease Stage	n	Treatment Backbone	
Cascinu, 2014	II	RCT	Sorafenib	LAPC/IV	43:44	Gemcitabine + cisplatin	
Chiorean, 2014	I	Dose escalation	Sorafenib	LAPC/IV	27:59	Gemcitabine + RT	
Dragovich, 2014	II	Single arm	Vatalinib	IV	67:64	-	
Bergmann, 2015	II	RCT	Sunitinib	LAPC/IV	54:52	Gemcitabine	
Makielski, 2015	II	Single arm	Sorafenib	LAPC/IV	24:63	Oxaliplatin + capecitabine	
Kessler, 2016	I	Dose escalation	Vandetanib	Any	10:55	Gemcitabine + capecitabine	
Zhen, 2016	I	Dose escalation	Cabozantinib	LAPC/IV	12:61	Gemcitabine	
Bozzarelli, 2016	II	Single arm	Regorafenib	LAPC/IV	20	-	
Middleton, 2017	II	RCT	Vandetanib	LAPC/IV	72:70	Gemcitabine	
<b>Anti-Hedgehog</b>							
Richards, 2012	Ib/II	Single arm	IPI-926	IV	16	Gemcitabine	
DeJesus-Acosta, 2014	II	Single arm	Vismodegib	IV	59:80	Gemcitabine + nab-paclitaxel	
Kim, 2014	I	Single arm	Vismodegib	IV	25:65	Gemcitabine	
Catenacci, 2015	Ib/II	RCT	Vismodegib	IV	53:53	Gemcitabine	
Ko, 2016	I	Dose escalation	IPI-926	LAPC/IV	15:58	FOLFIRINOX	
Macarulla, 2016	Ib	Dose-escalation	Sonidegib	IV	19	Gemcitabine	
Lee, 2017	Ib	Dose-escalation	Sonidegib	IV	26	Gemcitabine + nab-paclitaxel	
<b>Anti-Hyaluronic acid</b>							
Hingorani, 2016	Ib	Dose escalation	PEGPH20	IV	28	Gemcitabine	
Hingorani, 2018	II	RCT	PEGPH20	IV	166:113	Gemcitabine + nab-paclitaxel	
Ramanathan, 2019	Ib/II	RCT	PEGPH20	IV	59:55	FOLFIRINOX	
<b>Other stromal targets</b>							
Evans, 2001	II	RCT	Marimastat (MMP)	MMP	any	113	-
Moore, 2003	III	RCT	BAY 12-9566 (MMP)	MMP	IV	138:139	-
Friess, 2006	II	RCT	Cilengitide (integrin)	Integrin	LAPC	46:43	Gemcitabine
Infante, 2011	I	Dose-escalation	Pomalidomide	VEGF/TNF $\alpha$	IV	22	Gemcitabine
Shi, 2012	II	Single arm	Thalidomide	VEGF/TNF $\alpha$	LAPC/IV	31	Capecitabine
Infante, 2013	II	Single arm	Lenalidomide	VEGF/TNF $\alpha$	IV	72	Gemcitabine
Deplanque, 2015	III	RCT	Masitinib	cKit/PDGFR	LAPC/IV	172:178	Gemcitabine
Ullenhag, 2015	Ib	Dose-escalation	Pomalidomide	VEGF/TNF $\alpha$	LAPC/IV	12	Gemcitabine
O'Reilly, 2017	II	RCT	Necuparanib	Heparanase	IV	120	Gemcitabine + nab-paclitaxel

Trials that were discussed in multiple publications are shown here as most recent publication. Randomized control trial (RTC); locally advanced pancreatic cancer (LAPC); radiotherapy (RT); metalloproteinase (MMP); tumor necrosis factor alpha (TNF $\alpha$ ); Vascular endothelial growth factor (VEGFR).

In most trials included in this review, gemcitabine was the standard of care, five trials did not treat patients with any chemotherapy, and only two trials treated patients with FOLFIRINOX as backbone. Five of the more recent trials used the combination of gemcitabine and nab-paclitaxel as backbone [25,41,43,65,112].

### 2.1. Targeting Angiogenesis in Pancreatic Adenocarcinoma (PDAC)

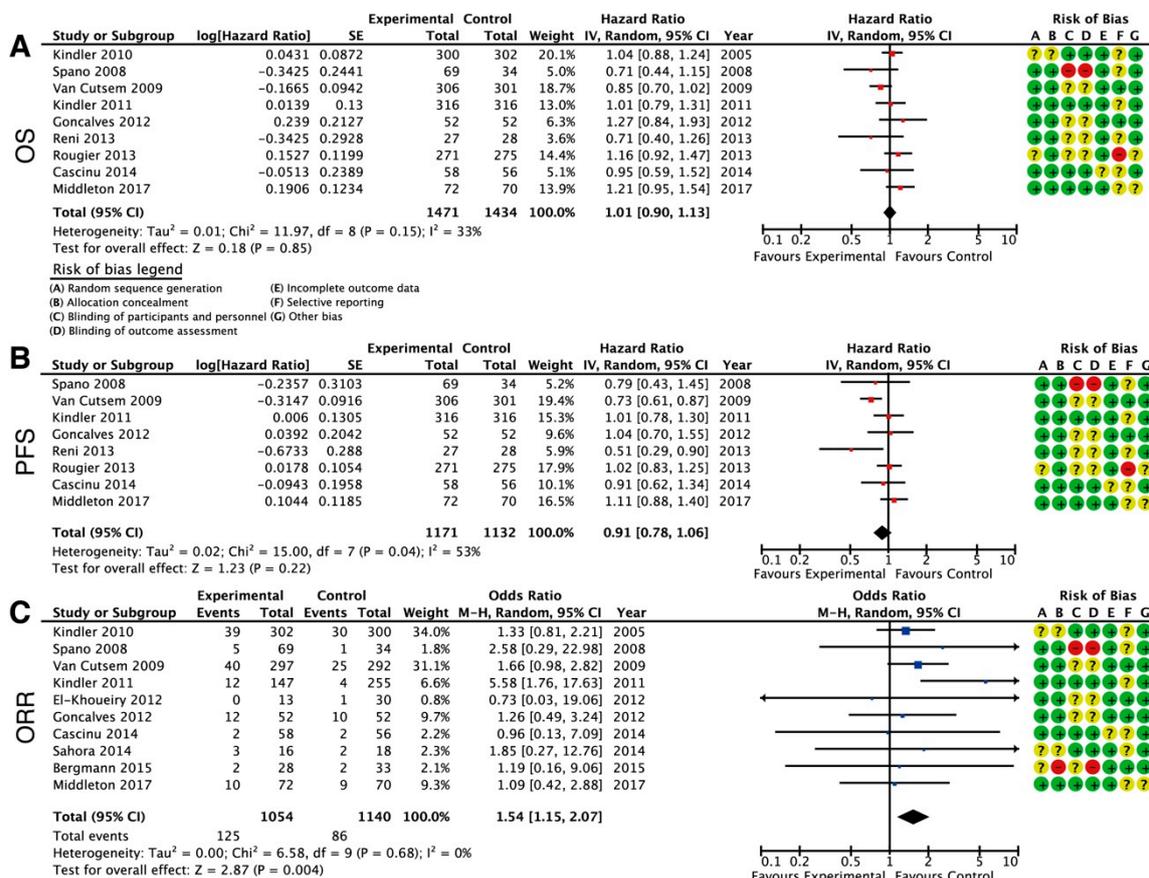
Most trials (51/70) targeted angiogenesis, with many of these trials (26/51) assessing the treatment benefit of bevacizumab, a monoclonal antibody that binds vascular endothelial growth factor A (VEGF A). These clinical trials included patients with locally advanced or metastatic diseases. In a pre-clinical setting, anti-angiogenic treatment reduced pancreatic tumor cell growth, and an overexpression of VEGF was associated with tumor progression and poor prognosis [114,115]. These results, and the clinical benefits observed in other tumor types, provided a rationale to investigate the use of bevacizumab for the treatment of pancreatic cancer.

In a single-arm phase II trial, the combination of bevacizumab and gemcitabine for metastatic disease showed promising results [57]. Several clinical trials followed, with some alterations to the chemotherapy backbone; these trials showed mixed results [21,22,51,62]. Kindler et al. demonstrated, in a large phase III trial with 603 patients, that the addition of bevacizumab did not increase overall survival (5.8 vs. 5.9 months,  $p = 0.95$ ) for patients with advanced diseases [59]. Yet, some benefit of treatment was seen in progression free survival (PFS), albeit not significant (3.8 vs. 2.9 months,  $p = 0.075$ ). Several phase I and II trials followed, with alternative chemo(radio)therapy backbones, but no benefit of bevacizumab addition was observed. Next, the combination of VEGF and an epidermal growth factor receptor (EGFR) inhibition was assessed, as the addition of erlotinib to gemcitabine had shown some treatment benefit [116]. In a phase III trial bevacizumab was combined with erlotinib and gemcitabine, but no significant increase in overall survival was found (7.1 vs. 6.0 months,  $p = 0.21$ ) [104]. However, a benefit was seen in PFS: 4.6 vs 3.6 months ( $p = 0.0002$ ). Three phase I [17,24,106] and three phase II [61,64,66] clinical trials followed. None of these trials showed an increase in overall survival.

Axitinib and sorafenib, both small molecule tyrosine kinase receptor inhibitors (TKI) and aflibercept, a VEGF “trap” fusion protein, were used to target angiogenesis in advanced pancreatic cancer [58,87,96,97]. In a phase II trial, the combination of axitinib, a pan-VEGF receptor inhibitor, and gemcitabine did not show an increase in overall survival compared to gemcitabine alone (6.9 vs. 5.6 months) [96]. In a large phase III trial, Kindler et al. confirmed that the addition of axitinib did not increase overall survival: 8.5 months versus 8.3 months [58]. The treatment benefit of sorafenib, an inhibitor of VEGFR 2 and 3, platelet derived growth factor receptor (PDGFR) and Raf family kinases, was assessed in multiple trials, but none of these trials demonstrated a treatment benefit [11,12,14,18,28,32,60,67,69]. In a phase III randomized clinical trial no significant difference had been observed in median OS: 8.0 vs. 9.2 months when combined with gemcitabine [32]. Thereafter, sorafenib was assessed in combination with EGFR inhibition, but no benefit for OS or PFS was observed [19,20]. Targeting the VEGF, a ligand targeting agent aflibercept was added to gemcitabine in a phase III trial but also yielded no significant difference in overall survival (6.5 months vs. 7.8 months) [87]. Other TKIs that also target the VEGF receptor were assessed in combination with chemotherapy in seven clinical trials (see Table 1). None of the clinical trials assessing the TKIs sunitinib, vandetanib, regorafenib, cabozantinib, or vatalinib demonstrated a treatment benefit [26,27,45,52,71,79,84,88,91,107].

A meta-analysis did not show a treatment benefit in OS of all VEGF or VEGFR-targeting treatments (Figure 3A). This analysis is based on the information of ten clinical trials, with a total of 1471 patients in the experimental arms and 1434 patients in the control arms. The combined HR for OS across all studies was 1.01 (95% CI, 0.90–1.13), showing that the addition of bevacizumab, axitinib, sorafenib, or aflibercept does not improve overall survival. Data on PFS was reported in eight out of ten studies; again, no treatment benefit was seen for PFS with a pooled HR of 0.91 (95% CI, 0.78–1.06) (Figure 3B). The combined overall response rate (ORR) of the VEGF targeting clinical trials suggests a detrimental

effect of anti-VEGF, with a combined HR of 1.54 (95% CI, 1.15–2.07) (Figure 3C). Removing treatment heterogeneity and compiling the clinical trials that used only bevacizumab (Pooled HR 0.94 (0.77–1.16)), axitinib (Pooled HR 0.90 (0.65–1.25)), or sorafenib (Pooled HR 1.12 (0.82–1.53)), showed that there was no increase in overall survival from the addition of any VEGF targeting drug.



**Figure 3.** Meta-analysis results of treatment with anti-angiogenic therapies for overall survival, (A) progression free survival (B) overall objective response rate (C) with random effects model. HR = hazard ratio, CI = confidence interval, IV = inverse-variance approach, M-H = Mantel-Haenszel test. Red: high risk of bias, Green: low risk of bias, Yellow: unclear risk of bias.

### 2.2. Targeting the Hedgehog Pathway in PDAC

The Hedgehog (Hh) pathway plays a critical role in tumor progression in pre-clinical PDAC models [117,118]. This is recapitulated in human pancreatic tumors, as the pathway’s ligand Sonic Hedgehog (Shh) is overexpressed in 70% of pancreatic tumors, and is identified as one of the core signaling pathways that undergo alterations in pancreatic cancer [119,120]. Interestingly, Shh is absent from both the developing and the healthy pancreas but increases dramatically from the pancreatic intraepithelial neoplasia (PanIN) stages to carcinoma [119,121]. The stromal compartment responds to Hedgehog ligands secreted by tumor cells to support the latter indirectly, in contrast to other Hedgehog driven cancers, such as basal cell carcinoma, where the Hedgehog pathway is often upregulated through loss of function mutations in Patched homologue 1 (PTCH1) [122,123].

Vismodegib (GDC-0449, Genentech) and other Hedgehog inhibitors have been tested in several clinical trials. In a genetically engineered mouse model of PDAC, Olive et al. demonstrated an improved delivery of gemcitabine, following administration of saridegib, which warranted human clinical trials [117]. Twenty-five patients in a single arm clinical trial were enrolled for vismodegib treatment combined with gemcitabine [53]. The primary endpoint of this trial was the effect of vismodegib on stem cell population in core-biopsies before and after treatment, but no significant

treatment effect was seen. Treatment benefit for OS (5.3 months (95% CI, 3.6–8.4)) or PFS (2.8 months (95% CI, 1.4–4.7)) was not found, compared to historical controls [53].

The phase Ib/II randomized clinical trial, evaluating the addition of vismodegib to gemcitabine, showed no treatment benefit for OS nor PFS [16]. The median OS was 6.9 and 6.1 months, respectively (adjusted HR, 1.04; 95% CI, 0.69–1.58). The median PFS was 4.0 months in the vismodegib arm versus 2.5 months in placebo (HR, 0.83; 95% CI, 0.55–1.23) [16]. In another phase II trial vismodegib was added to a combination treatment of gemcitabine and nab-paclitaxel [25]. Preliminary results have been presented and showed a median OS of 10 months (95% CI, 7.3–11 months), compared to 8.7 months for treatment with nab-paclitaxel and gemcitabine. Median PFS was estimated to be 5.5 months (95% CI, 5.2–5.9 months) [25]. With 57 out of 80 patients included in 2014, final results were not presented [25].

The Hedgehog pathway inhibitor, saridegib (IPI-926, Infinity), has been used in several clinical trials [85,100]. After a successful phase 1b trial with IPI-926 and gemcitabine demonstrating good tolerability of the combination, the trial continued in a randomized, double blind phase II trial. However, the phase II part of this trial was halted due to the early detection of a shorter median OS in the experimental arm compared to the placebo arm [124]. The same drug was assessed in a phase I trial combined with FOLFIRINOX [63]. This trial was halted early, with just 15 patients included, due to the cancellation of the phase II trial described above and the lack of treatment benefit with vismodegib treatment thus far.

In two phase I clinical trials, the Shh inhibitor, sonidegib (LDE225, Novartis, Basel, Switzerland) was assessed in combination with gemcitabine monotherapy or in combination with nab-paclitaxel [65,68]. Even though efficacy was not the primary outcome for these trials, Lee et al. reported a median PFS of 4.9 months: This combination did not seem to confer additional clinical benefit [68].

With only one clinical trial publishing HRs, a meta-analysis could not be done for anti-Hedgehog therapies.

### 2.3. Targeting Hyaluronic Acid in PDAC

The extracellular matrix is thought to play an important role in the development and progression of PDAC. The dense matrix consists mainly of several types of glycans and collagens. The predominant glycosaminoglycan is hyaluronic acid (HA). This protein retains water, which increases interstitial fluid pressure, restricts vascular tissue, and may reduce chemotherapeutic delivery [125]. In normal tissues, the balance of hyaluronic acid is maintained by synthesizing and degrading enzymes. In pancreatic cancer tissues, this balance is shifted towards a higher concentration of HA, which is associated with poor survival [126,127]. Therapeutic strategies that target hyaluronic acid can either inhibit synthesis, block HA signaling, or break down stromal HA, as reviewed by Sato et al. [128].

Targeting HA deposition in PDAC is currently being assessed in clinical trials for several tumor types. PEGPH20 (HALOzyme) is the PEGylated form of a recombinant human hyaluronidase, which breaks down HA. In two phase I trials for solid tumors, dosing schedules and tolerability were assessed of PEGPH20 [129]. PEGPH20 was used in combination with gemcitabine and nab-paclitaxel in a phase Ib/II trial with previously untreated stage IV PDAC patients [42]. The phase II part of this trial showed clinically meaningful improvements in PFS and ORR for patients with HA<sup>high</sup> tumors: An increase in PFS from 6.3 ( $n = 21$ ) to 9.2 ( $n = 22$ ) months for the addition of PEGPH20 to gemcitabine and nab-paclitaxel treatment. In a second phase II trial from Hingorani et al., the median OS in the experimental arm was found to be 6.0 months (95% CI, 4.0–11.5), but stratification of patients based on HA expression showed a significant treatment benefit for HA<sup>high</sup> patients with a median OS of 13.0 months (95% CI, 6.9–19.0) and a PFS of 7.2 months (95% CI, 5.2–9.0) [43]. For HA<sup>low</sup> patients the treatment benefit was markedly less: OS of 5.7 months (95% CI, 1.1–9.6) and PFS of 3.5 months (95% CI, 0.5–5.3). In addition to the phase II trial with nab-paclitaxel and gemcitabine, a phase 1b/II trial with PEGPH20 and FOLFIRINOX was initiated concurrently [82]. This trial was closed in 2017 when a planned interim analysis, with 114/138 patients included, showed a detrimental effect of PEGPH20 addition: Median OS for treatment with FOLFIRINOX only was 14.4 months and with PEGPH20

just 7.7 months. The HR of 2.07 (95% CI, 1.28–3.34) clearly shows favor for a FOLFIRINOX only treatment [82].

As demonstrated in the phase II trial, PFS for patients with HA<sup>high</sup> tumors was significantly improved when treated with PEGPH20 in combination with chemotherapy, compared to chemotherapy alone (HR 0.51, 95%CI, 0.26–1.00  $p = 0.048$ ) [43]. Currently, this treatment regimen is being tested in a large randomized, double blinded phase III trial only for patients with HA<sup>high</sup> pancreatic tumors in combination with gemcitabine and nab-paclitaxel [130].

#### 2.4. Targeting Other Stromal Targets in PDAC

Several clinical trials target tumor-stroma interactions through additional targets, which are summarized below: Targeting of the platelet derived growth factor (PDGF) receptor has been investigated in multiple clinical trials. This receptor is expressed on cancer-associated fibroblasts and has been shown to correlate with poor prognosis in pancreatic cancer [131]. Several of the TK inhibitors discussed above also inhibit PDGF, albeit with lower affinity. Masitinib is a PDGFR inhibitor and was assessed for treatment of pancreatic cancer in combination with gemcitabine in a phase III clinical trial. Median OS was similar between treatment-arms: 7.7 and 7.1 months, with a HR of 0.89 (95% CI, 0.70–1.13) [109].

Thalidomide and its derivatives, such as pomalidomide, are thought to have immunomodulating effects in addition to having anti-angiogenic and anti-inflammatory properties [132]. Thalidomide was tested in combination with capecitabine in a phase II trial but, with a median PFS of 2.7 months (95% CI, 2.4–3.3) and median OS of 6.1 months (95% CI, 5.3–6.9), results were not convincing [111]. The more potent derivative pomalidomide was used in a phase I study for pancreatic cancer in combination with gemcitabine [47]. Efficacy data are limited due to the number of patients, but three out of 20 patients showed a partial response. Lenalidomide was also assessed in a phase I clinical trial in combination with gemcitabine [101].

Several matrix metalloproteinase (MMP) inhibitors have been studied in the clinical setting. MMPs are involved in extracellular matrix remodeling and may provide favorable conditions for cancer cell migration [133]. MMP inhibitors, BAY 12-9566 and Marimastat mono-therapy, were compared to gemcitabine, but failed to improve survival [72,108,110].

Integrins  $\alpha_v$  were involved in angiogenesis through VEGF and fibroblast growth factor (FGF) signaling pathways [134]. An integrin receptor inhibitor, cilengitide was assessed for anti-angiogenic capabilities in a phase II clinical trial in combination with gemcitabine for patients with advanced diseases [31]. With a median OS of 6.7 months, compared to 7.7 months for gemcitabine alone, there was no benefit of the addition of cilengitide [31].

### 3. Discussion

Treatment of pancreatic cancer with stroma-targeting therapies is aimed to reduce tumor bulk, or increase delivery of chemotherapeutic agents to tumor cells, to improve immune-surveillance and inhibit tumor-promoting signaling from the stroma. However, as shown in this systematic review, clinical trials with stroma-targeting therapies have so far shown limited treatment benefits for patients with advanced diseases, with an exception for hyaluronidase, which may improve its clinical outcome when combined with gemcitabine and nab-paclitaxel and is currently being assessed in a phase III clinical trial.

Treatment with anti-angiogenic drugs was thought to be beneficial in pancreatic cancer, as tumor cell expression of VEGF is associated with metastases and poor prognosis [114,135]. In other tumor types, such as breast cancer, non-small-cell lung cancer, and colorectal cancer, the addition of bevacizumab to chemotherapeutic regimens has been shown to be beneficial [136–139]. Despite numerous clinical trials with varying treatment combinations and dosages, this meta-analysis demonstrates no clinical benefit of any VEGF or VEGFR-targeted treatment: Neither bevacizumab, sorafenib, axitinib, or aflibercept increased the overall survival compared to controls. There may even be an adverse effect

as seen in the objective response. This lack of efficacy for pancreatic tumors is difficult to explain; it has been shown that large parts of the pancreatic tumor are already hypoxic due to the extensive desmoplasia and limited vasculature, therefore anti-angiogenic agents directed against the ligand, such as bevacizumab, may have limited effects [140]. In addition, there may be other effects of targeting angiogenesis, unrelated to vasculature, as reviewed in Ellis et al. [141]. However, some parts of the pancreatic tumor are oxygenated, and targeting VEGF in these regions could induce normalization of the tumor-associated aberrant vasculature. In turn, this would increase chemotherapeutic delivery. Timing is important for this concept to work, as proposed by Huang et al. [142]. In the trials discussed in this review, anti-angiogenic therapies were given concurrently with chemotherapeutics. This could be improved by administration of anti-angiogenic treatment several days before chemotherapeutic delivery, as vasculature in rat models was normalized between two and four days after treatment [143]. Van der Veldt et al. investigated the process of vasculature normalization using bevacizumab in vivo and observed that treatment with bevacizumab actually induced an overall decrease in tumor perfusion [144]. This reduction started several hours after treatment and continued for several days. This is contrary to observations published before and, therefore, more studies are required that investigate the timing of anti-angiogenic treatment.

Pre-clinical studies often do not reflect the more complex human pancreatic cancer biology. This was observed in the clinical trial with the Smo inhibitor IPI-926: In the pre-clinical trial, IPI-926 reduced desmoplasia and increased intratumoral gemcitabine concentrations [117]. In the subsequent human clinical trial, treatment with IPI-926, the experimental arm, showed an increase in progressive disease compared to gemcitabine monotherapy [124]. Further investigation in mice, Rhim et al. demonstrated that Shh deletion increased metastasis formation, generated poorly differentiated tumors, and, more importantly, significantly reduced overall survival [145]. This was also confirmed in KPC mice, which spontaneously develop pancreatic tumors, where long-term treatment with IPI-926 reduced overall survival [145]. In other mouse models, it was shown that cancer-associated fibroblasts and the desmoplasia limit epithelial growth, thus function to restrain pancreatic cancer [9,146]. This example demonstrates that our understanding of tumor-stroma interactions is still too limited to fundamentally advance the treatment for pancreatic cancer.

A more successful strategy that aims to deplete some of the mechanical properties of the stroma in PDAC is to target components of the extracellular matrix, such as hyaluronic acid. In several clinical trials, the increased median OS and median PFS for HA<sup>high</sup> patients showed that stroma depletion by breaking down hyaluronic acid can improve survival for pancreatic cancer patients [43]. In the ongoing phase III trial, patient selection is based on high HA levels in tumor biopsies. This is of particular importance because assessment of biopsies identifies patients that may benefit most from this treatment. Not only does this limit over-treatment of patients who will not benefit from treatment, but more importantly, patients are given the optimal treatment for their specific tumor. In addition, patient selection improves our design of clinical trials. The promising results of treatment with PEGPH20 for HA<sup>high</sup> patients may not have been found without patient selection [43]. The detrimental overall efficacy results of the PEGPH20 trial with FOLFIRINOX backbone confirm that patient selection before the start of treatment is necessary [82]. A similar approach for anti-angiogenic treatment has been assessed several times in multiple cancer types, but despite holding prognostic significance, none of the VEGF ligands or receptors can be used to determine or predict response to anti-angiogenic treatment, regardless of assessment in biopsy material or in blood samples [147].

Patient selection using tumor biopsies is invasive, and developing multiple stainings for regular clinical practice is laborious and expensive. Therefore, a less invasive and expensive alternative is warranted, such as blood-based biomarkers or biomarker-based imaging. In addition, biomarkers can be used for early detection of PDAC, which could provide more patients with surgery as part of their curative treatment plan. Progress and challenges in their development have been reviewed by Root et al. [148]. Biomarkers can be used for a specific treatment, such as circulating levels of VEGF-A in blood samples, but more interesting are biomarkers for stroma, either specific for PDAC or for

multiple cancer types. ADAM12 was recently identified as a marker for stromal activation and is predictive for response to chemotherapy in pancreatic cancer [149]. This stromal marker is not only predictive for response in pancreatic cancer, but also correlates with the tumor stage in breast and bladder cancer and has prognostic value in small-cell lung cancer [150–152]. The usage of a general stromal biomarker could provide clinical relevance for stroma-targeting therapies, spanning cancer types and decreasing expense, while optimizing treatment.

This systematic review and meta-analysis have some limitations that need to be taken into account. Our meta-analysis of all anti-angiogenic therapies combines several different types of anti-VEGF treatments. Even when limiting the meta-analysis to a single drug, e.g., bevacizumab, substantial heterogeneity between the studies was present, because different dosing and treatment schedules were used. The meta-analysis of anti-hyaluronic acid treatment was limited by the total number of patients, and this small cohort combines patients with different tumor biologies.

## 4. Materials and Methods

### 4.1. Search Strategy

A systematic search of MEDLINE/PubMed, the EMBASE, and the Cochrane database was performed through August 2018 and updated in March 2019, in line with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for systematic reviews and meta-analyses by two independent researchers (MM, CS) [113]. We identified eligible research articles, evaluating the effect of stroma-targeting therapies on the median overall survival in pancreatic adenocarcinoma. Medical subject headings (MeSH) terms were used where possible. General stroma search terms such as “stroma”, “desmoplasia”, and “extracellular matrix” were used in combination with general search terms related to PDAC. In addition, specific search terms were added for angiogenesis, Hedgehog, and hyaluronic acid inhibitors, to ensure that all studies targeting these pathways were included. In the search, we excluded pre-clinical research using key words such as “cell line”, “culture”, and “tissue samples”. The search strategy for MEDLINE/PubMed was rewritten for the EMBASE and Cochrane databases. All strategies are shown in Appendices A–C. Additionally, reference lists of full-text articles were searched manually for relevant literature. The search results were analyzed by two independent investigators (MM, CS) and any disagreement was resolved by discussion.

### 4.2. Eligibility Criteria

Studies considered eligible for inclusion in the systematic review of the following inclusion criteria were met: Studies concerned pancreatic adenocarcinoma, studies described the effect of a treatment targeting the tumor stroma, studies were prospective clinical trials, and studies were published in English. Discordances between conference abstracts and final papers were assessed, and final papers were referenced where possible.

### 4.3. Quality and Risk of Bias Assessment

The Cochrane bias assessment tool was used for the randomized controlled trials (RCTs). Each study was assessed with a higher or lower risk for selection bias on their patient population, performance bias, detection bias, attrition bias, reporting bias, and other possible biases, with a “high risk”, “unclear risk”, or “low risk”. The following outcomes of interest were defined: Overall survival (OS), progression-free survival (PFS), and overall objective response rate (ORR, defined by the rate of complete response with partial response and stable disease). An adjusted version of the Joanna Briggs Institute (JBI) critical appraisal checklist for case series was used to assess the quality of the single-arm open-label studies. The studies were evaluated on their inclusion methods, standardization of disease measurements, reporting of demographics of patients, reporting of follow-up, outcomes of the objectives, and the statistical analysis method, by scoring each study a “yes”, “no”, or “unclear”.

#### 4.4. Data Extraction and Synthesis

For the eligible studies for full-text reading, we extracted data on type and phase of study, stroma-targeting treatment, chemotherapeutic backbone, dosage and timing schedule, stage of the tumor, number and age of patients in cohorts, the efficacy outcomes median overall survival, progression-free survival and overall response rate, and the primary objective of the studies. We focused on the following efficacy outcomes: Overall survival (OS), defined as the time between the beginning of the study until time of death, progression-free survival (PFS), defined as the time between the treatment initiation until disease progression, and overall objective response rate (ORR), defined as the rate of complete response with partial response. Treatments targeting the VEGF, Hedgehog, or hyaluronic acid pathway, respectively, were combined in a meta-analysis if hazard ratios (HR) were published. OS and PFS HRs were used to assess the efficacy outcomes in a random effects model, whereas a Mantel-Haenszel test was used for the ORR outcome, both using Review Manager 5.3.

#### 5. Conclusions

In conclusion, the interactions between tumor and stroma in pancreatic cancer as a treatment target remain interesting, albeit complicated. Anti-VEGF treatment has not shown treatment benefit. However, treatment with the hyaluronic acid-modulator PEGPH20 has shown treatment benefit for only HA<sup>high</sup> patients. With these results we can conclude that the stromal compartment of pancreatic tumors needs to be considered. More importantly, trials need to stratify patients to identify subgroups that may benefit from anti-tumor stroma therapies, which can be achieved with treatment specific biopsies or with less invasive blood or imaging-based biomarkers. Only then can we make full use of our increased understanding of the pancreatic tumor stromal biology.

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**Conflicts of Interest:** The authors declare no conflict of interest.

#### Appendix A

Pubmed search query: ((Angiogenic Proteins[MeSH] or Hedgehog Proteins[MeSH] or Vascular Endothelial Growth Factors[MeSH] or Hyaluronic Acid[MeSH] or Shh protein, human[Supplementary Concept] or Hedgehog[tiab] or Shh[tiab] or IHH[tiab] or VEGF[tiab] or hyaluronan[tiab] or hyaluronic acid[tiab] ) AND (antagonists and inhibitors[Subheading] or inhibitor[tiab] or antagonist[tiab] or inhibiting[tiab] OR Angiogenesis Inhibitors[Pharmacological Action] or ciliobrevin A[tiab] OR VEGF Trapon[TIAB] or 5-nitro-2-3-phenylpropylaminobenzoic acid[tiab] or Anecortave[tiab] or bevacizumab[tiab] or cytochalasin E[tiab] or Endostatins[tiab] or fumagillin[tiab] or halofuginone[tiab] or homoharringtonine[tiab] or Interleukin-12[tiab] or Interleukin-23[tiab] or LECT1[tiab] or lenalidomide[tiab] or O-chloroacetylcarbamoylefumagillol[tiab] or pomalidomide[tiab] or Ranibizumab[tiab] or roquinimex[tiab] or semaxinib[tiab] or squalamine[tiab] or sunitinib[tiab] or tetra4-N-methylpyridylporphine[tiab] or tetrathiomolybdate[tiab] or Thalidomide[tiab] or thymogen[tiab] or trebananib[tiab] or Tumor Necrosis Factor Ligand Superfamily Member 15[tiab] or volociximab[tiab] or zhengguangmycin[tiab] or sonidegib[tiab] or vismodegib[tiab] or IPI-926[tiab] or LDE225[tiab] or LY2940680[tiab] or ramucirumab[tiab] or regorafenib[tiab] or sorafenib[tiab] or sunitinib[tiab] or axitinib[tiab] or PEGPH20[tiab] OR “tumor microenvironment”[MeSH Terms] OR stroma\* [tiab] OR desmoplasia [tiab] OR “Extracellular Matrix”[Mesh] OR “extracellular matrix proteins”[MeSH Terms] OR “Connective Tissue Cells”[Mesh] OR “Stromal Cells”[Mesh] OR microenvironment [tiab])AND (Pancreatic Neoplasms[MeSH] or pancreatic tumor\*[tiab] or

pancreatic tumor\*[tiab] or pancreatic cancer[tiab] or pancreatic adenocarcinoma[tiab] or pancreatic ductal adenocarcinoma[tiab] or pancreatic carcinoma[tiab]) NOT (histoculture[tiab] or HDRA[tiab] or cell culture[tiab] or cells, cultured[MeSH] or single-cell suspension[tiab] or single-cell suspensions[tiab] or single cell suspensions[tiab] or suspension cultures[tiab] or cell-line[tiab] or cell-lines[tiab] or cell line [tiab] or cell lines[tiab] or xenograf\*[tiab] or tumor line[tiab] or tumor lines[tiab] or primary cell cultures[tiab] or in vitro model[tiab] or tissue samples[tiab] or clonogenic assay[tiab] or TCA[tiab] or cells[tiab] AND culture[tiab] OR squamospheres[tiab] OR cell culture techniques[MeSH] or (animals[mesh] NOT humans[meSH]))

## Appendix B

Cochrane search query: (([mh "Angiogenic Proteins"] OR [mh "Hedgehog Proteins"] OR [mh "Vascular Endothelial Growth Factors"] OR [mh "Hyaluronic Acid"] OR Hedgehog:ti,ab OR Shh:ti,ab OR IHH:ti,ab OR VEGF:ti,ab OR hyaluronan:ti,ab OR "hyaluronic acid":ti,ab) AND (inhibitor:ti,ab OR antagonist:ti,ab OR inhibiting:ti,ab OR [mh "Angiogenesis Inhibitors"] OR "ciliobrevin A":ti,ab OR "VEGF Trapon":ti,ab OR "5-nitro-2-3-phenylpropylaminobenzoic acid":ti,ab OR Anecortave:ti,ab OR bevacizumab:ti,ab OR "cytochalasin E":ti,ab OR Endostatins:ti,ab OR fumagillin:ti,ab OR halofuginone:ti,ab OR homoharringtonine:ti,ab OR Interleukin-12:ti,ab OR Interleukin-23:ti,ab OR LECT1:ti,ab OR lenalidomide:ti,ab OR O-chloroacetylcarbamoylefumagillol:ti,ab OR pomalidomide:ti,ab OR Ranibizumab:ti,ab OR roquinimex:ti,ab OR semaxinib:ti,ab OR squalamine:ti,ab OR sunitinib:ti,ab OR "tetra4-N-methylpyridylporphine":ti,ab OR tetrathiomolybdate:ti,ab OR Thalidomide:ti,ab OR thymogen:ti,ab OR trebananib:ti,ab OR "Tumor Necrosis Factor Ligand Superfamily Member 15":ti,ab OR volociximab:ti,ab OR zhengguangmycin:ti,ab OR sonidegib:ti,ab OR vismodegib:ti,ab OR IPI-926:ti,ab OR LDE225:ti,ab OR LY2940680:ti,ab OR ramucirumab:ti,ab OR regorafenib:ti,ab OR sorafenib:ti,ab OR sunitinib:ti,ab OR axitinib:ti,ab OR PEGPH20:ti,ab OR [mh "tumor microenvironment"] OR stroma\*:ti,ab OR desmoplasia:ti,ab OR [mh "Extracellular Matrix"] OR [mh "Connective Tissue Cells"] OR [mh "Stromal Cells"] OR microenvironment:ti,ab or [mh "extracellular matrix proteins"])) AND ([mh "Pancreatic Neoplasms"] OR pancreatic tumor\*:ti,ab OR pancreatic tumors:ti,ab OR "pancreatic cancer":ti,ab OR "pancreatic adenocarcinoma":ti,ab OR "pancreatic ductal adenocarcinoma":ti,ab OR "pancreatic carcinoma":ti,ab))

## Appendix C

Embase search query: ((exp vasculotropin/ OR exp hyaluronic acid/ OR exp angiogenic protein/ OR exp Hedgehog signaling/ or exp sonic Hedgehog protein/ or (Shh or Hedgehog or IHH or VEGF or vasculotropin or hyaluronan or "hyaluronic acid"):ti,ab,kw) AND (exp pancreas cancer/ or (pancreatic adj2 (carcinoma or tumor\* or tumour\* or cancer or adenocarcinoma)).ti,ab,kw.) AND (exp \*angiogenesis inhibitor/ or ("ciliobrevin A" or "VEGF Trapon" or "5-nitro-2-(3-phenylpropylamino)benzoic acid" or "Anecortave" or Bevacizumab or "cytochalasin E" or Endostatins or fumagillin or halofuginone or homoharringtonine or "Interleukin-12" or "Interleukin-23" or LECT1 or lenalidomide or "O-(chloroacetylcarbamoyle)fumagillol" or pomalidomide or Ranibizumab or roquinimex or Semaxinib or squalamine or sunitinib or "tetra(4-N-methylpyridyl)porphine" or tetrathiomolybdate or Thalidomide or thymogen or trebananib or "Tumor Necrosis Factor Ligand Superfamily Member 15" or volociximab or zhengguangmycin or sonidegib or vismodegib or IPI-926 or LDE225 or LY2940680 or ramucirumab or regorafenib or sorafenib or sunitinib or axitinib or PEGPH20).ti,ab,kw. or exp tumor microenvironment/ or exp extracellular matrix/ or exp connective tissue cell/ or exp stroma cell/ or exp scleroprotein/ or (stroma\* or microenvironmen or desmoplasia).ti,ab) NOT (exp in vitro study/ or ("cell culture" or "single-cell suspension" or "single-cell suspensions" or "single cell suspensions" or "suspension cultures" or cell-line or cell-lines or "cell line" or "cell lines" or xenograf\* or "tumor line" or "tumor lines" or "primary cell cultures" or "in vitro model" or "tissue samples" or "clonogenic assay" or tca or (cells and culture) or squamospheres).ti,ab,kw. OR ((exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp

experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/) OR neuroendocrine.ti,ab.))

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