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**State of the art biological therapies in pancreatic cancer**

Di Marco M *et al.* Biological therapies in pancreatic cancer

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**Abstract**

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a five-year survival rate of approximately 5%. Several target agents have been tested in PDAC, but almost all have failed to demonstrate efficacy in late phase clinical trials, despite the better understanding of PDAC molecular biology generated by large cancer sequencing initiatives in the past decade. Eroltinib (a small-molecule tyrosine-kinase inhibitor of epidermal growth factor receptor) plus gemcitabine is the only schedule with a biological agent approved for advanced pancreatic cancer, but it has resulted in a very modest survival benefit in unselected patients. In our work, we report a summary of the main clinical trials (closed and ongoing) that refer to biological therapy evaluation in pancreatic cancer treatment.

**Key words:** Pancreatic cancer; Targeted therapy; Molecular characterization; Epidermal growth factor receptor inhibitors; Embryonic pathway inhibitors; Antiangiogenic therapies

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**Core tip:** Our study aims to give an overview of the progress made in molecular targeted therapy for pancreatic cancer in recent years and the current status of clinical trials in the field. Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a five-year survival rate of approximately 5%. Several target agents have been tested in PDAC but almost all have failed to demonstrate efficacy in late phase clinical trials, even with a better understanding of PDAC molecular biology generated by large cancer sequencing initiatives in the past decade. Eroltinib (small-molecule tyrosine-kinase inhibitor of epidermal growth factor receptor) plus gemcitabine is actually the only schedule with a biological agent approved for advanced pancreatic cancer, but it resulted in a very modest survival benefit in unselected patients. In our work, we reported a summary of the main clinical trials (close and ongoing) that refer to biological therapy evaluation in pancreatic cancer treatment.

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**INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies, representing the fourth leading cause of cancer death. The five-year survival rate is approximately 5%, and surgery remains the most effective treatment[1].

Unfortunately, only 20% of patients are suitable for radical resection, and recurrence of disease occurs in 80% of patients who undergo resection[2].

The most important improvement concerns the conventional chemotherapy, represented by FOLFIRINOX and gemcitabine plus nab-paclitaxel regimens, but it results in a modest outcome advantage[3,4].

No significant progress has been made in the field of targeted therapy. Eroltinib [a small-molecule tyrosine-kinase inhibitor of epidermal growth factor receptor (EGFR)] plus gemcitabine is actually the only schedule with a biological agent approved for pancreatic cancer, but it results in a very modest survival benefit in unselected patients[5].

In recent decades, several combinations of classic chemotherapy and novel biological agents have been studied, but they have not improved overall survival, and furthermore, those trials did not use biomarkers to select responder patients[6].

Our study aims to give an overview of the progress made in molecularly targeted therapy for pancreatic cancer in recent years and the current status of clinical trials in the field, as summarized in Tables 1-3.

**MOLECULAR CHARACTERIZATION OF PDAC: HAS A BETTER UNDERSTANDING OF THE TUMOUR’S MOLECULAR BIOLOGY REALLY IMPROVED TARGETED THERAPY APPLICATIONS?**

Large cancer sequencing initiatives generated a large quantity of data in the past decades. Those findings showed a complex genomic landscape characterized particularly by inter-tumoural and intra-tumoural heterogeneity involving genomic aberration[7].

With the exception of the well-known KRAS, TP53, CDKN2A and SMAD4 alterations occurring at respective frequencies of 71%, 49%, 22% and 20%, a large number of genomic rearrangements with mutational frequencies less than 2% were found[8,9].

The majority of single gene mutations in pancreatic cancer can be grouped into common cellular pathways. Jones *et al*[10] identified 69 mutated gene sets in most of the 24 samples analysed in their pioneering sequencing study, of which 31 could be grouped into 12 core signalling pathways. These pathways included KRAS signalling, the transforming growth factor ß (TGF-ß) pathway, DNA damage control, apoptosis, regulation of G1/S cell cycle transition, Hedgehog signalling, the homophilic cell adhesion pathway, integrin signalling, TGF-ß signalling, Wnt/Notch signalling, and the invasion pathway[10].

Genomic heterogeneity, a characteristic of PDAC, implies genomic instability, which is due to the acquisition of telomere dysfunction and abnormal cell-cycle control occurring predominantly in early cancer stages, but it persists after cancer dissemination, resulting in parallel evolution among different metastases. Cell clones arranging metastasis may require other driver mutations compared with primary tumour cells implementing genetic variation in pancreatic cancer[11,12].

Given this molecular complexity, it is very difficult to separate passenger from driver mutations, to identify molecular mutations with a crucial role in pancreatic carcinogenesis that can be developed into actionable molecular targets of novel biological agents or to identify patients potentially responsive to existing agents already approved for human use in other cancers (Figure 1), and currently no predictive or prognostic biological factors are employed in clinical practice.

**TARGETED THERAPY IN PDAC**

***EGFR pathway inhibitors***

EGFR is a transmembrane receptor member of the ErbB family with a tyrosine kinase domain that is activated by many ligands including epidermal growth factor (EGF), TGF-α, heparin-binding EGF, amphiregulin, epiregulin, betacellulin and neuregulin (an epidermal growth factor). EGFR is involved in cell cycle regulation, cell survival, adhesion and differentiation through activation of the Ras/MAP kinase, phosphatidylinositol 3’-kinase (PI3K)/Akt, Janus kinase/Stat and phospholipase C/protein kinase C pathways. Several trials showed that EGFR is overexpressed in up to 90% of pancreatic cancer samples. Therefore, inhibitors targeting EGFR have been considered a promising therapeutic agent[13].

Eroltinib is a tyrosine kinase inhibitor (TKI) molecule that competes with ATP for binding to the kinase domain, thereby blocking downstream signal transduction. A possible therapeutic role was evaluated in a large phase III trial, enrolling 569 chemotherapy naïve patients with locally advanced or metastatic pancreatic adenocarcinoma randomized to receive gemcitabine plus placebo or gemcitabine plus erlotinib 100–150 mg daily. The median survival time (mOS) and progression free survival (PFS) were modestly, but statistically significantly, improved in the combination arm, 6.24 *vs* 5.91 mo (*P* = 0.038) and 3.75 *vs* 3.55 mo (*P* = 0.004), respectively[5].

Neither EGFR status nor KRAS status analysed in the subgroup of patients treated with erlotinib was shown to be predictive of a survival benefit in patients receiving the combination schedule[14].

Erlotinib has been approved by the FDA in combination with gemcitabine as a first-line treatment for advanced pancreatic adenocarcinoma.

Cetuximab is a monoclonal antibody binding the extracellular domain of EGFR. After encouraging results in a phase I trial, subsequent studies in association with gemcitabine-based chemotherapy have failed to demonstrate any survival benefit[15,16].

A phase II study has evaluated the possible therapeutic role of gefitinib, a competitive inhibitor of ATP binding to the intracellular kinase domain of EGFR, in combination with gemcitabine in inoperable or metastatic pancreatic cancer patients. The combination demonstrated promising activity with a mOS and PFS in the combination arm of 7.3 and 4.1 mo, respectively, but other evidence supporting a role of gefitinib in PDAC treatment is lacking[17].

Another ErbB family of transmembrane tyrosine kinase receptors is HER-2, which is overexpressed in 11% of pancreatic adenocarcinoma cases. HER2-positive status has also been correlated with shorter survival[18].

Trastuzumab plus gemcitabine was tested in 34 metastatic pancreatic cancer patients with HER-2 overexpression as determined by immunohistochemistry, and partial responses were observed in 6% of cases[19]. Harder *et al*[20], in a multicentre phase II study, investigated the efficacy and toxicity of the HER2 antibody, trastuzumab, plus capecitabine in patients with pancreatic cancer and HER2 overexpression, but this treatment did not perform favourably with respect to either PFS or OS compared with standard chemotherapy.

After FDA approval of lapatinib, clinical trials have been initiated to test the effect of this HER-2 inhibitor combined with chemotherapy in pancreatic carcinoma. In particular, lapatinib was tested in combination with capecitabine as a second-line treatment in advanced pancreatic cancer with promising preliminary results. Further studies are needed to evaluate the real effectiveness and role of this molecule in the treatment of PADC[21].

Nimotuzumab, another anti-EGFR monoclonal antibody, showed promising results[22]. In a phase II trial where advanced pancreatic cancer patients were randomized to receive second-line monotherapy with nimotuzumab, Strumberg *et a*[23]*l* showed PFS after 1 year of 10.3% and median overall survival of 18.1 wk with a tolerable toxicity profile.

Based on preclinical evidence, afatinib, an inhibitor of EGFR, HER2 and HER4, is under evaluation in an ongoing phase II trial[24,25].

***The KRAS pathway and downstream signalling cascade inhibitors***

KRAS activating mutations are present in 70% to 90% of cases of pancreatic cancer. K-Ras is a GTPase protein belonging to the Ras protein family, which has oncogenic activity, and gain-of-function mutations resulting in constitutive activation promote proliferation and inhibit apoptosis through the RAF/MEK/ERK and PIK3/AKT pathways. K-Ras is very difficult to target, and no inhibitors are actually available to use in clinical practice[26].

Preclinical study has shown that farnesylation is an important post-translational modification required for Ras activation, allowing the protein to be attached to the plasma membrane for signal transduction[27].

After promising results in terms of anti-proliferative activity in pancreatic tumour cell lines, farnesyl-transferase inhibitors, particularly tipifarnib, failed to improve overall survival either as a single agent or in combination with gemcitabine in a phase III trial[28,29].

Due to the difficulty of targeting Ras directly, a possible solution could be to block targets downstream of KRAS, such as the protein kinase MEK. Selumetinib is an oral small molecule that inhibits MEK1/2. In a phase II trial, patients were randomized to receive single-agent capecitabine or selumetinib as a second-line treatment for advanced pancreatic cancer. The selumetinib arm showed a median overall survival of 5.4 mo *vs* 5.0 mo in the capecitabine arm, but this result was not statistically significant[30].

Another MEK1/2 inhibitor, trametinib, was tested in pancreatic cancer in combination with gemcitabine against a regimen of gemcitabine plus placebo in a phase II randomized multicentre study. Nevertheless, no significant advantages were demonstrated in terms of overall survival or PFS[31].

Rigosertib, a first-in-class Ras mimetic and small molecule inhibitor of multiple signalling pathways, including polo-like kinase 1 (PLK1) and phosphoinositide 3-kinase (PI3K), was assessed in combination with gemcitabine in patients with treatment-naïve metastatic pancreatic adenocarcinoma in a phase II/III randomized study, but the combination regimen did not improve survival or response, as recently presented at the 2015 ASCO Annual Meeting[32].

Research in this field is in development, but the available trials have failed to show any survival benefit.

***IGFR pathway inhibitors***

Another possible target in ductal pancreatic cancer is represented by insulin like growth factor 1 receptor (IGF1R), which is highly expressed in pancreatic cells, and upon ligand binding activates several pathways involved in cell proliferation and cell survival such as the PIK3/AKT pathway[33].

Monoclonal antibodies against IGFR (cixutumumab, ganitumab) were evaluated in PDAC treatment, but unfortunately, they failed to show a statically significant survival benefit[34].

In particular, the phase III trial assessing ganitumab in combination with gemcitabine was closed early based on a pre-planned futility analysis: the median overall survival was 7.1 mo in the maximum dose ganitumab arm *vs* 7.2 mo in the placebo arm (HR, 0.97, *P* = 0.397)[35].

***Angiogenesis pathway inhibitors***

Neoangiogenesis is essential for tumour progression and metastatization mechanisms. Vascular endothelial growth factor (VEGF) stimulates the proliferation of endothelial cells and is overexpressed in human pancreatic cancer. Nevertheless, neoangiogenesis inhibitors, particularly VEGF inhibitors, failed to improve overall survival in combination with gemcitabine in advanced pancreatic cancer. After encouraging results, phase III trials that tested the efficacy of bevacizumab in association with gemcitabine alone, or gemcitabine plus erlotinib, did not confirm previous findings[36,37].

Aflibercept, a new recombinant fusion protein with extracellular portions of VEGFR-1 and VEGFR-2, which binds VEGF-A, VEGF-B and placental growth factors 1 and 2 thereby inhibiting VEGF-ligand-dependent signalling processes, suppresses tumour growth in pancreatic cell lines and xenografts. Nevertheless, a phase III study aiming to investigate OS in metastatic pancreatic cancer patients receiving standard gemcitabine and either aflibercept or placebo demonstrated that adding aflibercept to gemcitabine did not improve OS in metastatic pancreatic cancer patients[38].

Similarly sorafenib, an oral multikinase inhibitor of Raf-kinase, VEGF-R2/-R3 and PDGFR-ß, tested alone or in combination with gemcitabine in small phase I and II trials, and axitinib, an anti-angiogenesis agent assessed in combination with gemcitabine, showed no statistically significant efficacy in a phase III trial in advanced PDAC[39-41].

Phase II studies combining chemotherapy with promising new anti-angiogenic molecular agents, such as TL-118, a nonsteroidal anti-inflammatory oral medication, or necuparanib, which is re-engineered from heparin with possible anti-tumour activity, are underway[42,43].

***Embryonic pathway inhibitors***

Hedgehog signalling has a critical role in cell proliferation and survival during embryonic development. Normal pancreatic cells silence this pathway, but pathological activation is observed in many solid tumours, particularly in PADC. Hedgehog binds to the extracellular receptor Patched, which, in the absence of Hedgehog, suppresses activation of the G-protein–coupled receptor Smoothened and upregulates glioma associated oncogene homolog1 (Gli1) transcriptional activity. Cancer cell lines show both Hedgehog ligand-dependent and -independent mechanisms of aberrant signalling[44].

Bailey *et al*[45] showed how Sonic hedgehog (SHH) and other proteins downstream of the Hedgehog pathway, detected in precursor lesions and in PDAC primary tumour samples, contribute to the formation of the desmoplastic reaction, an important characteristic of pancreatic cancer that limits the effective delivery of anticancer agents to pancreatic cancer cells. Genetically engineered mouse models demonstrated a depletion of tumour matrix from SHH pathway inhibition, which could be a promising strategy in pancreatic cancer therapy[46].

Vismodegib (GDC-0449), an oral small-molecule inhibitor targeting Smoothened[47], is under assessment in open phase II trials in combination with gemcitabine in advanced cancer, in combination with gemcitabine and nab-paclitaxel in metastatic settings with promising preliminary data[48], and as a single agent in neoadjuvant settings followed by surgery[49-51].

The Smoothened inhibitor saridegib (IPI-926) was tested in association with gemcitabine against gemcitabine plus placebo in a randomized, double-blind, placebo-controlled phase II trial enrolling patients with metastatic disease. Unfortunately, this study was closed ahead of time due to evidence of decreased patient survival in the saridegib arm[52].

Hedgehog inhibitors are an active research field, and several clinical trials are ongoing[53]. Notch signalling is another embryonic pathway crucial for pancreatic organogenesis, but after pancreas development, it is active only in a stem cell subgroup. This pathway is upregulated in PDAC and promotes tumourigenesis. Binding of Notch ligand to its receptor promotes a cascade of proteolytic cleavages, mediated by γ-secretase (presenilin). The activated form ICN (intra cellular notch) forms part of a transcription complex that, after translocating to the nucleus, regulates transcription of several genes involved in proliferation and differentiation of cells, interacting with other pathways such as Hedgehog, KRAS and NF-kB signalling[54,55].

RO4929097 is a selective inhibitor of the γ-secretase enzyme with anti-tumour activity in preclinical studies[56].

A recent phase II single-arm trial assessed the possible role of RO4929097, enrolling 18 previously treated advanced PDAC patients. The treatment was well tolerated; the median survival was 4.1 mo, and the median progression-free survival was 1.5 mo[57].

Encouraging clinical results were observed testing demcizumab, an anti- Delta-like ligand 4 antibody, plus gemcitabine and nab-paclitaxel in advanced PDAC in a phase Ib trial. Further evidence is needed to confirm these preliminary data[58].

***PARP inhibitors***

Mutations affecting BRCA pathway components, especially the tumour suppressor gene BRCA2, which is associated with hereditary predisposition to breast, ovarian and pancreatic cancer, promote deficiency in DNA damage repair mechanisms and genomic instability[11].

Poly ADP-ribose polymerase (PARP) is a nuclear enzyme recruited to repair cell DNA damage, and as recent evidence showed, patients with defects in the homologous DNA recombination pathway may benefit from the use of PARP inhibitors as monotherapy or in combination with radiation or other chemotherapeutic agents. Clinical trials testing those new agents in selected patients are currently in the development phase[59-61].

***mTOR and PI3K/Akt pathway inhibitors***

After activation, Ras can phosphorylate PI3K, which activates Akt, a serine/threonine kinase. Signal transduction by activated PI3K/Akt plays a role in tumour cell proliferation, survival and metabolism, usually through several downstream targets, including the mammalian target of rapamycin (mTOR)[62].

Several trials testing PI3K/AKT axis inhibitors are currently ongoing in advanced pancreatic cancer patients after encouraging preclinical model results[63]. These trials included the following PI3K/AKT axis inhibitors: BKM120, a PI3K inhibitor tested in combination with the mFOLFOX-6 schedule; RX-0201, an Akt antisense oligonucleotide tested in a phase II study plus gemcitabine; and BEZ235, a combined inhibitor of PI3K and mTOR assessed in a phase study in combination with the MEK inhibitor MEK162[64-66].

Wolpin *et al*[67] evaluated a possible role of everolimus, an oral mTOR inhibitor, as monotherapy in 33 gemcitabine-refractory pancreatic cancer patients. The PFS and OS were 1.8 and 4.5 mo, respectively.

Recently, the results of a single arm phase II study where everolimus was tested in combination with capecitabine were published. The median OS was 8.9 mo and PFS was 3.6 mo[68].

The results of a phase I/II study testing everolimus in combination with gemcitabine in advanced settings and the results of a phase II trial testing temsirolimus, another mTOR inhibitor, in locally advanced or metastatic settings are anticipated[69,70].

***Tumour stroma inhibitors***

The stroma is a dynamic compartment of pancreatic tumours that is critically involved in tumour formation, progression and the metastasis process. Therefore, targeting stromal microenvironment elements could be an efficient therapeutic strategy in addition to previously described trials evaluating Hedgehog signalling inhibitors[71].

After promising data derived from a preliminary clinical study on the possible role of PEGPH20, a pegylated formulation of recombinant hyaluronidase, a phase II trial is currently in the recruitment phase. The purpose of that study is to enrol untreated patients with metastatic disease to receive a combination of PEGPH20, nab-naclitaxel and gemcitabine or a combination of nab-paclitaxel and gemcitabine[72,73].

Additionally, inhibition of PDGFR, a receptor expressed in stromal cells with a critical role in recruiting pericytes and in interstitial fluid pressure in the tumour stroma, could be an interesting molecular target, as suggested by preclinical studies using an orthotopic pancreatic tumour mouse model[74].

TKI258, a PDGFR inhibitor, is under evaluation in a phase I dose assessment for advanced pancreatic cancer patients[75].

In the past, matrix metalloproteinase inhibitors such as marimastat were tested. Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes responsible for the degradation of connective tissue proteins, and aberrant MMP expression is observed in PDAC. Nevertheless, the results of a phase III trial provided no evidence to support a combination of marimastat with gemcitabine in patients with advanced pancreatic cancer[76].

**CONCLUSION**

Knowledge of the molecular biology of PDAC has important potential clinical relevance, but current efforts to improve understanding of the mutational profile of this tumour have not provided any significant advantage in the use of targeted therapy. Several agents have been tested in PDAC, but almost all have failed to demonstrate efficacy in late phase clinical trials. Only erlotinib has been approved by the FDA for advanced pancreatic cancer treatment, but the improvement of overall survival is barely 2 wk compared with gemcitabine alone[5].

There could be many reasons for those unsatisfying results. First of all, the extreme genomic heterogeneity of PDAC is an important block to identifying new candidate actionable molecular targets or to testing existing biological therapies already approved for human use for other cancers. In addition, no significant results have been observed by matching targeted agents with patients harbouring the cognate molecular abnormality, such as, for example, the use of trastuzumab in HER2 overexpression cases. Due to poor results derived from targeting a single molecule, new strategies using multitargeted agents or molecular agent combinations are in the development phase in order to block more than one driving genomic aberration and to prevent or evade resistance.

Additionally, the type of chemotherapy used in combination could be a failure factor. Indeed, the majority of trials have combined target agents with gemcitabine, but actually, the first-line schedules are represented by FOLFIRINOX or gemcitabine plus Nab-paclitaxel. Therefore, greater efficacy may be obtained from the combination of target agents with those chemotherapeutic drugs.

Furthermore, most studies in which molecular or chemotherapeutic agents in pancreatic cancer were tested enrolled an unselected population of patients to treat. In the last 3 years, approximately 116 trials specific for PDAC systemic therapy were registered of which only about 8% applied criteria to select a patient subset based upon molecular biomarkers[77].

**FUTURE CHALLENGES**

Most studies in which molecular or chemotherapeutic agents in pancreatic cancer were tested enrolled an unselected population of patients to treat. In the last 3 years, approximately 116 trials specific for PDAC systemic therapy were registered of which only about the 8% applied criteria to select a patient subset based upon molecular biomarkers[77].

To stratify patients, the Australian Pancreatic Cancer Genome Initiative has started a pilot study to evaluate the feasibility of assessing a more stratified approach in the management of pancreatic cancer through predefined actionable molecular phenotypes. Patients are enrolled in this trial, called IMPaCT (Individualised Molecular Pancreatic Cancer Therapy), after a preliminary phenotype screening in order to compare the use of gemcitabine in an unselected population to a stratified approach. The aim of the study is to create a tailored approach to pancreatic cancer treatment, which seems to be one of the major challenges for the future[78].

Finally, thanks to biotechnology advancement, biological agents can find application in cancer treatment by tumour-targeted delivery of cytotoxic drugs. Particularly, Ahn *et al*[79] developed antibody fragment-installed polymeric micelles *via* maleimide-thiol conjugation for selective delivery of platinum drugs to pancreatic tumours. This antibody-drug conjugate significantly suppressed the growth of pancreatic tumour xenografts. This technology, with potential activity *in vitro* and in a mouse model, could be a promising future strategy in pancreatic cancer therapy[79].

In conclusion, the lack of efficacy of targeted therapy in PDAC represents a challenge for the future, and more efforts are needed in order to make pancreatic cancer a curable disease.

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**REFERENCES**

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; **65**: 5-29 [PMID: 25559415 DOI: 10.3322/caac.21254]

2 **Sohn TA**, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000; **4**: 567-579 [PMID: 11307091]

3 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

4 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]

5 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677]

6 **Di Marco M**, Di Cicilia R, Macchini M, Nobili E, Vecchiarelli S, Brandi G, Biasco G. Metastatic pancreatic cancer: is gemcitabine still the best standard treatment? (Review). *Oncol Rep* 2010; **23**: 1183-1192 [PMID: 20372829]

7 **Chang DK**, Grimmond SM, Biankin AV. Pancreatic cancer genomics. *Curr Opin Genet Dev* 2014; **24**: 74-81 [PMID: 24480245 DOI: 10.1016/j.gde.2013.12.001]

8 **Hudson TJ**, Anderson W, Artez A, Barker AD, Bell C, Bernabé RR, Bhan MK, Calvo F, Eerola I, Gerhard DS, Guttmacher A, Guyer M, Hemsley FM, Jennings JL, Kerr D, Klatt P, Kolar P, Kusada J, Lane DP, Laplace F, Youyong L, Nettekoven G, Ozenberger B, Peterson J, Rao TS, Remacle J, Schafer AJ, Shibata T, Stratton MR, Vockley JG, Watanabe K, Yang H, Yuen MM, Knoppers BM, Bobrow M, Cambon-Thomsen A, Dressler LG, Dyke SO, Joly Y, Kato K, Kennedy KL, Nicolás P, Parker MJ, Rial-Sebbag E, Romeo-Casabona CM, Shaw KM, Wallace S, Wiesner GL, Zeps N, Lichter P, Biankin AV, Chabannon C, Chin L, Clément B, de Alava E, Degos F, Ferguson ML, Geary P, Hayes DN, Hudson TJ, Johns AL, Kasprzyk A, Nakagawa H, Penny R, Piris MA, Sarin R, Scarpa A, Shibata T, van de Vijver M, Futreal PA, Aburatani H, Bayés M, Botwell DD, Campbell PJ, Estivill X, Gerhard DS, Grimmond SM, Gut I, Hirst M, López-Otín C, Majumder P, Marra M, McPherson JD, Nakagawa H, Ning Z, Puente XS, Ruan Y, Shibata T, Stratton MR, Stunnenberg HG, Swerdlow H, Velculescu VE, Wilson RK, Xue HH, Yang L, Spellman PT, Bader GD, Boutros PC, Campbell PJ, Flicek P, Getz G, Guigó R, Guo G, Haussler D, Heath S, Hubbard TJ, Jiang T, Jones SM, Li Q, López-Bigas N, Luo R, Muthuswamy L, Ouellette BF, Pearson JV, Puente XS, Quesada V, Raphael BJ, Sander C, Shibata T, Speed TP, Stein LD, Stuart JM, Teague JW, Totoki Y, Tsunoda T, Valencia A, Wheeler DA, Wu H, Zhao S, Zhou G, Stein LD, Guigó R, Hubbard TJ, Joly Y, Jones SM, Kasprzyk A, Lathrop M, López-Bigas N, Ouellette BF, Spellman PT, Teague JW, Thomas G, Valencia A, Yoshida T, Kennedy KL, Axton M, Dyke SO, Futreal PA, Gerhard DS, Gunter C, Guyer M, Hudson TJ, McPherson JD, Miller LJ, Ozenberger B, Shaw KM, Kasprzyk A, Stein LD, Zhang J, Haider SA, Wang J, Yung CK, Cros A, Liang Y, Gnaneshan S, Guberman J, Hsu J, Bobrow M, Chalmers DR, Hasel KW, Joly Y, Kaan TS, Kennedy KL, Knoppers BM, Lowrance WW, Masui T, Nicolás P, Rial-Sebbag E, Rodriguez LL, Vergely C, Yoshida T, Grimmond SM, Biankin AV, Bowtell DD, Cloonan N, deFazio A, Eshleman JR, Etemadmoghadam D, Gardiner BB, Kench JG, Scarpa A, Sutherland RL, Tempero MA, Waddell NJ, Wilson PJ, McPherson JD, Gallinger S, Tsao MS, Shaw PA, Petersen GM, Mukhopadhyay D, Chin L, DePinho RA, Thayer S, Muthuswamy L, Shazand K, Beck T, Sam M, Timms L, Ballin V, Lu Y, Ji J, Zhang X, Chen F, Hu X, Zhou G, Yang Q, Tian G, Zhang L, Xing X, Li X, Zhu Z, Yu Y, Yu J, Yang H, Lathrop M, Tost J, Brennan P, Holcatova I, Zaridze D, Brazma A, Egevard L, Prokhortchouk E, Banks RE, Uhlén M, Cambon-Thomsen A, Viksna J, Ponten F, Skryabin K, Stratton MR, Futreal PA, Birney E, Borg A, Børresen-Dale AL, Caldas C, Foekens JA, Martin S, Reis-Filho JS, Richardson AL, Sotiriou C, Stunnenberg HG, Thoms G, van de Vijver M, van't Veer L, Calvo F, Birnbaum D, Blanche H, Boucher P, Boyault S, Chabannon C, Gut I, Masson-Jacquemier JD, Lathrop M, Pauporté I, Pivot X, Vincent-Salomon A, Tabone E, Theillet C, Thomas G, Tost J, Treilleux I, Calvo F, Bioulac-Sage P, Clément B, Decaens T, Degos F, Franco D, Gut I, Gut M, Heath S, Lathrop M, Samuel D, Thomas G, Zucman-Rossi J, Lichter P, Eils R, Brors B, Korbel JO, Korshunov A, Landgraf P, Lehrach H, Pfister S, Radlwimmer B, Reifenberger G, Taylor MD, von Kalle C, Majumder PP, Sarin R, Rao TS, Bhan MK, Scarpa A, Pederzoli P, Lawlor RA, Delledonne M, Bardelli A, Biankin AV, Grimmond SM, Gress T, Klimstra D, Zamboni G, Shibata T, Nakamura Y, Nakagawa H, Kusada J, Tsunoda T, Miyano S, Aburatani H, Kato K, Fujimoto A, Yoshida T, Campo E, López-Otín C, Estivill X, Guigó R, de Sanjosé S, Piris MA, Montserrat E, González-Díaz M, Puente XS, Jares P, Valencia A, Himmelbauer H, Quesada V, Bea S, Stratton MR, Futreal PA, Campbell PJ, Vincent-Salomon A, Richardson AL, Reis-Filho JS, van de Vijver M, Thomas G, Masson-Jacquemier JD, Aparicio S, Borg A, Børresen-Dale AL, Caldas C, Foekens JA, Stunnenberg HG, van't Veer L, Easton DF, Spellman PT, Martin S, Barker AD, Chin L, Collins FS, Compton CC, Ferguson ML, Gerhard DS, Getz G, Gunter C, Guttmacher A, Guyer M, Hayes DN, Lander ES, Ozenberger B, Penny R, Peterson J, Sander C, Shaw KM, Speed TP, Spellman PT, Vockley JG, Wheeler DA, Wilson RK, Hudson TJ, Chin L, Knoppers BM, Lander ES, Lichter P, Stein LD, Stratton MR, Anderson W, Barker AD, Bell C, Bobrow M, Burke W, Collins FS, Compton CC, DePinho RA, Easton DF, Futreal PA, Gerhard DS, Green AR, Guyer M, Hamilton SR, Hubbard TJ, Kallioniemi OP, Kennedy KL, Ley TJ, Liu ET, Lu Y, Majumder P, Marra M, Ozenberger B, Peterson J, Schafer AJ, Spellman PT, Stunnenberg HG, Wainwright BJ, Wilson RK, Yang H. International network of cancer genome projects. *Nature* 2010; **464**: 993-998 [PMID: 20393554 DOI: 10.1038/nature08987]

9 **Biankin AV**, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu J, Chang DK, Cowley MJ, Gardiner BB, Song S, Harliwong I, Idrisoglu S, Nourse C, Nourbakhsh E, Manning S, Wani S, Gongora M, Pajic M, Scarlett CJ, Gill AJ, Pinho AV, Rooman I, Anderson M, Holmes O, Leonard C, Taylor D, Wood S, Xu Q, Nones K, Fink JL, Christ A, Bruxner T, Cloonan N, Kolle G, Newell F, Pinese M, Mead RS, Humphris JL, Kaplan W, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chou A, Chin VT, Chantrill LA, Mawson A, Samra JS, Kench JG, Lovell JA, Daly RJ, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N, Kakkar N, Zhao F, Wu YQ, Wang M, Muzny DM, Fisher WE, Brunicardi FC, Hodges SE, Reid JG, Drummond J, Chang K, Han Y, Lewis LR, Dinh H, Buhay CJ, Beck T, Timms L, Sam M, Begley K, Brown A, Pai D, Panchal A, Buchner N, De Borja R, Denroche RE, Yung CK, Serra S, Onetto N, Mukhopadhyay D, Tsao MS, Shaw PA, Petersen GM, Gallinger S, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Schulick RD, Wolfgang CL, Morgan RA, Lawlor RT, Capelli P, Corbo V, Scardoni M, Tortora G, Tempero MA, Mann KM, Jenkins NA, Perez-Mancera PA, Adams DJ, Largaespada DA, Wessels LF, Rust AG, Stein LD, Tuveson DA, Copeland NG, Musgrove EA, Scarpa A, Eshleman JR, Hudson TJ, Sutherland RL, Wheeler DA, Pearson JV, McPherson JD, Gibbs RA, Grimmond SM. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012; **491**: 399-405 [PMID: 23103869 DOI: 10.1038/nature11547]

10 **Jones S**, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008; **321**: 1801-1806 [PMID: 18772397 DOI: 10.1126/science.1164368]

11 **Waddell N**, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, Johns AL, Miller D, Nones K, Quek K, Quinn MC, Robertson AJ, Fadlullah MZ, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Wani S, Wilson PJ, Markham E, Cloonan N, Anderson MJ, Fink JL, Holmes O, Kazakoff SH, Leonard C, Newell F, Poudel B, Song S, Taylor D, Waddell N, Wood S, Xu Q, Wu J, Pinese M, Cowley MJ, Lee HC, Jones MD, Nagrial AM, Humphris J, Chantrill LA, Chin V, Steinmann AM, Mawson A, Humphrey ES, Colvin EK, Chou A, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Pettitt JA, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N, Jamieson NB, Graham JS, Niclou SP, Bjerkvig R, Grützmann R, Aust D, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Falconi M, Zamboni G, Tortora G, Tempero MA, Gill AJ, Eshleman JR, Pilarsky C, Scarpa A, Musgrove EA, Pearson JV, Biankin AV, Grimmond SM. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015; **518**: 495-501 [PMID: 25719666 DOI: 10.1038/nature14169]

12 **Campbell PJ**, Yachida S, Mudie LJ, Stephens PJ, Pleasance ED, Stebbings LA, Morsberger LA, Latimer C, McLaren S, Lin ML, McBride DJ, Varela I, Nik-Zainal SA, Leroy C, Jia M, Menzies A, Butler AP, Teague JW, Griffin CA, Burton J, Swerdlow H, Quail MA, Stratton MR, Iacobuzio-Donahue C, Futreal PA. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature* 2010; **467**: 1109-1113 [PMID: 20981101 DOI: 10.1038/nature09460]

13 **Tobita K**, Kijima H, Dowaki S, Kashiwagi H, Ohtani Y, Oida Y, Yamazaki H, Nakamura M, Ueyama Y, Tanaka M, Inokuchi S, Makuuchi H. Epidermal growth factor receptor expression in human pancreatic cancer: Significance for liver metastasis. *Int J Mol Med* 2003; **11**: 305-309 [PMID: 12579331]

14 **da Cunha Santos G**, Dhani N, Tu D, Chin K, Ludkovski O, Kamel-Reid S, Squire J, Parulekar W, Moore MJ, Tsao MS. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3. *Cancer* 2010; **116**: 5599-5607 [PMID: 20824720 DOI: 10.1002/cncr.25393]

15 **Cascinu S**, Berardi R, Labianca R, Siena S, Falcone A, Aitini E, Barni S, Di Costanzo F, Dapretto E, Tonini G, Pierantoni C, Artale S, Rota S, Floriani I, Scartozzi M, Zaniboni A. Cetuximab plus gemcitabine and cisplatin compared with gemcitabine and cisplatin alone in patients with advanced pancreatic cancer: a randomised, multicentre, phase II trial. *Lancet Oncol* 2008; **9**: 39-44 [PMID: 18077217]

16 **Philip PA**, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, Rowland KM, Atkins JN, Mirtsching BC, Rivkin SE, Khorana AA, Goldman B, Fenoglio-Preiser CM, Abbruzzese JL, Blanke CD. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010; **28**: 3605-3610 [PMID: 20606093 DOI: 10.1200/JCO.2009.25.7550]

17 **Fountzilas G**, Bobos M, Kalogera-Fountzila A, Xiros N, Murray S, Linardou H, Karayannopoulou G, Koutras AK, Bafaloukos D, Samantas E, Christodoulou C, Economopoulos T, Kalogeras KT, Kosmidis P. Gemcitabine combined with gefitinib in patients with inoperable or metastatic pancreatic cancer: a phase II Study of the Hellenic Cooperative Oncology Group with biomarker evaluation. *Cancer Invest* 2008; **26**: 784-793 [PMID: 18798073 DOI: 10.1080/07357900801918611]

18 **Kimura K**, Sawada T, Komatsu M, Inoue M, Muguruma K, Nishihara T, Yamashita Y, Yamada N, Ohira M, Hirakawa K. Antitumor effect of trastuzumab for pancreatic cancer with high HER-2 expression and enhancement of effect by combined therapy with gemcitabine. *Clin Cancer Res* 2006; **12**: 4925-4932 [PMID: 16914581]

19 **Safran H**, Iannitti D, Ramanathan R, Schwartz JD, Steinhoff M, Nauman C, Hesketh P, Rathore R, Wolff R, Tantravahi U, Hughes TM, Maia C, Pasquariello T, Goldstein L, King T, Tsai JY, Kennedy T. Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu. *Cancer Invest* 2004; **22**: 706-712 [PMID: 15581051]

20 **Harder J**, Ihorst G, Heinemann V, Hofheinz R, Moehler M, Buechler P, Kloeppel G, Röcken C, Bitzer M, Boeck S, Endlicher E, Reinacher-Schick A, Schmoor C, Geissler M. Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer. *Br J Cancer* 2012; **106**: 1033-1038 [PMID: 22374460 DOI: 10.1038/bjc.2012.18]

21 **Safran H**, Miner T, Resnick M, Dipetrillo T, McNulty B, Evans D, Joseph P, Plette A, Millis R, Sears D, Gutman N, Kennedy T. Lapatinib/gemcitabine and lapatinib/gemcitabine/oxaliplatin: a phase I study for advanced pancreaticobiliary cancer. *Am J Clin Oncol* 2008; **31**: 140-144 [PMID: 18391597 DOI: 10.1097/COC.0b013e318145b9a5]

22 **Su D**, Jiao SC, Wang LJ, Shi WW, Long YY, Li J, Bai L. Efficacy of nimotuzumab plus gemcitabine usage as first-line treatment in patients with advanced pancreatic cancer. *Tumour Biol* 2014; **35**: 2313-2318 [PMID: 24142531 DOI: 10.1007/s13277-013-1306-x]

23 **Strumberg D**, Schultheis B, Scheulen ME, Hilger RA, Krauss J, Marschner N, Lordick F, Bach F, Reuter D, Edler L, Mross K. Phase II study of nimotuzumab, a humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody, in patients with locally advanced or metastatic pancreatic cancer. *Invest New Drugs* 2012; **30**: 1138-1143 [PMID: 21170759 DOI: 10.1007/s10637-010-9619-8]

24 **Ioannou N**, Dalgleish AG, Seddon AM, Mackintosh D, Guertler U, Solca F, Modjtahedi H. Anti-tumour activity of afatinib, an irreversible ErbB family blocker, in human pancreatic tumour cells. *Br J Cancer* 2011; **105**: 1554-1562 [PMID: 21970876 DOI: 10.1038/bjc.2011.396]

25 **PD Dr. med. Volker Heinemann**. Afatinib as Cancer Therapy for Exocrine Pancreatic Tumours (ACCEPT). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT01728818> NLM Identifier: NCT01728818

26 **di Magliano MP**, Logsdon CD. Roles for KRAS in pancreatic tumor development and progression. *Gastroenterology* 2013; **144**: 1220-1229 [PMID: 23622131 DOI: 10.1053/j.gastro.2013.01.071]

27 **Takashima A**, Faller DV. Targeting the RAS oncogene. *Expert Opin Ther Targets* 2013; **17**: 507-531 [PMID: 23360111 DOI: 10.1517/14728222.2013.764990]

28 **Pylayeva-Gupta Y**, Grabocka E, Bar-Sagi D. RAS oncogenes: weaving a tumorigenic web. *Nat Rev Cancer* 2011; **11**: 761-774 [PMID: 21993244 DOI: 10.1038/nrc3106]

29 **Van Cutsem E**, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, Schoffski P, Post S, Verslype C, Neumann H, Safran H, Humblet Y, Perez Ruixo J, Ma Y, Von Hoff D. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 2004; **22**: 1430-1438 [PMID: 15084616]

30 **Bodoky G**, Timcheva C, Spigel DR, La Stella PJ, Ciuleanu TE, Pover G, Tebbutt NC. A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. *Invest New Drugs* 2012; **30**: 1216-1223 [PMID: 21594619 DOI: 10.1007/s10637-011-9687-4]

31 **Infante JR**, Somer BG, Park JO, Li CP, Scheulen ME, Kasubhai SM, Oh DY, Liu Y, Redhu S, Steplewski K, Le N. A randomised, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. *Eur J Cancer* 2014; **50**: 2072-2081 [PMID: 24915778 DOI: 10.1016/j.ejca.2014.04.024]

32 **Scott AJ,** O'Neil BH, Ma WW, Cohen SJ, Aisner D, Menter AR, Abdulaziz Tejani M. A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. ASCO Annual Meeting. *J Clin Oncol* 33 2015; abstr 4117

33 **Sachdev D**, Yee D. Disrupting insulin-like growth factor signaling as a potential cancer therapy. *Mol Cancer Ther* 2007; **6**: 1-12 [PMID: 17237261]

34 **Philip PA**, Goldman B, Ramanathan RK, Lenz HJ, Lowy AM, Whitehead RP, Wakatsuki T, Iqbal S, Gaur R, Benedetti JK, Blanke CD. Dual blockade of epidermal growth factor receptor and insulin-like growth factor receptor-1 signaling in metastatic pancreatic cancer: phase Ib and randomized phase II trial of gemcitabine, erlotinib, and cixutumumab versus gemcitabine plus erlotinib (SWOG S0727). *Cancer* 2014; **120**: 2980-2985 [PMID: 25041791 DOI: 10.1002/cncr.28744]

35 **Fuchs CS**, Azevedo S, Okusaka T, Van Laethem JL, Lipton LR, Riess H, Szczylik C, Moore MJ, Peeters M, Bodoky G, Ikeda M, Melichar B, Nemecek R, Ohkawa S, Świeboda-Sadlej A, Tjulandin SA, Van Cutsem E, Loberg R, Haddad V, Gansert JL, Bach BA, Carrato A. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. *Ann Oncol* 2015; **26**: 921-927 [PMID: 25609246 DOI: 10.1093/annonc/mdv027]

36 **Kindler HL**, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010; **28**: 3617-3622 [PMID: 20606091 DOI: 10.1200/JCO.2010.28.1386]

37 **Van Cutsem E**, Vervenne WL, Bennouna J, Humblet Y, Gill S, Van Laethem JL, Verslype C, Scheithauer W, Shang A, Cosaert J, Moore MJ. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol* 2009; **27**: 2231-2237 [PMID: 19307500 DOI: 10.1200/JCO.2008.20.0238]

38 **Rougier P**, Riess H, Manges R, Karasek P, Humblet Y, Barone C, Santoro A, Assadourian S, Hatteville L, Philip PA. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. *Eur J Cancer* 2013; **49**: 2633-2642 [PMID: 23642329 DOI: 10.1016/j.ejca.2013.04.002]

39 **Chiorean EG**, Schneider BP, Akisik FM, Perkins SM, Anderson S, Johnson CS, DeWitt J, Helft P, Clark R, Johnston EL, Spittler AJ, Deluca J, Bu G, Shahda S, Loehrer PJ, Sandrasegaran K, Cardenes HR. Phase 1 pharmacogenetic and pharmacodynamic study of sorafenib with concurrent radiation therapy and gemcitabine in locally advanced unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2014; **89**: 284-291 [PMID: 24726286 DOI: 10.1016/j.ijrobp.2014.02.024]

40 **Kindler HL**, Wroblewski K, Wallace JA, Hall MJ, Locker G, Nattam S, Agamah E, Stadler WM, Vokes EE. Gemcitabine plus sorafenib in patients with advanced pancreatic cancer: a phase II trial of the University of Chicago Phase II Consortium. *Invest New Drugs* 2012; **30**: 382-386 [PMID: 20803052 DOI: 10.1007/s10637-010-9526-z]

41 **Kindler HL**, Ioka T, Richel DJ, Bennouna J, Létourneau R, Okusaka T, Funakoshi A, Furuse J, Park YS, Ohkawa S, Springett GM, Wasan HS, Trask PC, Bycott P, Ricart AD, Kim S, Van Cutsem E. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 2011; **12**: 256-262 [PMID: 21306953 DOI: 10.1016/S1470-2045(11)70004-3]

42 **Tiltan Pharma Ltd**. Investigator's Initiated Phase II Study for Pancreatic Cancer Patients. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT01659502> NLM Identifier: NCT01659502

43 **Momenta Pharmaceuticals, Inc**. M402 in Combination With Nab-Paclitaxel and Gemcitabine in Pancreatic Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT01621243> NLM Identifier: NCT01621243

44 **Goldman J**, Eckhardt SG, Borad MJ, Curtis KK, Hidalgo M, Calvo E, Ryan DP, Wirth LJ, Parikh A, Partyka J, Faessel H, Gangolli E, Stewart S, Rosen LS, Bowles DW. Phase I dose-escalation trial of the oral investigational Hedgehog signaling pathway inhibitor TAK-441 in patients with advanced solid tumors. *Clin Cancer Res* 2015; **21**: 1002-1009 [PMID: 25501576 DOI: 10.1158/1078-0432.CCR-14-1234]

45 **Bailey JM**, Swanson BJ, Hamada T, Eggers JP, Singh PK, Caffery T, Ouellette MM, Hollingsworth MA. Sonic hedgehog promotes desmoplasia in pancreatic cancer. *Clin Cancer Res* 2008; **14**: 5995-6004 [PMID: 18829478 DOI: 10.1158/1078-0432.CCR-08-0291]

46 **Olive KP**, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KK, Denicola G, Feig C, Combs C, Winter SP, Ireland-Zecchini H, Reichelt S, Howat WJ, Chang A, Dhara M, Wang L, Rückert F, Grützmann R, Pilarsky C, Izeradjene K, Hingorani SR, Huang P, Davies SE, Plunkett W, Egorin M, Hruban RH, Whitebread N, McGovern K, Adams J, Iacobuzio-Donahue C, Griffiths J, Tuveson DA. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009; **324**: 1457-1461 [PMID: 19460966 DOI: 10.1126/science.1171362]

47 **Singh BN**, Fu J, Srivastava RK, Shankar S. Hedgehog signaling antagonist GDC-0449 (Vismodegib) inhibits pancreatic cancer stem cell characteristics: molecular mechanisms. *PLoS One* 2011; **6**: e27306 [PMID: 22087285 DOI: 10.1371/journal.pone.0027306]

48 **De Jesus-Acosta A,** O'Dwyer P, Ramanathan R, Von Hoff D, Maitra A, Rasheed Z. A phase II study of vismodegib, a hedgehog (Hh) pathway inhibitor, combined with gemcitabine and nab-paclitaxel (nab-P) in patients (Pts) with untreated metastatic pancreatic ductal adenocarcinoma (PDA). *ASCO Gastrointestinal Cancer Symposium* 2014; Abstract No. 257

49 **National Cancer Institute (NCI)**. Gemcitabine Hydrochloride With or Without Vismodegib in Treating Patients With Recurrent or Metastatic Pancreatic Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT01064622> NLM Identifier: NCT01064622

50 **Sidney Kimmel Comprehensive Cancer Center**. Pancreas, Hedgehog Inhibitors for Metastatic Adenocarcinoma of the Pancreas. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT01088815> NLM Identifier: NCT01088815

51 **Lisa Bax**. Hedgehog Inhibition for Pancreatic Ductal Adenocarcinoma (PDAC) in the Preoperative Setting (HIPPoS). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT01096732> NLM Identifier: NCT01096732

52 Infinity Reports Update from Phase 2 Study of Saridegib Plus Gemcitabine in Patients with Metastatic Pancreatic Cancer. Available from: http: //www.businesswire.com

53 **Sidney Kimmel Comprehensive Cancer Center**. Gemcitabine + Nab-paclitaxel With LDE-225 (Hedgehog Inhibitor) as Neoadjuvant Therapy for Pancreatic Adenocarcinoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT01431794> NLM Identifier: NCT01431794

54 **Sjölund J**, Manetopoulos C, Stockhausen MT, Axelson H. The Notch pathway in cancer: differentiation gone awry. *Eur J Cancer* 2005; **41**: 2620-2629 [PMID: 16239105]

55 **Ristorcelli E**, Lombardo D. Targeting Notch signaling in pancreatic cancer. *Expert Opin Ther Targets* 2010; **14**: 541-552 [PMID: 20392166 DOI: 10.1517/14728221003769895]

56 **Plentz R**, Park JS, Rhim AD, Abravanel D, Hezel AF, Sharma SV, Gurumurthy S, Deshpande V, Kenific C, Settleman J, Majumder PK, Stanger BZ, Bardeesy N. Inhibition of gamma-secretase activity inhibits tumor progression in a mouse model of pancreatic ductal adenocarcinoma. *Gastroenterology* 2009; **136**: 1741-9.e6 [PMID: 19208345 DOI: 10.1053/j.gastro.2009.01.008]

57 **De Jesus-Acosta A**, Laheru D, Maitra A, Arcaroli J, Rudek MA, Dasari A, Blatchford PJ, Quackenbush K, Messersmith W. A phase II study of the gamma secretase inhibitor RO4929097 in patients with previously treated metastatic pancreatic adenocarcinoma. *Invest New Drugs* 2014; **32**: 739-745 [PMID: 24668033 DOI: 10.1007/s10637-014-0083-8]

58 **Hidalgo M,** Cooray P, Jameson MB, Carrato A, Parnis F, Jeffery M, Grimison PS, Stagg RJ, Kapoun AM, Dupont J. A phase Ib study of the anti-cancer stem cell agent demcizumab (DEM) & gemcitabine (GEM) /- paclitaxel protein bound particles (nab-paclitaxel) in pts with pancreatic cancer. 2015 ASCO Annual Meeting. *J Clin Oncol 33* 2015; abstr 4118

59 **Tangutoori S**, Baldwin P, Sridhar S. PARP inhibitors: A new era of targeted therapy. *Maturitas* 2015; **81**: 5-9 [PMID: 25708226 DOI: 10.1016/j.maturitas.2015.01.015]

60 **AstraZeneca**. Study to Assess the Safety & Tolerability of a PARP Inhibitor in Combination With Gemcitabine in Pancreatic Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://clinicaltrials.gov/ct2/show/NCT00515866> NLM Identifier: NCT00515866

61 **National Cancer Institute (NCI)**. Gemcitabine Hydrochloride and Cisplatin With or Without Veliparib or Veliparib Alone in Patients With Locally Advanced or Metastatic Pancreatic Cancer. Available at: <https://clinicaltrials.gov/ct2/show/NCT01585805> NLM Identifier: NCT01585805

62 **Hezel AF**, Kimmelman AC, Stanger BZ, Bardeesy N, Depinho RA. Genetics and biology of pancreatic ductal adenocarcinoma. *Genes Dev* 2006; **20**: 1218-1249 [PMID: 16702400]

63 **Ito D**, Fujimoto K, Mori T, Kami K, Koizumi M, Toyoda E, Kawaguchi Y, Doi R. In vivo antitumor effect of the mTOR inhibitor CCI-779 and gemcitabine in xenograft models of human pancreatic cancer. *Int J Cancer* 2006; **118**: 2337-2343 [PMID: 16331623]

64 **UNC Lineberger Comprehensive Cancer Center**. BKM120 + mFOLFOX6 in Advanced Solid Tumors With Expansion Cohort Pancreatic Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: <https://clinicaltrials.gov/ct2/show/NCT01571024> NLM Identifier: NCT01571024

65 **Rexahn Pharmaceuticals, Inc**. A Safety and Efficacy Study of RX-0201 Plus Gemcitabine in Metastatic Pancreatic Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: <https://clinicaltrials.gov/ct2/show/NCT01028495> NLM Identifier: NCT01028495

66 **Novartis Pharmaceuticals**. Safety, Pharmacokinetics and Pharmacodynamics of BEZ235 Plus MEK162 in Selected Advanced Solid Tumor Patients. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: <https://clinicaltrials.gov/ct2/show/NCT01337765> NLM Identifier: NCT01337765

67 **Wolpin BM**, Hezel AF, Abrams T, Blaszkowsky LS, Meyerhardt JA, Chan JA, Enzinger PC, Allen B, Clark JW, Ryan DP, Fuchs CS. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol* 2009; **27**: 193-198 [PMID: 19047305 DOI: 10.1200/JCO.2008]

68 **Kordes S**, Klümpen HJ, Weterman MJ, Schellens JH, Richel DJ, Wilmink JW. Phase II study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol* 2015; **75**: 1135-1141 [PMID: 25822310 DOI: 10.1007/s00280-015-2730-y]

69 **Novartis Pharmaceuticals**. Treatment of Patients Suffering From a Progressive Pancreas Carcinoma With Everolimus (RAD001) and Gemcitabine. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: <https://clinicaltrials.gov/ct2/show/NCT00560963> NLM Identifier: NCT00560963

70 **National Cancer Institute (NCI)**. CCI-779 in Treating Patients With Locally Advanced or Metastatic Pancreatic Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: <https://clinicaltrials.gov/ct2/show/NCT00075647> NLM Identifier: NCT00075647

71 **Heinemann V**, Reni M, Ychou M, Richel DJ, Macarulla T, Ducreux M. Tumour-stroma interactions in pancreatic ductal adenocarcinoma: rationale and current evidence for new therapeutic strategies. *Cancer Treat Rev* 2014; **40**: 118-128 [PMID: 23849556 DOI: 10.1016/j.ctrv.2013.04.004]

72 **Provenzano PP**, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell* 2012; **21**: 418-429 [PMID: 22439937 DOI: 10.1016/j.ccr.2012.01.007]

73 **Halozyme Therapeutics**. PEGPH20 Plus Nab-Paclitaxel Plus Gemcitabine Compared With Nab-Paclitaxel Plus Gemcitabine in Subjects With Stage IV Untreated Pancreatic Cancer (HALO-109-202). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: https://clinicaltrials.gov/ct2/show/NCT01839487 NLM Identifier: NCT01839487

74 **Hwang RF**, Yokoi K, Bucana CD, Tsan R, Killion JJ, Evans DB, Fidler IJ. Inhibition of platelet-derived growth factor receptor phosphorylation by STI571 (Gleevec) reduces growth and metastasis of human pancreatic carcinoma in an orthotopic nude mouse model. *Clin Cancer Res* 2003; **9**: 6534-6544 [PMID: 14695158]

75 **Roswell Park Cancer Institute**. Dovitinib Lactate, Gemcitabine Hydrochloride, and Capecitabine in Treating Patients With Advanced or Metastatic Solid Tumors, Pancreatic Cancer and Biliary Cancers. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: https://clinicaltrials.gov/ct2/show/NCT01497392 NLM Identifier: NCT01497392

76 **Bramhall SR**, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer* 2002; **87**: 161-167 [PMID: 12107836]

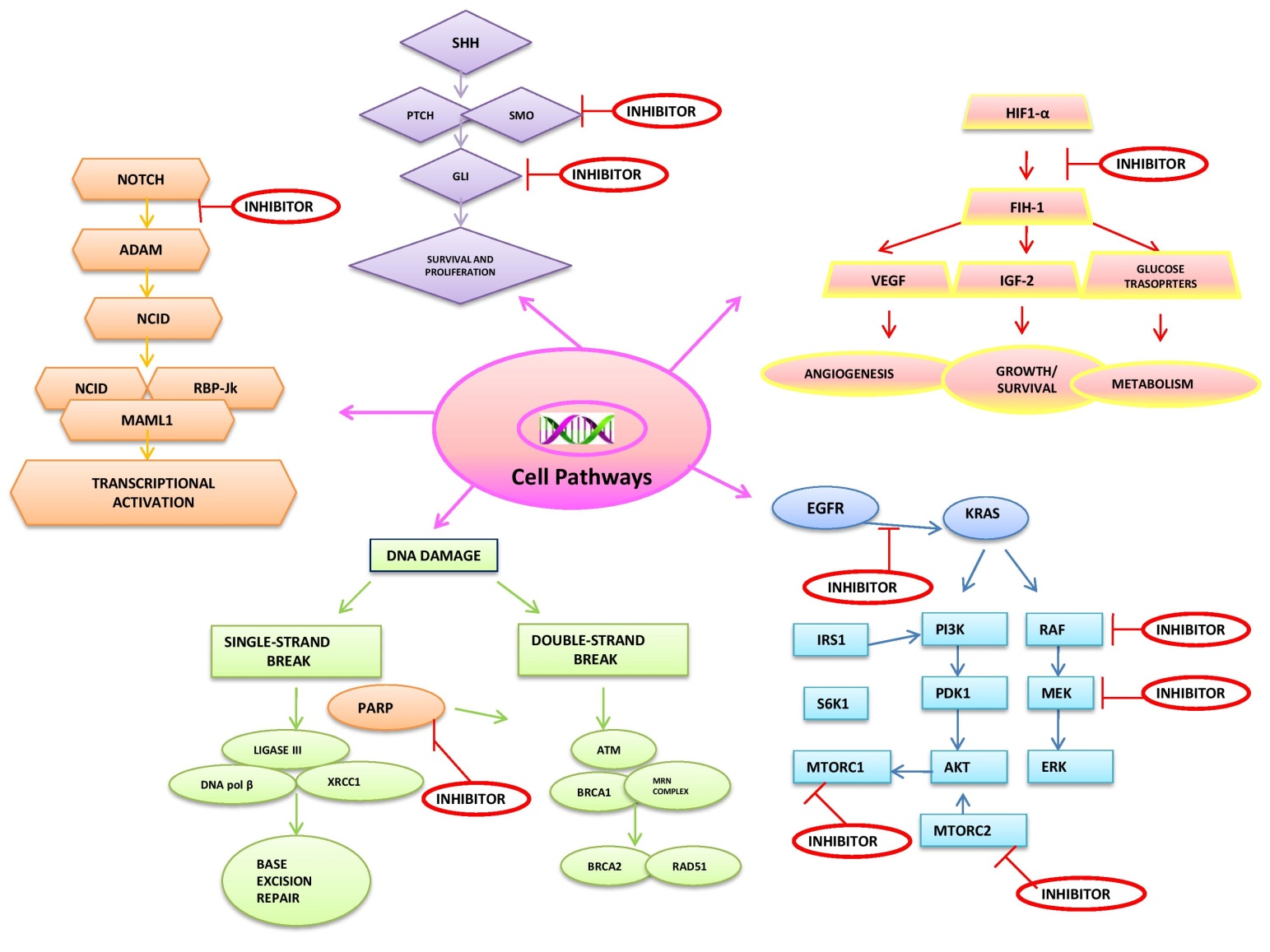
77 **ClinicalTrials.gov**. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [accessed 2015 May]. Available at: http: //www.clinicaltrials.gov

78 **Chantrill LA**, Nagrial AM, Watson C, Johns AL, Martyn-Smith M, Simpson S, Mead S, Jones MD, Samra JS, Gill AJ, Watson N, Chin VT, Humphris JL, Chou A, Brown B, Morey A, Pajic M, Grimmond SM, Chang DK, Thomas D, Sebastian L, Sjoquist K, Yip S, Pavlakis N, Asghari R, Harvey S, Grimison P, Simes J, Biankin AV. Precision Medicine for Advanced Pancreas Cancer: The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial. *Clin Cancer Res* 2015; **21**: 2029-2037 [PMID: 25896973 DOI: 10.1158/1078-0432.CCR-15-0426]

79 **Ahn J**, Miura Y, Yamada N, Chida T, Liu X, Kim A, Sato R, Tsumura R, Koga Y, Yasunaga M, Nishiyama N, Matsumura Y, Cabral H, Kataoka K. Antibody fragment-conjugated polymeric micelles incorporating platinum drugs for targeted therapy of pancreatic cancer. *Biomaterials* 2015; **39**: 23-30 [PMID: 25477168 DOI: 10.1016/j.biomaterials]

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**Figure 1 Principal cell signaling pathways involved in pancreatic ductal adenocarcinoma carcinogenesis and actionable molecular targets.**

**Table 1 Principal phase III clinical trials involving targeted therapy in pancreatic cancer**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Agent | Target pathway | Treatment | Setting | N | mOS (mo) | PFS (mo) | FDA approval | Ref. |
| Erlotinib | EGFR signaling | GEM plus erlotinib  *vs* GEM plus P | M/LA | 569 | 6.24 *vs* 5.91  (*P* = 0.038) | 3.75 *vs* 3.55  (*P* = 0.004) | Yes | [5] |
| Cetuximab | EGFR signaling | GEM plus cetuximab  *vs* GEM | M/LA | 766 | 6.5. *vs*. 6  (*P* = 0.14) | 3.5 *vs* 3  (*P* = 0.058) | No | [17] |
| Tipifarnib | KRAS pathway | GEM plus tipifarnib  *vs* GEM | M/LA | 688 | 6.3 *vs* 6  (*P* = 0.75) | 3.7 *vs* 3.6  (*P* = 0.72) | No | [30] |
| Ganitumab | IGFR pathway | GEM plus ganitumab (12 mg/kg or 20 mg/kg)  *vs* GEM plus P | M | 800 | 12 mg/kg arm  7.0 *vs* 7.2  (*P* = 0.494)  60 mg/kg arm  7.1 *vs* 7.2  (*P* = 0.397) | 12 mg/kg arm  3.7 *vs* 3.6  (*P* = 0.520)  60 mg/kg arm  3.7 *vs* 3.7  (*P* = 0.403) | No | [35] |
| Bevacizumab | Angiogenesis | GEM plus bevacizumab  *vs* GEM plus P | M/LA | 602 | 5.7 *vs* 6.0  (*P* = 0.40) | 4.8 *vs* 4.3  (*P* = 0.99) | No | [36] |
| Aflibercept | Angiogenesis | GEM plus aflibercept  *vs* GEM plus P | M/LA | 546 | 6.5 *vs* 7.8  (*P* = 0.203) | 3.7 *vs* 3.7  (*P* = 0.864) | No | [38] |
| Axitinib | Angiogenesis | GEM plus axitinib  *vs* GEM plus P | M/LA | 632 | 8.5 *vs* 8.2  (*P* = 0.543) | 4.4 *vs* 4.4  (*P* = 0.520) | No | [41] |
| Marimastat | Tumor stroma | GEM plus marimastat  *vs* GEM | M/LA | 239 | 5.4 *vs* 5.4  (NA) | 3 *vs* 3.1  (NA) | No | [75] |

GEM: Gemcitabine; P: Placebo; mOS: Median overall survival; PFS: Progression free survival; N: Number of patients enrolled; LA: Locally advanced cancer; M: Metastatic cancer; NA: Not available.

**Table 2 Principal phase II clinical trials involving targeted therapy in pancreatic cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Agent | Target pathway | Treatment | Setting | N | Ref. |
| Cetuximab | EGFR signaling | GEM plus cisplatin plus cetuximab  *vs*  GEM plus cisplatin | M/LA | 84 | [16] |
| Gefitinib | EGFR signaling | GEM plus gefitinib  (single arm) | M/LA | 57 | [18] |
| Trastuzumab | EGFR signaling | GEM plus trastuzumab  (single arm) | M/LA  2+/3+ HER-2 expression | 34 | [20] |
| Trastuzumab | EGFR signaling | Capecitabine plus trastuzumab  (single arm) | M/LA  3+ HER-2 expression or gene amplification | 17  (212 screened) | [21] |
| Nimotuzumab | EGFR signaling | GEM plus nimotuzumab  (single arm) | M/LA | 18 | [23] |
| Nimotuzumab | EGFR signaling | nimotuzumab monotherapy  (single arm) | Refractory to first line standard chemotherapy M/LA | 56 | [24] |
| Selumetinib | KRAS/MEK pathway | Capecitabine plus selumetinib  *vs*  Capecitabine | Refractory to first line standard chemotherapy M/LA | 70 | [31] |
| Trametinib | KRAS/MEK pathway | GEM plus trametinib  *vs* GEM plus P | M/LA | 160 | [32] |
| Sorafenib | Angiogenesis | GEM plus sorafenib  (single arm) | M/LA | 70 | [40] |
| RO4929097 | Hedgehog signaling | RO4929097 monotherapy  (single arm) | Refractory to first line standard chemotherapy M | 18 | [57] |
| Everolimus | mTor pathway | everolimus plus capecitabine  (single arm) | M/LA | 31 | [67] |

GEM: Gemcitabine; P: Placebo; N: Number of patients enrolled; LA: Locally advanced cancer; M: Metastatic cancer.

**Table 3 Principal ongoing trials involving targeted therapy in pancreatic cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| ClinicalTrials.gov identifier | Agent | Target | Status |
| NCT01728818 | Afatinib | EGFR signaling | Recruiting |
| NCT01659502 | TL-118 | Angiogenesis | Not yet recruiting |
| NCT01621243 | Necuparanib | Angiogenesis | Recruiting |
| NCT01088815 | Vismodegib | Hedgehog signaling | Recruiting |
| NCT01096732 | Vismodegib | Hedgehog signaling | Terminated |
| NCT01431794 | LDE-225 | Hedgehog signaling | Recruiting |
| NCT00515866 | KU-0059436 | PARP inhibitor | Completed |
| NCT01585805 | Veliparib | PARP inhibitor | Recruiting |
| NCT01571024 | BKM120 | mTor and PI3K/Akt pathway | Recruiting |
| NCT01028495 | RX-0201 | mTor and PI3K/Akt pathway | Completed |
| NCT01337765 | BEZ235 + MEK162 | mTor and PI3K/Akt pathway | Completed |
| NCT00560963 | Everolimus | mTor pathway | Completed |
| NCT00075647 | Temsirolimus | mTor pathway | Completed |
| NCT01839487 | PEGPH20 | Tumor stroma | Recruiting |