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Authors

Kim, Edward J
Semrad, Thomas J
Bold, Richard J

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Phase II clinical trials on Investigational drugs for the Treatment of Pancreatic Cancers

Edward J. Kim, MD, PhD[1], **Thomas J. Semrad, MD, MAS**[1], and **Richard J. Bold, MD**[2]

[1]Division of Hematology and Oncology, UC Davis Cancer Center, Sacramento, CA 95817, USA

[2]Division of Surgical Oncology, UC Davis Cancer Center, Sacramento, CA 95817, USA

Abstract

Introduction—Despite some recent advances in treatment options, pancreatic cancer remains a devastating disease with poor outcomes. In a trend contrary to most malignancies, both incidence and mortality continue to rise due to pancreatic cancer. The majority of patients present with advanced disease and there are no treatment options for this stage that have demonstrated a median survival greater than 1 year. As the penultimate step prior to phase III studies involving hundreds of patients, phase II clinical trials provide an early opportunity to evaluate the efficacy of new treatments that are desperately needed for this disease.

Areas Covered—This review covers the results of published phase II clinical trials in advanced pancreatic adenocarcinoma published within the past 5 years. The treatment results are framed in the context of the current standards of care and the historic challenge of predicting phase III success from phase II trial results.

Expert opinion—Promising therapies remain elusive in pancreatic cancer based on recent phase II clinical trial results. Optimization and standardization of clinical trial design in the phase II setting, with consistent incorporation of biomarkers, is needed to more accurately identify promising therapies that warrant phase III evaluation.

1. Introduction

It is an exciting time in cancer therapeutics with new drug treatments arriving at a rapid pace. Greater understanding of tumor biology as well as robust drug development programs have led to enhanced alignment of therapy with an increasingly complex sub-categorization of malignancies. One malignancy for which therapeutic development has remained relatively stagnant is pancreatic cancer, perhaps due to its well-deserved notoriety for poor prognosis. In fact, it is the only cancer with continued rise in cancer mortality among both sexes[1]. In the past 15 years, only two phase III trials have demonstrated a clinically meaningful improvement in survival for patients with advanced disease[2, 3]. However, even

Correspondence: Richard J. Bold, MD, Division of Surgical Oncology, Suite 3010, UC Davis Cancer, Center 4501 X Street, Sacramento, CA 95817, Phone: (916) 734-7269, Fax: (916) 703-5267, richard.bold@ucdmc.ucdavis.edu.

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these improvements are incremental, with the resultant median overall survival for advanced stage disease of less than 12 months. The need for truly meaningful improvement is palpable.

Since phase II trials are typically the earliest phase for evaluating new therapeutics in a disease-specific context, they provide an opportunity to evaluate a later stage of the current pipeline of promising therapeutics. In this review, we highlight the results of recently published phase II trials in advanced pancreatic cancer and place the results into the context of current standard treatment paradigms. While there are also multiple studies recently presented in abstract form, the published results of phase II studies frequently do not exactly match abstract published[4]. Our focus here on published phase II trials serves as a platform to highlight opportunities to change how we approach drug development for pancreatic cancer, with the goal to improve survival in this lethal disease.

2. Historical context

2.1 Gemcitabine Era

Modern treatment of pancreatic cancer can be traced back to the late 1990s with FDA approval of gemcitabine for advanced pancreatic cancer. This approval was granted based on a phase III trial which demonstrated improvement in clinical benefit with gemcitabine over 5-fluorouracil (5FU) utilizing a composite primary endpoint of pain, Karnofsky performance status, and weight (23.8% vs 4.8%, $P = 0.0022$)[5]. 1-year survival was notably better with gemcitabine at 18% vs 2% with 5FU; median overall survival for gemcitabine was 5.6 months. Based on this study, gemcitabine was adopted as a standard of care for advanced pancreatic cancer and served as the control arm in multiple subsequent phase III studies with the ~6 month median survival proving to be very reproducible. Therefore, in the decade following the approval of gemcitabine, this benchmark was used to determine if a new therapy had enough potential in phase II to be worth studying in a phase III randomized trial. The common approach was to use gemcitabine as a backbone to a combination regimen with either other cytotoxic chemotherapy and/or a novel agent. Some gemcitabine-based combinations which showed relative promise in phase II studies included addition of a second cytotoxic chemotherapy (5FU[6] or capecitabine[7], cisplatin[8, 9], oxaliplatin[10], irinotecan[11, 12], pemetrexed[13]) or a targeted agent (cetuximab[14], bevacizumab[15], sorafenib[16, 17]). However, in all cases, there was no benefit to the addition of any of these drugs to gemcitabine monotherapy when tested rigorously in randomized phase III trials[18–31] (Table 1). There are a host of potential causes for the discordance between the Phase II and subsequent Phase III trials that include the transition from single institution to multi-center studies, differences in inclusion criteria, selection bias by both the trial participant and the enrolling physician, and stringency of endpoint assessment.

Nevertheless, there may be some benefit of gemcitabine-based regimens. In a recent metaanalysis of gemcitabine-based combination regimens including 23 Phase III studies, there was a modest benefit observed in combination regimens compared to gemcitabine alone[32]. In addition, an additional notable case is the combination of gemcitabine and erlotinib, which was tested in a phase III trial without a preceding phase II experience[33]. The result was a statistical improvement in survival of 6.24 months for the combination

compared to 5.91 months with gemcitabine (HR 0.82, $P = .038$). This result was met with muted enthusiasm given the minimal clinical benefit of an improvement in median survival by only ~10 days. Additionally, the combination of cisplatin, epirubicin, gemcitabine, and 5FU (PEFG) did not become standard regimen despite an observed improvement in 4-month progression free survival compared to gemcitabine monotherapy in a 104-patient phase III study[33]. Several other negative phase III trials were reported without preceding phase II results[35–37]. Despite the understandable desire to quickly advance promising therapies, the plethora of negative results in this era highlights the need for careful assessment of phase II trial design and interpretation in order to avoid wasteful use of limited patient and funding resources.

2.2 Recent Advances – Phase III success

Against this backdrop of frustrating failure to improve on gemcitabine monotherapy, two recent successful phase III trials in the first line treatment of advanced pancreatic cancer have re-ignited hope for achieving greater clinical benefit in this disease. The first trial was a multi-center trial conducted in France which randomized untreated patients with metastatic pancreatic cancer to either gemcitabine or the three-drug regimen of leucovorin-modulated 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX)[3]. The primary endpoint of this study was overall survival. Gemcitabine once again proved to be predictable in benefit and response with a 6.8 months median overall survival and 9.4% response rate. FOLFIRINOX, in contrast, provided both a statistically and clinically meaningful improvement in both median overall survival at 11.1 months and a 31.6% response rate. Given prior failures of phase III trials to demonstrate improvement over gemcitabine monotherapy and the differential of improvement with this regimen, it is worth reviewing the phase II evidence with FOLFIRINOX that led to this phase III trial. Forty-six patients were treated in a phase II study and notably, nine (26%) of the thirty-five patients with metastatic disease experienced a response translating to a median overall survival of 9.5 months[38]. Although encouraging, there was reasonable concern given the small sample size and therefore the confirmatory study was designed as a phase II/III study. In the phase II portion, the primary endpoint was response and the investigators set a bar of 11 out of the first 40 patients (27.5%) treated with FOLFIRINOX having to achieve a response in order to continue on to the phase III portion. With a response rate of 31.8% in the phase II portion, the trial continued and yielded an almost identical final response rate of 31.6%. An important comment about the experience with FOLFIRINOX relates to its tolerability as well as the patients enrolled in the trials. Due to potentially severe toxicity, patients aged 75 and older were excluded from the trial and 42% of patients received growth factor support. Therefore, with the shift to combination therapy from gemcitabine, ongoing caution with regards to increasing toxicity is critical. Furthermore, pancreatic cancer is a malignancy of the elderly, so excluding a significant population from trial entry may limit generalizability of the conclusions.

Two years after the FOLFIRINOX results were published, results from a phase III trial of nab-paclitaxel and gemcitabine were reported which again demonstrated a regimen capable of achieving both a statistically and clinically significant improvement over gemcitabine. The combination proved superior to gemcitabine alone for response rate (23% vs 7%, p<.

001) and median overall survival (8.5m vs 6.7m)[2]. The regimen appears relatively well tolerated with primary differential toxicity of increased neuropathy and worse neutropenia and fatigue. However, the phase III study did not replicate the 48% response rate and 12.2 month median overall survival achieved in the preceding phase II trial of nab-paclitaxel and gemcitabine[39]. Nevertheless, the results of the phase III trial demonstrated that nab-paclitaxel and gemcitabine provides a real and clinically meaningful improvement over gemcitabine monotherapy. At this time, no direct comparison data and no biomarker exists to predict favorable response to one first line regimen over the other, and treatment assignment is primary based on the difference in the associated toxicity profile.

Finally, the CONKO-003 phase III study comparing oxaliplatin, folinic acid, and infusional 5FU (OFF) to folinic acid and infusional 5FU alone (FF) after failure of gemcitabine monotherapy was recently published[40]. Amongst 168 randomized patients, survival was improved from a median of 3.3 to 5.9 months (HR 0.66, *P* 0.010). These results preceded the rise of FOLFIRINOX and nab-paclitaxel and gemcitabine as standard regimens, but nonetheless validate the ability to improve outcomes after first line therapy for advanced pancreatic cancer.

While these advances have deservedly been met with celebratory approval, the overall results remain sobering. It is of little consolation to newly diagnosed patients and their families to hear that expected survival of less than a year is “better than it used to be”. No regimen has a proven biomarker to predict the therapy with the best chance for response in any given patient. Preliminary results from the phase III trial of nab-paclitaxel and gemcitabine have failed to validate a candidate predictive biomarker, secreted protein acidic and rich in cysteine (SPARC), that was identified in the phase I/II trial (median OS 17.8 months for high SPARC vs 8.1 months for low SPARC)[39]. Moreover, augmenting either regimen with additional agents may be challenging, although early experience does suggest that this is perhaps easier with nab-paclitaxel and gemcitabine. It is in this context of these phase III results that the recently published phase II data should be appraised.

3. Phase II clinical trials in advanced pancreatic cancer

We performed a search of the literature for recent reports of phase II studies in advanced pancreatic cancer. Using a Pubmed search term of “phase II pancreatic cancer” limited to the past 5 years and reports from clinical trials, we identified 95 relevant publications excluding studies conducted in the neoadjuvant (6 studies including 5 with radiation), adjuvant (8 studies including 6 with radiation), and locally advanced only, nonmetastatic setting (33 studies including 26 with radiation). In this review, we organize the trial results into 3 categories of studies; cytotoxic chemotherapy only, epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) inhibitors, and other drugs.

3.1 Cytotoxic chemotherapy only

Optimizing cytotoxic chemotherapy regimens continues to be an area of active research in pancreatic cancer. Although one can argue that the overall spectrum of oncology therapeutic development is shifting towards more selective drugs with known biologic targets, standard treatment for pancreatic cancer has not yet successfully made this shift. It is notable that the

only two treatment regimens with clinically significant impact have included cytotoxic chemotherapy without the addition of targeted or novel drugs. One can classify the recently reported phase II studies with only cytotoxic chemotherapy into 2 sub-categories: 1) regimens like FOLFIRINOX with unmodified traditional cytotoxic chemotherapy, and 2) regimens like nab-paclitaxel and gemcitabine which incorporate a modified cytotoxic chemotherapy (Table 2).

3.1.1 Unmodified traditional cytotoxic chemotherapy—Among the studies investigating unmodified traditional cytotoxic chemotherapy, the majority were done in the first line setting and in all cases, gemcitabine was used as the base drug for combination therapy. In the 2nd line setting, 5FU/capecitabine is most commonly used as the base drug. This reflects a pre-FOLFIRINOX era and again highlights the persistent approach to using gemcitabine as a base chemotherapy in first line and 5FU in 2nd line. Two-drug combinations with gemcitabine have included cisplatin[41], oxaliplatin[42, 43], 5FU[44, 45], docetaxel[41], irinotecan[38, 44], or etoposide[46]. Most were conducted prior to publication of corresponding phase III studies showing no benefit to addition of these agents in gemcitabine-based 2 drug regimens. With response rates ranging from 7% to 28% and median OS of 6.4 to 9.4 months, these studies provide little additional information to support continued investigation.

Compared to these 2-drug regimens, the benefit achieved with the 3-drug regimen of FOLFIRINOX raises the question of how much of that benefit was due to the specific drugs in FOLFIRINOX or simply combination of 3 different drugs. The results of multiple recent phase II studies provide some support for the 3 drug concept as combinations of gemcitabine, 5FU/capecitabine, and either oxaliplatin or docetaxel yielded response rates ranging from 33% to 41%, on par with FOLFIRNOX and clearly better than the 2 drug regimens[47–49]. However, the reported median OS between 7.8 and 9 months in these studies is worse than with FOLFIRINOX, despite a mixed population with 20–40% patients with locally advanced disease. In addition, the issue of cumulative toxicity seen with FOLFIRINOX was also a concern in these 3-drug regimens. If 3 drugs are better than 2, will 4 drugs do even better? One study compared two 4-drug regimens in 105 patients among whom 66% had metastatic disease[50]. The two regimens included lowered doses of gemcitabine, capecitabine, cisplatin, and either docetaxel or epirubicin. The response rates were high with 57% of metastatic patients receiving the docetaxel-containing regimen achieving a partial response versus 32% in the patients receiving the epirubicin regimen. Toxicity was surprisingly relatively moderate with low rates of grade 3/4 neutropenia (4% in the docetaxel arm and 13 % in the epirubicin arm) and only 1 grade 3 febrile neutropenia.

The most commonly tested traditional cytotoxic chemotherapy drugs tested in 2nd line setting include 5-fluorouracil and irinotecan. 5-fluorouracil has been commonly used as a backbone for second-line treatment after gemcitabine failure and 5-FU alone or in combination with oxaliplatin is an accepted standard 2nd line regimen. Irinotecan clearly has activity based on the FOLFIRINOX data and therefore is of interest either as a single agent or in combination with 5FU as FOLFIRI. Two separate studies of FOLFIRI in the 2nd line demonstrate low response rate (0–8%) and median OS of 4–5 months similar to FOLFOX (7% RR and 3.75 month overall survival)[51, 52]. Irinotecan has been tested as monotherapy in

the 2nd line setting and achieves similar results with one phase II study reporting 9% response rate and median OS of 6.6 months[53].

3.1.2 Modified cytotoxic agents—Modifications have been made to standard cytotoxic chemotherapy with goals of increasing efficacy and/or reducing toxicity. Nab-paclitaxel is an example of such a modification; it was designed to obviate the need for the obligatory paclitaxel diluent cremaphor, which can result in hypersensitivity reactions. The albumin coating may also fact enhance tumor deposition through interaction with secreted protein acidic rich in cysteine (SPARC) which is abundantly present in tumor stroma, although this remains to be clinically validated. Alternative modifications have been made to paclitaxel and reported in recent phase II studies. Polymeric micelles have been developed to envelop paclitaxel with the goal of increasing solubility without cremophor and also enhanced efficacy by virtue of delivering a higher dose of drug safely. A single agent phase II trial in 45 advanced pancreatic cancer patients treated with paclitaxel loaded into a polymeric micelle demonstrated mild activity with 1 complete remission and 2 partial remissions for an overall response rate of 6.7% and a 6.5 months median overall survival[54]. An attempt to increase efficacy by targeting delivery of paclitaxel to tumor endothelial cells was attempted using cationic liposomes with embedded paclitaxel[55]. Studied at 3 different doses of the novel formulation in combination with gemcitabine, a large phase II study showed response rates of 14–16% and median OS of 8.1 to 9.3 months. Neither formulation achieved a signal that is sufficiently superior to gemcitabine/nab-paclitaxel to reasonably warrant further exploration.

Gemcitabine has also been target of modification in an attempt to increase efficacy by overcoming a potential resistance mechanism. Gemcitabine is hydrophilic and therefore requires transporters to cross cell membrane. Low levels of one transporter protein in particular, human equilibrative nucleoside transporter-1 (hENT1) may predict decreased sensitivity to gemcitabine due to poor tumor cell uptake. CO-101 is gemcitabine linked to elaidic acid which allows it to circumvent the need for hENT1. In a biomarker-driven phase II study, this hypothesis for resistance to gemcitabine was tested by randomizing patients to either gemcitabine or CO-101 irrespective of hENT1 expression level[56]. CO-101 yielded a lower response rate than gemcitabine in both hENT1 high (9.1% vs 15.5%) and low (17.1% vs 26.3%) groups and resulted in no difference in median overall survival (5.2m vs 6.0m). This result along with the observed higher response rate to gemcitabine in the low hENT1 group raises doubt that hENT1 expression level is a useful predictive biomarker. Despite the negative result, we appreciate the study authors' efforts to incorporate a biomarker into the study design and analysis.

Irinotecan has enjoyed increased visibility as a useful drug in pancreatic cancer based on the success of the FOLFIRINOX regimen. Similar to paclitaxel, liposomal encapsulation has been tested as a way to increase efficacy through improved stability and tumor distribution. A 2nd line trial of nanoliposomal irinotecan sucrosofate (PEP02) demonstrated a 7.5% response rate with a 2.4 month progression-free survival and 5.2 months median overall survival[57]. Although this benefit is notably similar to the previously described findings with either FOLFIRI or irinotecan in the 2nd line, this modified formulation of irinotecan is currently being studied in a phase III trial based on its potential for greater tolerability

(NCT01494506). 5FU is used as the control arm for two separate experimental arms, PEP02 alone and 5FU in combination with PEP02. In the absence of an unmodified irinotecan containing control arm, it may be difficult to determine if modified irinotecan provides any greater benefit than simply FOLFIRI compared to 5FU.

The best studied modification to a cytotoxic chemotherapy is S-1, an oral combination of tegafur (5FU prodrug) with two modulating agents: 5-chloro-2,4-dihydroxypyridine (CDHP) which inhibits the 5FU-catabolizing enzyme dihydropyrimidine dehydrogenase, and potassium oxonate (Oxo) which reduces gastrointestinal toxicity. There have been multiple recent phase II studies combining S1 with gemcitabine in first line treatment of advanced pancreatic cancer including 2 randomized studies comparing gemcitabine/S1 to gemcitabine[58–63]. Overall response rates with the combination range from 13.5% to 44% which are generally higher than with gemcitabine alone. The median OS results reported in these studies also spans a broad range from 7.9 to 13.7 months which mainly reflects inclusion of varying percentage of locally advanced patients in addition to a majority of metastatic patients. Both randomized studies showed promising improvement in median OS with the combination over gemcitabine although the primary endpoints were PFS[59] and overall response rate[60]. S1 remains an interesting reformulation but with questionable broad applicability given the greater toxicity experienced by Western patients in comparison to Asian patients.

3.2 EGFR and VEGF inhibitors

3.2.1 EGFR inhibitors—EGFR inhibition has been tested in pancreatic cancer with both a small molecule inhibitor erlotinib and an anti-EGFR antibody cetuximab. As described previously, although the addition of erlotinib to gemcitabine provided a statistically significant improvement to survival, neither erlotinib nor cetuximab demonstrated strong clinical efficacy in combination with gemcitabine in phase III. Further exploration for a potentially more active regimen incorporating EGFR inhibition has involved intensifying the chemotherapy backbone. Phase II studies of gemcitabine, erlotinib in combination with either cisplatin[64] or capecitabine[65] have been performed and have yielded response rates of 26% and 33% respectively (Table 3). Consistent with other small phase II studies in pancreatic cancer, this improved response rate does not consistently translate to improved overall survival. Overall survival does not appear to be improved with addition of erlotinib to gemcitabine/cisplatin (median OS 6.8 months) but erlotinib added to gemcitabine/capecitabine did yield an intriguing extension in median OS to 12 months. Notably, 50% of the patients treated in the gemcitabine/capecitabine/erlotinib study had wild type KRAS suggesting benefit to this regimen irrespective of KRAS status. Adding cetuximab to intensified chemotherapy backbone has recently been tested in 2 separate phase II studies both using gemcitabine and oxaliplatin[66, 67]. Reported response rate to this triplet ranged from 24 to 33%, which was higher than gemcitabine monotherapy but disappointingly did not translate to improved survival with median OS of 6–7 months in metastatic patients.

3.2.2 VEGF inhibitors—In a similar story to the EGFR inhibitors, although targeting angiogenesis with either bevacizumab or sorafenib has failed to improve survival when added to gemcitabine in phase III trials, continued efforts have been made to combine anti-

angiogenesis with chemotherapy. Recent attempts to intensify gemcitabine-based chemotherapy to combine with bevacizumab have included addition of capecitabine[68], 5FU[69], or oxaliplatin[70]. The studies are similar in that they included untreated and mostly metastatic (72–94%) patients and achieved response rates ranging from 22–36% and median overall survival of 7.4 to 10.2 months. One study of gemcitabine/5FU/bevacizumab identified albumin as a predictor of response benefit with dramatically longer mOS in patients with albumin ≥ 3.4 g/dl achieving 11.7 months compared to only 3.2 months with less than 3.4 g/dl[69].

3.2.3 Combined EGFR and VEGF inhibition—Another approach to augmenting efficacy achieved with targeting either EGFR or VEGF has been to combine bevacizumab with either erlotinib or cetuximab. A phase II study of bevacizumab and cetuximab with or without gemcitabine was done in the first line setting for patients with advanced pancreatic cancer[71]. Patients treated without gemcitabine achieved a median OS of only 4.2 months and adding gemcitabine only increased this to 5.4 months which can be reasonably be expected with gemcitabine alone. In a second-line study for gemcitabine-refractory disease, bevacizumab and erlotinib similarly had minimal efficacy with 1 of 36 patients achieving a partial response translating to a mOS of 3.3 months[72]. Dual inhibition of EGFR/VEGF therefore does not appear to enhance efficacy.

3.3 Other drugs

Given the limited success from attempts to re-formulate cytotoxic chemotherapy or targeting EGFR/VEGF, there are continued efforts to develop truly novel drugs with new mechanisms of action that will hopefully provide meaningful benefit. Among recently reported phase II studies, gemcitabine predictably has continued to serve as a backbone to test efficacy. Disappointingly, negative study outcomes remain the norm with most studies plagued by small sample size, heterogeneous patient populations, variable endpoints, prohibitive toxicity, and/or lack of associated correlative science and integrated biomarker development. Some examples of novel drugs that failed to clearly augment efficacy when added to chemotherapy in single arm studies include curcumin[73, 74], masitinib (multi-tyrosine kinase inhibitor eg c-kit, PDGFR, Lyn)[75], Z-360 (gastrin inhibitor)[76], bryostatin-1 (protein kinase C inhibitor)[77], flavopiridol (pan-cyclin dependent kinase inhibitor)[78], and saracatinib (Src inhibitor)[79] (Table 4). Saracatinib has also been studied as a single agent in previously treated patients[80]. After determining lack of efficacy in unselected patients, the authors modified the trial to select patients based on 2 biomarkers predictive of response to Src inhibition in patient-derived xenografts. The low frequency of biomarker-selected patients led to study closure with a single biomarker positive patient experiencing rapid progression. Although clearly a negative outcome, this study is noteworthy because of the rarity of studies that incorporate biomarkers to gain understanding of both success and failures.

These studies all lacked a control arm which allowed some study authors to conclude sufficient success in some of these cases to warrant further investigation based on historical controls. Testing novel drugs in randomized phase II studies helps to reduce potential for overestimating significance of results. Some recent examples of novel drugs tested in randomized phase II studies in combination with chemotherapy that failed to add clear

benefit include brivudine (HSP27 inhibitor)[81], wild toad extract[82], ganitumab (IGF1-R inhibitor)[83], conatumumab (DR5 agonist)[83], LY293111 (leukotriene B4 inhibitor)[84], and enzastaurin (PKCβ and PI3K/AKT inhibitor)[85]. Although this last drug, enzastaurin, did not improve efficacy when combined to gemcitabine, the phase II study did notably embed evaluation of 5 potential biomarkers relevant to the targeted pathway. This allowed the authors to detect a trend towards longer overall survival in patients with low expression of one of their biomarkers, pGSK-3B. Based on this valuable information from a "negative" trial in unselected patients, it is reasonable to consider the possibility that a trial in selected patients may show benefit. A positive randomized phase II study testing AGS-1C4D4 (prostate stem cell antigen inhibitor) in combination with gemcitabine yielded a modest benefit in 6 month survival rate and median overall survival[86]. But like the enzastaurin study, the incorporation of a biomarker, in this case expression level of the target protein by immunohistochemistry, helped to define the subset of patients most likely to benefit from the experimental therapy.

KRAS remains a high-priority target in pancreatic cancer given the prevalence of mutations in pancreatic adenocarcinoma. However, it remains an elusive target for direct inhibition and therefore drug development has also been focused on finding ways to inhibit the downstream Ras/Raf/MEK/ERK and PI3K/AKT/mTOR pathways. Targeting the MEK pathway was tested in a randomized trial comparing selumetinib (MEK inhibitor) to capecitabine in the second-line setting[87]. With a primary endpoint of overall survival, median survival was equivalent between selumetinib and capecitabine (5.4m vs 5.0m, respectively). The mTOR inhibitors temsirolimus and everolimus (with erlotinib) have also been tested in two small studies with neither showing promising activity[88]. Multiple ongoing trials are testing the hypothesis that combining inhibition of both pathways is necessary to inhibit KRAS mutated tumor growth.

4.0 Trial Design

There are consistent challenges to the interpretation and extrapolation of the results of recent phase II studies in pancreatic cancer. This includes heterogenous entry criteria, inconsistent use of stratification variables known to affect prognosis, as well as diversity in trial endpoints defining the decision to proceed to phase III investigation. Lastly, the neoadjuvant setting is particularly attractive for testing of novel agents but has been poorly incorporated into the design of Phase II trials in pancreatic cancer.

4.1 Entry Criteria for Phase II trials

The entry criteria for clinical trials require a delicate balance between, a) removing unnecessary barriers to accrual and, b) maintaining sufficient homogeneity that results can be interpreted. The majority of the phase II studies we reviewed allowed for both metastatic and locally advanced disease. Although one could argue that it is reasonable to view locally advanced unresectable disease as "not yet visible" metastatic disease, the two groups nevertheless do have different prognoses. While survival results can be reported separately for different stages of disease within a single study, such analyses may result in too little power and poor prediction of phase III outcome. We therefore believe it is critically important that trials testing novel therapies should be restricted to a single stage of disease.

Although comparing results across trials is inherently fraught with biases, normalizing the patients entered will facilitate the interpretation of the significance of any positive result.

One way to address the challenges in comparing results with historical controls is to test novel therapies in randomized controlled studies. This obviously increases the number of patients needed which increases the challenges to meeting accrual. However, in this new era of setting big goals, randomized trials will help filter out incrementally beneficial therapies that appear tempting when resulted from single arm studies. Stratifying patients for known prognostic indicators such as performance status and baseline tumor marker levels will enhance the interpretation of results from phase II randomized studies. The heterogeneity of the patient population at the level of established clinical factors (age, co-morbidity, functional status), pathologic factors (extent of metastatic disease, site of metastatic disease, tumor grade and histologic subtype) require better stratification for trial entry and data analysis to allow meaningful endpoint abstraction.

Lastly, it is imperative that biomarker development is incorporated early into every new clinical trial investigating novel therapies. If we consider other malignancies such as melanoma, lung, and colon cancer which have experienced significant shifts in treatment and survival through increased molecular understanding and associated biomarker-driven targeted therapies, pancreatic cancer remains chained to the approaches taken in those malignancies a decade ago. Although viable targets remain elusive such as the seemingly “undruggable” KRAS mutation, the success derived through testing biomarker-driven targeted agents such as crizotinib for ALK-mutated non-small cell lung cancer and vemurafenib for BRAF-mutated melanoma are tantalizing[89, 90]. Hope lies in the output from the International Cancer Genome Consortium in pancreatic cancer to identify clinical and genomic subgroups of pancreatic cancer for targeted therapy. The identification of HER2/*neu* amplified tumors is just such an example.

As highlighted in the studies above, biomarker incorporation has been infrequent and there may be insufficient evidence to similarly select only patients positive for non-validated biomarkers. Pancreatic cancer is a genomically diverse disease and incorporation of known molecular drivers of biology in the trial design and stratification of endpoint analysis remains a significant area for improvement. By embedding biomarker development into phase II studies, we can gain critical information to understand both negative and positive results that can enhance the potential to identify the right patients to include in a phase III trial.

4.2 Endpoints for Phase II trials

Choosing appropriate endpoints are a critical early step in development of any clinical trial. Survival is the ultimate endpoint but is typically limited to large randomized phase III trials. Therefore, endpoints are chosen to serve as surrogates for survival. The selected endpoints will influence statistical analysis including number of patients needed to achieve a designated level of improvement with sufficient power. In the majority of cases, assessment of radiologic response is incorporated into the primary endpoint in some form, either as simply response rate, time to tumor progression or progression-free survival. One of the greatest challenges to interpreting phase II studies in pancreatic cancer is the lack of

consistent correlation between radiographic response and reported survival. The prior topic of entry criteria is worth noting again in the current context of limits to interpreting endpoints when the input population is either heterogeneous and/or non-stratified for known prognostic markers. Perhaps greater predictability of benefit that will translate into improved survival will require incorporation of novel surrogates that add information beyond radiographic response. Technological improvement in detection of either circulating tumor cells through advances in microfluidics or circulating shed DNA for tumor mutations such as KRAS need to be embedded in clinical trials to challenge the limits of our current surrogates for response to therapy[91–93]. Until the time when these and other novel modalities can be validated and broadly applied, we will need to continue to rely on radiographic assessment and associated survival endpoints in the phase II setting. How robust should the signal be in the phase II setting to warrant investment in a phase III trial? The new target for clinically meaningful improvement in the phase III setting is a 4–5 month improvement in median overall survival. It is again difficult to use overall survival as the primary endpoint in a phase II study given smaller number of patients. However, a similar 4–5 month improvement in progression-free survival in the phase II setting would be a reasonable goal with likely sufficient strength to predict success in a phase III evaluation.

4.3 Disease setting for Phase II trials

We chose to focus our review on the phase II studies conducted in patients with advanced pancreatic cancer. This is the primary disease setting for phase II studies in pancreatic cancer. The majority of pancreatic cancer patients present with advanced disease and therefore these patients represent the largest subset of patients eligible for trial evaluation of new drugs or new regimens. Furthermore, advanced disease allows for assessment of radiographic response thus allowing for relatively rapid assessment of efficacy. Studying novel therapies in the adjuvant setting is challenging because of requisite longer term follow-up to detect a signal of benefit in the form of improvement in relapse-free survival. Neoadjuvant therapy for borderline resectable disease has become an accepted standard practice without clinical trial evidence of an optimal regimen or treatment strategy including the potential utility of radiation. Response assessment in this stage is challenging due to several factors including limitations of current radiographic technology to accurately assess biologic response to therapy, prognostic impact of surgical resection, and limitations to tissue acquisition without surgical resection. Direct assessment of drug effect through tumor sampling is challenging as well but possible in the metastatic setting but requires serial biopsies. One potential setting that is rarely used for phase II studies is neoadjuvant treatment in upfront resectable disease. The major barrier is that the current standard of care is to attempt a surgical resection first before providing systemic therapy and therefore there is an inherent anxiety to minimize any delay to a potentially curative resection. But the harsh reality of pancreatic cancer is that even in this best case scenario of upfront resectable disease, the median overall survival with adjuvant therapy is still only ~2 years with majority of patients developing recurrence. With a relatively short course of neoadjuvant therapy (1–2 months), patients who develop apparent metastatic disease are unlikely to have benefitted anyways from surgery. Testing novel agents in the neoadjuvant setting would provide an optimal opportunity to evaluate novel therapies by providing tumor tissue from paired pre-treatment biopsy and post-operative resection. Thus, rather than using traditional

endpoints of radiologic response or survival response, these Phase II trials may focus on identification of subgroups most likely to respond (ie predictors of therapy using the pre-treatment biopsy) as well as demonstrating efficacy of therapeutic targeting (ie post treatment resection confirming molecular target response).

One potential limitation of testing novel drugs in the neoadjuvant setting may be accrual as less than 15% of patients present with resectable disease at presentation. However, the endpoint for this type of study would be to directly confirm drug activity in tumor (hitting the target), provide insight into determinants of drug sensitivity, and biomarker development. Therefore, not as many patients would be required as in a phase II study using radiographic response or survival endpoints. If there is promising biologic activity, the information derived from a neoadjuvant study would potentially provide critical information necessary for a more strategic approach to testing for clinical benefit in the advanced setting.

5.0 Conclusion

The overall lack of success in phase III trials for pancreatic cancer is highlighted by the fact that none have achieved a median overall survival over a year and this continues to cast a long shadow over the general outlook of future prognosis for patients with pancreatic cancer. Within this context, it is understandable to search for reasons to view even slight, incremental improvements as a positive result. However, we would argue that it is this very attitude and its passive acceptance of an intrinsic relative futility to treating pancreatic cancer that has allowed for so many marginally promising results to be further explored in phase III trials. In a bold and aggressive statement, new guidelines have been issued that have raised the bar for meaningful improvement in several oncologic diagnoses including pancreatic cancer[94]. A 4–5 month improvement in median overall survival beyond the 10–11 month survival achieved with FOLFIRINOX and 3–4 month improvement in median survival beyond the 8–9 month survival achieved with nab-paclitaxel and gemcitabine are now the benchmarks for clinically meaningful improvement in the frontline setting. We applaud this ambitious benchmark as an attitude adjustment necessary to take meaningful steps forward towards clinical progress. In regards to phase II drug studies, what needs to be done to develop therapies worth putting forth to clear that high bar for success in phase III trials? We believe the answers lie in clinical trial design for phase II studies.

6.0 Expert Opinion

The overwhelming majority of Phase II trials have not been successfully translated into positive Phase III trials in advanced pancreatic cancer. This is clearly not due to lack of effort given the numerous Phase II trials that have pursued three distinct approaches: 1) building on the gemcitabine backbone of chemotherapy, 2) polychemotherapy of novel combinations, 3) novel agents specifically targeting common molecular events in cancer. There are a variety of possible reasons for the failure of the Phase II trials to yield advances in the Phase III setting: 1) the very nature of pancreatic cancer as a chemoresistant malignancy such that gemcitabine should not be used as a backbone since the benefit in Stage IV disease is modest, at best, 2) the intense desmoplasia and lack of robust angiogenesis limits effective levels of chemotherapy diffusion into the tumor, 3) the focus

on response rates or progression free survival (compared to overall survival in Phase III trials, 4) the most common oncogenic molecular event in pancreatic cancer (KRAS mutation) has to date not been directly drugable, and 5) alternative molecular targets are either uncommon or are insignificant drivers of the neoplastic process. An additional limitation in the development of Phase III clinical trials is appropriate patient selection (both clinical criteria and molecular profiling) as pancreatic cancer really is a diverse disease given variability in frequency of molecular events as well as the recognized impact of various prognostic factors.

Despite these observations, there remains tremendous enthusiasm for ongoing clinical trials development in pancreatic cancer. We foresee changes in trial design that includes genomic profiling more integrated in inclusion criteria as well as more consistent homogenous patient groups enrolled in Phase II clinical trials. Furthermore, there is significant enthusiasm for targeting the MEK pathways as a downstream event in those tumors that are oncogenically driven by KRAS mutation. Optimization of predictors of response to targeted therapies as well as integration of surrogate biomarkers of response will also allow the identification of agents more likely to yield positive Phase III trials. Lastly, given the relatively minimal impact of gemcitabine on overall survival in metastatic pancreatic cancer, we foresee moving away from gemcitabine alone as a backbone when combining novel targeted agents with current chemotherapeutics.

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Article Highlights

- With the recent publication of successful chemotherapeutic combination studies, there is renewed excitement for drug development in pancreas cancer.
- In this review, we summarize the results of phase II clinical published in the last 5 years.
- The majority of prior of reportedly positive phase II studies in pancreas cancer haven't resulted in improvement in outcomes when tested formally against the standard of care.
- The lack of translation of phase II results into positive phase III outcomes highlights the need to standardize entry criteria, stratification, and outcome assessment to better select candidate drugs for phase III investigation.
- Predictive biomarkers have been uncommonly integrated into phase II studies but are essential to further advances in this lethal disease.

Table 1

Key Gemcitabine-based Phase III trials and associated Phase II trials

Regimen	Phase (II or III)		RR (%)	mOS (m)	mPFS (m)	1yr Survival (%)
gem + 5-fluorouracil	II	Berlin et al.[6]	14	4.3	2.4*	8.6
	III	Berlin et al.[18]	7	6.7	3.4	NR
gem + cape	II	Scheithauer et al.[7]	17	9.5	5.1*	31.8
	III	Cunningham et al.[19]	19	7.1	5.3	24.3
		Herrmann et al.[20]	10	8.4	4.3	NR
gem + irinotecan	II	Rocha Lima et al.[11]	24	5.7	2.8*	27
		Stathopoulos et al.[12]	25	7	7.0*	22.5
	III	Rocha Lima et al.[21]	16	6.3	3.5*	21
		Stathopoulos et al.[22]	15	6.4	2.8*	24.3
gem + cisplatin	II	Heinemann et al.[8]	11	8.2	4.3*	27
		Philip et al.[9]	26	7.1	5.4*	19
	III	Heinemann et al.[23]	10	7.5	5.3	25.3
		Colucci et al.[24]	26	7.5	5.0*	11.3
		Colucci et al.[25]	13	7.2	3.8	30.7
gem + oxaliplatin	II	Louvet et al.[10]	31	9.2	5.3	36
	III	Louvet et al.[26]	27	9.0	5.8	34.7
		Poplin et al.[27]	9	5.7	2.7	21
gem + pemetrexed	II	Kindler et al.[13]	6	6.5	4.0	28
	III	Oettle et al.[28]	15	6.2	3.0*	21.4
gem + cisplatin, epirubicin, 5FU	II	Reni et al.[95]	51	10	7.5*	40

Regimen	Phase (II or III)		RR (%)	mOS (m)	mPFS (m)	1yr Survival (%)
	III	Reni et al.[34]	38	NR	5.4	38.5
gem + exatecan	II	*No study*	*NA*	*NA*	*NA*	*NA*
	III	Abou-Alfa et al.[35]	7	6.7	3.7*	23
gem + erlotinib	II	*No study*	*NA*	*NA*	*NA*	*NA*
	III	Moore et al.[33]	9	6.24	3.75	23
gem + cetuximab	II	Xiong et al.[14]	12	7.1	3.8*	31.7
	III	Philip et al.[29]	12	6.3	2.3*	NR
gem+ bevacizumab	II	Kindler et al.[15]	21	8.8	5.4	29
	III	Kindler et al.[30]	13	5.8	3.8	NR
gem + sorafenib	II	Kindler et al.[17]	0	4	3.2	NR
		El-Khoueiry et al.[16]	3	6.5	2.9	NR
	III	Goncalves et al.[31]	23	8	3.8*	NR
gem + tipifarnib	II	*No study*	*NA*	*NA*	*NA*	*NA*
	III	Van Cutsem et al.[36]	6	6.3	3.7	27
gem + marimastat	II	*No study*	*NA*	*NA*	*NA*	*NA*
	III	Bramhall et al.[37]	11	5.4	3.5*	18

*time to progression.

Abbreviations: RR, response rate. mOS, median overall survival. mPFS, median progression-free survival. NA, not available. NR, not reported. Gem, gemcitabine. Cape, capecitabine.

Table 2

Cytotoxic chemotherapy

Regimen		Line of treatment	% metastastic	RR (%)	mOS (m)	mPFS (m)
Unmodified						
gem + cisplatin	Kulke et al.[41]	1st	100	13	6.7	4.5*
gem + oxaliplatin	Lee et al.[42]	1st	75	18	9.4	5.6*
	Afchain et al.[43]	1st	100	27	7.6	4.0
gem + 5FU	Roehrig et al.[44]	1st	100	7	7.3	4.0*
	Pelzer et al.[45]	1st	78	10	6.8	4.6*
gem + docetaxel	Kulke et al.[41]	1st	100	12	6.4	4.1*
gem + irinotecan	Kulke et al.[41]	1st	100	14	7.1	4.0*
gem + etoposide	Melnik et al.[46]	1st	83	29	7.2	3.1*
gem + oxaliplatin + 5FU	Ch'ang et al.[47]	1st	80	33	8.7	5.1*
gem + oxaliplatin + cape	Hess et al.[48]	1st	76	41	7.8	4.3
gem + docetaxel + cape	Xenedis et al.[49]	1st	60	40	9.0	6.0
gem + cisplatin + cape + epirubicin	Reni et al.[50]	1st	65	37	11.0	7.6
gem + cisplatin + cape + docetaxel	Reni et al.[50]	1st	66	60	10.7	7.4
FOLFIRI	Yoo et al.[51]	2nd	100	0	4.2	2.1
	Zaniboni et al.[52]	2nd	100	8	5.0	3.3
FOLFOX	Yoo et al.[51]	2nd	100	2	3.7	1.5
irinotecan	Yi et al.[53]	2nd	100	9	6.6	2.0
Modified						
paclitaxel (polymeric micelle)^	Saif et al.[54]	1st	78–91	0–7	2.5–6.5	1.3–3.2*
gem + *paclitaxel* (cationic liposome)^	Lohr et al.[55]	1st	76–84	14–16	8.1–9.3	4.1–4.6
CO-101 (*gem* linked to elaidic acid)	Poplin et al.[56]	1st	100	16	5.2	2.7–3.1
PEP02 (nanoliposomal *irinotecan*)	Ko et al.[57]	2nd	100	8	5.2	2.4
gem + S1 (*tegafur* + oxo + CDHP)	Song et al.[58]	1st	100	14	9.4	4.6

Regimen		Line of treatment	% metastastic	RR (%)	mOS (m)	mPFS (m)
	Nakai et al.[59]	1st	72	19	13.5	5.4
	Ozaka et al.[60]	1st	75	28	13.7	6.2
	Ueno et al.[61]	1st	100	44	10.1	5.9
	Oh et al.[62]	1st	84	29	8.4	5.4*
	Lee et al.[63]	1st	91	44	7.9	4.9*

*time to progression.

^3 dose levels studied.

Abbreviations: RR, response rate. mOS, median overall survival. mPFS, median progression-free survival. NA, not available. NR, not reported. 5FU, 5-fluorouracil. Gem, gemcitabine. Cape, capecitabine. FOLFIRI, folinic acid, 5FU, irinotecan. FOLFOX, folinic acid, 5FU, oxaliplatin. Oxo, potassium oxonate. CDHP, 5-chloro-2,4-dihydroxypyridine.

Table 3

EGFR and VEGFR targeted drugs

Regimen		Line of treatment	% metastastic	RR (%)	mOS (m)	mPFS (m)
gem + cisplatin + *erlotinib*	Hwang et al.[64]	1st	64	26	6.8	4.0
gem + cape + *erlotinib*	Oh et al.[65]	1st	100	33	12.0	6.5
gem + oxaliplatin + *cetuximab*	Merchan et al.[66]	1st	49	24	11.3	6.9
gem + oxaliplatin + *cetuximab*	Kullmann et al.[67]	1st	100	33	7.0	3.9*
gem + cape + *bevacizumab*	Javle et al.[68]	1st	94	22	9.8	5.8
gem + 5FU + *bevacizumab*	Martin et al.[69]	1st	95	30	7.4	5.9
gem + oxaliplatin + *bevacizumab*	Fogelman et al.[70]	1st	72	36	11.9	4.9
gem + *bevacizumab* + *cetuximab*	Ko et al.[71]	1st	83	14	5.4	3.6
bevacizumab + *erlotinib*	Ko et al.[72]	2nd^	100	3	3.3	1.3*

* time to progression.

^ included patients with at least 1 prior therapy.

Abbreviations: RR, response rate. mOS, median overall survival. mPFS, median progression-free survival. TTP, time to progression. NA, not available. NR, not reported. 5FU, 5-fluorouracil. Gem, gemcitabine. Cape, capecitabine.

Table 4

Other Drugs

Regimen		Line of treatment	% metastastic	RR (%)	mOS (m)	mPFS (m)
gem + *curcumin*	Epelbaum et al.[73]	1st	76	9	5.0	2.5*
gem + S1 + *curcumin*	Kanai et al.[74]	2nd	NR	0	5.4	NR
gem + *masitinib*	Mitry et al.[75]	1st	59	23	7.1	6.4*
gem + *Z-360*	Meyer et al.[76]	1st	NR	0	NR	NR
paclitaxel + *bryostatin-1*	Lam et al.[77]	1st/2nd	NR	5	NR	1.9*
docetaxel + *flavopiridol*	Carvajal et al.[78]	2nd	100	0	4.2	2.0*
gem + *saracatinib*	Renouf et al.[79]	1st	57	9	6.2	NR
saracatinib	Arcaroli et al.[80]	2nd	100	0	2.5	1.6
gem + *brivudine*	Heinrich et al.[81]	1st	75	NR	6.7	NR
gem + *wild toad extract*	Meng et al.[82]	1st/2nd	76	8	5.3	3.3*
gem + *ganitumab*	Kindler et al.[83]	1st	100	10	8.7	5.1
gem + *conatumumab*	Kindler et al.[83]	1st	100	3	7.5	4.0
gem + *LY293111*	Saif et al.[84]	1st	87	10	7.1	3.7
gem + *enzastaurin*	Richards et al.[85]	1st	91	9	5.6	3.4
gem + *AGS-1C4D4*	Wolpin et al.[86]	1st	100	22	7.6	3.8
selumetinib	Bodoky et al.[87]	2nd	100	5	5.4	2.1
temsirolimus	Javle et al.[88]	2nd^	100	0	1.5	0.7
everolimus	Javle et al.[88]	2nd^	100	0	2.9	1.6

*time to progression.

^included patients with at least 1 prior therapy.

Abbreviations: RR, response rate. mOS, median overall survival. mPFS, median progression-free survival. NR, not reported. 5FU, 5-fluorouracil. Gem, gemcitabine. Cape, capecitabine.