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REVIEW ARTICLE

Liposomal Irinotecan in the Treatment of Refractory Pancreatic Cancer

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Abstract: Effective therapies against metastatic pancreatic cancer remain limited, and despite treatment, many will ultimately progress. Previously, few options were available for second line therapy in metastatic pancreatic cancer. Liposomal encapsulated irinotecan, in combination with leucovorin-modulated fluorouracil, was found to significantly increase overall survival in patients who have progressed after gemcitabine-based therapy in a large, international, randomized clinical trial (NAPOLI-1). We reviewed the background of systemic therapy for metastatic pancreatic cancer, examined putative mechanisms for the success of encapsulated drugs, and identified recent patent applications on the use of liposomal irinotecan in pancreatic cancer. The landmark NAPOLI-1 trial established a second-line option for those with metastatic pancreatic cancer refractory to gemcitabine chemotherapy, but effective therapies with long duration of response are still lacking. Alternative techniques targeting key driver genes in pancreatic cancer and novel methods of early detection and targeting drugs are currently being explored. How liposomal irinotecan can be integrated into chemotherapy regimens, including neoadjuvant or first line combinations, are currently being tested in clinical trials and covered by several new patent applications.

Keywords: Liposomal irinotecan, MM-398, Nal-IRI, NAPOLI-1, pancreatic cancer, refractory cancer.

1. INTRODUCTION

Pancreatic cancer, specifically pancreatic ductal adenocarcinoma (PDAC), is a deadly disease projected to become the second leading cause of cancer deaths by 2020 [1]. Part of the difficulty in treating pancreatic cancer is the frequent presence of an oncogenic driver mutation in the *KRAS* gene, found in more than 90% of PDAC [2]. While recent advances in drug development have enabled targeting of several driver mutations in the RAS pathway including epidermal growth factor receptor (EGFR) [3], PI-3-kinase-δ (PIK3CD) [4], and mitogen activated protein kinase (MAP2K1/2) [5], *KRAS* remains the most notorious driver mutation against which no effective inhibitor currently exists despite intensive research efforts [6]. The hyper-active *KRAS* mutation results in abnormally strong RAS pathway signaling which in turn drives proliferation. A KRAS mutation, by itself, may not be sufficient to transform pancreatic acinar cells into malignancy [7]. Additional mutations, frequently in tumor suppressor genes such as *TP53* or *CDKN2A*, are likely required to bypass oncogene induced senescence and ultimately transform into a truly malignant lesion [8]. Thus, advanced pancreatic cancer often harbors multiple somatic mutations [2] and aberrant expression of many signaling proteins [9].

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Another contributing factor to the poor prognosis of PDAC is the frequency of advanced disease at initial diagnosis. Only about 20% of PDAC cases are amendable to potentially curative resection [10], either due to metastasis or involvement of major blood vessels. Even after surgical resection with curative intent followed by adjuvant chemotherapy, the vast majority of these patients will still relapse with metastatic disease resulting in 5 year survival at a dismal 21% [11, 12].

Metastatic PDAC remains almost uniformly fatal and historically systemic therapy has not been particularly effective. This is evident by the nearly equal incidence and mortality of PDAC [13] with the most recent estimate of 5 year overall survival ranging from 5-10% [14]. Thus, effective therapy for metastatic PDAC is a major area of research for both National Cancer Institute (NCI) and pharmaceutical industries with rising numbers of new patent applications in the area of drug discovery and delivery.

2. FRONT-LINE SYSTEMIC CHEMOTHERAPY

The mainstay of chemotherapy for metastatic PDAC had been gemcitabine after a Phase III randomized trial demonstrated the superiority of gemcitabine over 5-flurouracil (5-FU) in quality of life and median overall survival (OS) from 4.41 months to 5.65 months [15]. Since then, multiple trials have been conducted with various combinations of chemotherapy agents with gemcitabine. Until recently, most of the trials were disappointingly negative with few exceptions

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[16]. One successful combination was erlotinib with gemcitabine, although it resulted in a very modest survival benefit of just 10 days compared to gemcitabine alone, both still reporting overall survival in the 6 months range [17]. A subsequent analysis examining risk-benefit of adding erlotinib to gemcitabine found no significant benefit compared to the increased risks of adverse effects [18]. Few studies reported overall survival beyond 6 months.

The first Phase III clinical trial showing a markedly improved overall survival was reported in a new combination therapy with leucovorin-modulated 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX) yielding a median survival of 11.1 months [19]. The triple drug combination had toxicities with 45% grade 3 or higher neutropenia, 5% febrile neutropenia, 12.7% grade 3 or higher diarrhea, and 9% grade 3 or higher sensory neuropathy. The study limited accrual to young patients with good performance status. Therefore, selecting the right patient population is critical in getting the most benefit with this triplet regimen.

Another new combination gemcitabine regimen with nanoparticle albumin bound (nab)-paclitaxel (Abraxane) was introduced in the Metastatic Pancreatic Adenocarcinoma Trial (MPACT) Phase III clinical trial [20, 21]. This gemcitabine doublet increased median overall survival to 8.7 months compared to 6.6 months with gemcitabine monotherapy. More importantly, gemcitabine plus (nab)-paclitaxel had less toxicity than FOLFIRINOX and included patients with performance status 0-2 without any exclusion based on age. Currently, this is the most widely used regimen in the community setting for patients with newly diagnosed metastatic pancreatic cancer in United States.

3. SECOND LINE SYSTEMIC CHEMOTHERAPY

In spite of the impressive gains made with the two newer regimens, FOLFIRINOX and gemcitabine with (nab)-paclitaxel, the progression free survival in both regimens remained around 6 months. This means that many patients treated with either of the two regimens will ultimately progress and require second line therapy. Even for those with preserved performance status, the benefit of second line chemotherapy over best supportive care has only been examined in two small studies with few subjects in the supportive care arm finding a trend towards improved survival with chemotherapy [22]. Large-scale studies with best supportive care as comparator arms are difficult to accrue making it unlikely that a definitive randomized study will establish a second line regimen against supportive care alone [23].

Despite the lack of evidence, second line therapy is common, particularly in clinical trials. Follow-up of the Charité Onkologie (CONKO) pancreatic cancer clinical trials showed about 50% of trial subjects received second line therapy with an overall survival of 5.1 months [12]. In the community setting where patients tend to be older than those in clinical trials [24], the actual proportion of patients receiving second line therapy is likely less than 50%.

Patients who were initially treated with FOLFIRINOX and have preserved performance status may benefit from second line therapy with gemcitabine and (nab)-paclitaxel. Portal *et al.* reported an overall survival of 8.8 months with the gemcitabine combination after progression on FOLFIRONX [25], although the objective response rate was low at 17.5%. Combined, median overall survival since initiation of first line therapy approached 18 months, a dramatic increase from the historical 6 months with gemcitabine alone for metastatic pancreatic cancer.

The majority of patients with advanced pancreatic cancer are not likely to be good candidates for intensive FOLFIRINOX therapy. Instead, most will be treated with gemcitabine alone or with (nab)-paclitaxel depending on their performance status. Progression after treatment failure with gemcitabine monotherapy or combination leaves few options.

The CONKO-003 randomized clinical trial compared infusional and bolus 5-FU (FF) with or without oxaliplatin for those who have progressed on gemcitabine monotherapy. A significant benefit was found for the addition of oxaliplatin in a regimen termed "OFF" with median overall survival of 5.9 months at the cost of increased paresthesia and neuropathy [26]. It remains to be seen whether a similar benefit can be seen in those previously treated with a gemcitabine combination therapy.

Investigators have tested irinotecan with 5-FU, known as the FOLFIRI regimen. This regimen was initially tried in the first line setting with few reports suggesting possible benefit [27], including a mixed etiology trial with 15 PDAC patients combined with 17 with gallbladder or biliary carcinoma in the locally advanced (30%) or metastatic (60%) setting [28]. While the median overall survival for the entire group was impressive at 14.5 months, the heterogeneity of the group makes it difficult to interpret the findings in metastatic PDAC. In the second line setting, promising results were noted for FOLFIRI in several small Phase I/II studies summarized in Table **1**. In particular, Gebbia *et al.* reported an overall survival of 6 months in a study of 40 patients who had progressed on gemcitabine [29]. Another study of 63 patients with metastatic PDAC who had progressed on both gemcitabine and a platinum (typically oxaliplatin) reported an overall survival of 6.6 months with FOLFIRI [30]. Unfortunately, as is typical for second line therapies, response rates were low. Most studies reported OS in the range of 5 to 6 months [31].

Irinotecan monotherapy was also tested in the second line setting. Among 33 patients treated with irinotecan for metastatic PDAC who progressed after gemcitabine therapy until progression or unacceptable toxicity, median overall survival was 6.6 months with toxicity limited mostly to nausea (64%) and diarrhea (36%) [32]. Contrasting the positive results was a report on 56 patients treated with irinotecan in the second or third line setting (after progression on gemcitabine and/or S-1, an oral fluoropyrimidine) with median overall survival of just 2.9 months [33]. The dismal survival rate may be due to the inclusion of third-line subjects in a small patient population.

In summary, second line treatment options varied with most reports finding overall survival between 3 to 6 months. Most of the studies were small and none of them were randomized clinical trials except for the CONKO-3 study. Therefore, larger confirmatory studies are warranted to prove if any of these agents are effective in refractory pancreatic cancer.

Table 1. Summary of Clinical Trials in Second Line Treatment of Metastatic Pancreatic Cancer.

Regimen	*N* (MPC)	PFS/TTP	OS	PR	SD
Gemcitabine+(nab)-paclitaxel [25], prospective cohort, multicenter, open label	57 (53)	5.1 (3.2-6.2)	8.8 (6.2-9.7)	17.5%	40.5%
FOLFIRI [29], retrospective, single institution	40 (33)	3.7 (1-6.5)†	6 (2-8.2)†	15%	35%
FOLFIRI [30], prospective, two sites, open label	63 (63)	3 (2.1-3.9)	6.6 (5.3-8.1)	8%	32%
FOLFIRI [31], prospective, multicenter, open label Phase II	50 (37)	3.2 (1-11)†	5 (1-17) †	8%	28%
FOLFIRI [28], prospective, single institution, mixed etiology, open label	21 (15)	3.5 (2.6-4.4)	6.2 (5.4-7.0)	0%	43%
Irinotecan [32], prospective, single institution, metastatic pancreatic cancer, open label Phase II	33 (33)	2.0 (0.7-3.3)	6.6 (5.8-7.4)	9%	39%

N is the Number of Patients Enrolled in the Treatment Arm and the Number with Metastatic Pancreatic Cancer (MPC) is in Parentheses. PFS is Progression Free Survival and TTP is Time to Progression in Months. OS is Overall Survival in Months. PR is Partial Response and SD is Stable Disease. Data Shown as Median with 95% Confidence Interval Except as Noted. NR is Not Reported. †Range Reported Rather than 95% Confidence Interval.

4. ENCAPSULATED CHEMOTHERAPEUTICS

Albumin bound paclitaxel represents a novel reformulation of a traditional chemotherapy drug, paclitaxel. *In vitro* studies on the potential mechanism for success of (nab)-paclitaxel over paclitaxel suggests changes in pancreatic cancer cell metabolism favoring the use of glutamine rather than glucose as the primary energy source, and their scavenging of extra-cellular proteins such as albumin to generate a glutamate energy source may preferentially target (nab)-paclitaxel to PDAC cells [34]. In addition, increased local delivery of (nab)-paclitaxel is thought to occur due to increased SPARC (secreted protein acidic and rich in cysteine) expression in stromal cells surrounding pancreatic cancer cells. SPARC binds to albumin and thus might concentrate (nab)-paclitaxel [35]. Yet, SPARC was found to be down-regulated in PDAC tissue, and no correlation was observed between SPARC expression and benefit from (nab)-paclitaxel with gemcitabine [36].

Regardless of the mechanism, clinically, (nab)-paclitaxel appears to have an advantage over unadorned taxanes. Most small studies examining taxanes alone or in combination with gemcitabine or other cytotoxic agents did not perform as well as (nab)-paclitaxel with gemcitabine [37]. Furthermore, another liposomal cationic formulation of paclitaxel, EndoTAG, was also found to be rather effective in a medium-sized Phase II clinical trial of 212 subjects with median overall survival at 9.3 months with the highest tested dose of EndoTAG [38]. Taken together, the success of (nab)-paclitaxel and promise of EndoTAG hint at the possibility of improving traditional chemotherapy agents with novel formulations or encapsulation.

Simply encapsulating old drugs may not always prove effective. Liposomal doxorubicin, for example, was found to be not effective in PDAC [39] despite showing promise in ovarian [40] and breast cancers [41]. Clearly, a distinct mechanism is at play with encapsulated chemotherapeutics in pancreatic cancer which may be dependent on the chemotherapy agent itself. In addition to encapsulating chemotherapeutic drugs, liposomes have also been proposed as a vehicle for targeted delivery of anti-cancer agents in a recent patent application using antibodies to target liposomes containing temozolomide to brain malignancies [42].

5. LIPOSOMAL IRINOTECAN

Irinotecan, in particular, may benefit from liposomal encapsulation. Irinotecan is rapidly inactivated and then cleared at neutral to basic pH, including the blood environment. The active drug form of irinotecan, SN-38, requires hydrolysis by an enzyme in the liver. SN-38 is then excreted in the bile risking gastrointestinal toxicity including the distinct adverse effect of diarrhea. Inactivation of SN-38 is by glucuronidation via the enzyme UGT1A1. Some patients have seven TA repeats in the TATA box of the UGT1A1 promoter (*UGT1A1*28* allele) resulting in decreased UGT1A1 expression and thus higher SN-38 activity at the expense of greater toxicity [33, 43].

Encapsulating irinotecan masks the pro-drug from the neutral pH of blood and thereby increases the drug half-life [44]. The major breakthrough in encapsulating irinotecan was the discovery that a multivalent anionic trapping agent such as sucrose octasulfate can be used to "trap" irinotecan within liposomes with high efficiency [45]. The addition of polyethylene glycol (PEG) with the liposome was then found to enhance drug delivery in a mouse model [46]. Using a mouse xenograft model of human colon cancer cell lines, the active metabolite of irinotecan was augmented in tumors compared to serum concentrations by approximately five-fold when irinotecan was encapsulated in a formulation designated MM-398 or PEP02 containing octasulfate bound irinotecan surrounded by a pegylated liposomal envelope (Fig. **1**) [47]. A Phase I pharmacokinetic study in advanced solid malignancies found higher area-under-curve (AUC) levels of MM-398 compared to historical data on free-base irinotecan, likely due to the observed decrease in peak concentration and markedly increased half-life [48]. Unfortunately, intra-tumoral levels were not reported and therefore it remains to be determined whether liposomal irinotecan increases drug concentration within tumors in human subjects.

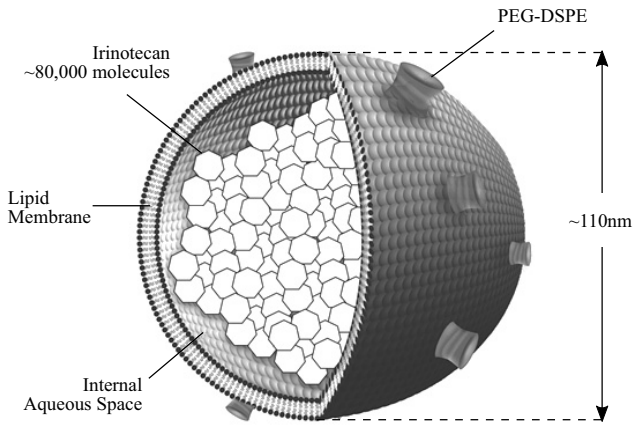

Fig. (1). Schematic of nanoliposomal irinotecan (nal-IRI) molecule consisting of a liposomal envelope decorated by poly(ethylene glycol) distearoylphosphatidylethanolamine (PEG-DSPE) about 110nm in diameter surrounding irinotecan molecules. *Schematic courtesy of Merrimack Pharmaceuticals and used with their permission.*

In addition, liposomal encapsulation might target chemotherapy to specific niche target organs, e.g. liver and spleen, increasing its effectiveness against disseminated metastatic disease. However, the tissue distribution of liposomal irinotecan in humans has not been extensively studied or reported. Peggylated distearoylphosphatidylethanolamine (DSPE) liposomes containing irinotecan, e.g. MM-398, were found to be markedly higher in blood, lower in liver and lung, and higher in intestines compared to free-base irinotecan in a mouse model [46]. How this tissue distribution contributes to liposomal irinotecan's efficacy is not clear. In particular, the increased distribution to intestines and decreased distribution to liver and lungs is particularly concerning for disadvantages of liposomal encapsulation. Sites of metastatic disease often include liver and lung, and GI toxicity is the principal adverse effect of irinotecan. At least one patent application has suggested the utility of attaching targeting ligands such as antibodies or antibody fragments to target specific cell types [42].

Patent Review of Liposomal Irinotecan

A search for world-wide patents containing the terms "liposome" and "irinotecan" in the abstract on the PATENTSCOPE web application [49] yielded 46 patent applications, 14 of which are recent (since 2010). Of the 14, five are from Merrimack Pharmaceuticals for combination therapy with liposomal irinotecan for pancreatic cancer [50]. Most of the others are duplicates of liposomal formulation in various countries. One was for using antibody decorated liposomes for targeting [42]. A search for all US patents with the keyword "liposome" and "irinotecan" resulted in only 4 issued patents. The earliest was issued to NeoPharm in 2005 for "Liposomal formulation of irinotecan" where irinotecan was mixed with cardiolipin and envisioned for use as anti-neoplastic therapy [51]. Next in 2010 Yoshino *et al.* was issued a patent covering the use of ion gradients to increase drug loading [52]. In 2013, Bally *et al.* patented the process of encapsulating irinotecan in an acidic buffer with copper ions and optionally an ionophore with improved drug retention [53].

There have been multiple patent filings on generating liposomal irinotecan, but many have lapsed or have been withdrawn [54-56]. Liposomal irinotecan encapsulated by sucrose octasulfate was patented by Hermes Biosciences in 2005 [57] and subsequently transferred to Merrimack Pharmaceuticals. In June 2013, Merrimack Pharmaceuticals filed a patent for treatment of pancreatic cancer using liposomal irinotecan combinations [50].

Efficacy and Safety

The effectiveness of nanoliposomal irinotecan (nal-IRI, MM-398, or PEP02) (nal-IRI) was shown in a small open-label, non-randomized Phase II clinical trial of 40 patients with metastatic PDAC who have progressed on gemcitabine-based therapy [58]. Median overall survival was 5.2 months with diarrhea as the most common adverse effect (75%), as expected for irinotecan's mechanism of action. Grade 3 or higher adverse effects were primarily neutropenia, leukopenia, and abdominal pain. Severe diarrhea (grade 3 or higher) was reported in 15%. Severe (grade 3) fatigue was reported in 20% of the patients, but this may be due to cumulative toxicity of prior therapy rather than toxicity from nal-IRI itself.

Liposomal irinotecan was then tested in a large, international, open-label randomized clinical trial comparing nal-IRI and folinic acid modulated 5-flurouracil (FF), alone or in combination, in the NAPOLI-1 trial [59]. Most of the patients had metastatic PDAC and progressed on gemcitabine-based therapy (88%). 417 patients were randomized into three groups: liposomal irinotecan monotherapy given at 100mg/m^2 free-base equivalent every 3 weeks, FF monotherapy with 200mg/m^2 folinic acid intravenously followed by 2000mg/m^2 5-flurouracil (5-FU) over 24 hours weekly for 4 weeks out of the 6 week cycle, or the combination 70mg/m^2 free-base equivalent of liposomal irinotecan followed by 400mg/m^2 folinic acid intravenously and 2400mg/m^2 5-FU continuous infusion over 46 hours every 2 weeks. While the total amount of free-base irinotecan administered is about one-third that of comparable irinotecan containing regimens such as FOLFIRI [28] or FOLFIRINOX [19], the Phase I pharmacokinetic study suggested that liposomal irinotecan AUC was about three times that of free-base irinotecan. Nevertheless, the median duration of treatment for nal-IRI monotherapy or combination therapy was about 9 weeks with a 6-week mean dose intensity of 167.5mg/m^2 out of planned 210mg/m^2 (80%) and 188mg/m^2 out of planned 200mg/m^2 (94%), respectively. About one third of test subjects required dose reductions in both the combination and monotherapy arm. Subjects identified to be homozygous for the *UGTA1A*28* polymorphism (about 5% in each arm) had the initial liposomal irinotecan dose reduced by 20mg/m^2 and increased to standard dose if tolerated. Objective response rates were 16% for the combination of liposomal irinotecan and FF compared to 1% with FF alone. Irinotecan monotherapy resulted in 6% objective response rate. Median overall survival was 6.1 months (95% CI 4.8-8.9) with the combination, a statistically significant improvement over FF alone at 4.2 months (hazard ratio (HR) 0.67, 95% CI 0.49-0.92). Liposomal irinotecan monotherapy resulted in 4.9 months OS (95% CI 4.2-5.6) and was not significantly better than FF alone (HR 0.99, 95% CI 0.77-1.28).

The pre-specified sub-group analyses did not show any particular sub-group to have a statistically significant advantage or disadvantage.

The most frequent adverse event for arms containing nal-IRI reported was diarrhea (65%), consistent with Phase II clinical trial results and the known mechanism of action of irinotecan, but only 13% were grade 3 or higher in the combination nal-IRI arm and 21% in nal-IRI monotherapy. The most common grade 3 or 4 adverse event was neutropenia (27%) followed by fatigue (14%) for combination nal-IRI with FF. Febrile neutropenia was relatively rare at 3% with the combination therapy and compared favorably with FF monotherapy (4%). In summary, nal-IRI with FF appeared safe and was superior to FF alone.

NAPOLI-1 is the largest multicenter randomized Phase 3 clinical trial conducted in refractory pancreatic cancer that showed superiority of combination treatment (liposomal irinotecan and 5-FU) with 6.1 months overall survival over infusional 5-FU alone. The hazard ratio (HR) of 0.66 (95% confidence interval 0.48 to 0.91) in the CONKO 003 is very comparable to that of liposomal irinotecan (Table **2**) over FF (HR 0.67). However recent Canadian PANCREOX study have shown that there was no survival benefit of adding oxaliplatin over 5-FU treatment [60]. Absent a head-to-head study comparing OFF to nal-IRI with FF, the relative efficacy and safety of the two regimens can only be surmised from dangerous cross-trial comparisons. However one practical benefit of liposomal irinotecan is lack of neurotoxicity associated with both oxaliplatin and taxane derivatives. With recent FDA approval, combination liposomal irinotecan and 5-FU is becoming standard of care in patients who fail gemcitabine based therapy in United States.

6. CURRENT & FUTURE DEVELOPMENTS

In addition to encapsulation, new efforts are underway to modify existing agents to generate new therapies. Phospho-compounds of valproic acid and farnesylthiosalicyclic acid have shown promise in pre-clinical testing. Phospho-valproic acid (MDC-1112), a novel valproic acid derivative, inhibited the growth of human pancreatic cancer xenografts in mice by 60%-97% by targeting STAT3 [61]. Phospho-farnesylthiosalicylic acid (MDC-1016), a novel farnesylthiosalicylic acid derivative, is a direct Ras inhibitor and significantly reduced pancreatic tumor growth in two complementary models of pancreatic cancer [62].

Alternative approaches to targeting Ras are also showing promise. Bunda *et al.* recently showed that targeting SHP2, a tyrosine phosphatase which increases Ras mediated activation of downstream signals, is an effective way to inhibit mutant *KRAS* activity in a glioblastoma model [63]. Whether the same approach would be effective in pancreatic cancer remains to be seen. In addition, locking mutant KRAS in an inactive, GDP bound state, has been successfully reported with a small molecule inhibitor, ARS-853 [64]. The clinical efficacy of such an approach needs to be tested.

Identifying new biomarkers remains an important task not just for earlier diagnosis but also as potential therapeutic target. Cadherin-2 (CDH2 or N-cadherin) is up-regulated in PDAC [65, 66] and could serve as a potential biomarker. While screening for monoclonal antibodies suitable for use in antibody-drug conjugates, a monoclonal antibody against MUC13 was identified and over-expression of MUC13 reported for PDAC cells [67]. There is already a patent application proposing to use CDH2 or MUC13 as both biomarkers and therapeutic targets [68].

Merrimack Pharmaceuticals also has a patent application describing the use of contrast-enhanced MRI to identify patients who may benefit the most from encapsulated drug therapies such as nal-IRI [69]. No publications to date have reported on the use of contrast enhanced MRI in selection of liposomal drugs.

It is important to note that a critical aspect of testing new therapies is an accurate model of pancreatic cancer. Traditionally, preclinical models of pancreatic cancer used human pancreatic cancer cell lines cultured *in vitro* on flat plastic surfaces. Such models lack the complex, 3-D, tumor microenvironment present in PDAC. The development of genetically-engineered mouse models that recapitulate pancreatic cancer pathogenesis have been useful [70], but the presence of germline mutations driving carcinogenesis makes its translation to human sporadic disease tenuous. Improved models such as patient-derived tumor xenografts grown in immunodeficient mice move closer to personalized medicine but lack an intact immune response thought to be

Table 2. Comparison Between CONKO-003 and NAPOLI-1 Trial Results Show Remarkable Similarity in Their Hazard Ratios.

Trial	Regimen	*N* (MPC)	PFS	OS	HR
CONKO-003[26]	Oxaliplatin with 5-FU (OFF)	76 (67)	2.9 (2.4-3.2)	5.9 (4.1-7.4)	0.66 (0.48-0.91)
	5-FU (FF)	84 (74)	2.0 (1.6-2.3)	3.3 (2.7-4.0)	1.0
NAPOLI-1[60]	Nal-IRI with 5-FU	117 (117)	3.1 (2.7-4.2)	6.1 (4.8-8.9)	0.67 (0.49-0.92)
	Nal-IRI alone	151 (151)	2.7 (2.1-2.9)	4.9 (3.6-4.9)	0.99 (0.77-1.28)
	5-FU (FF)	149 (149)	1.5 (1.4-1.8)	4.2 (3.3-5.3)	1.0

N is the Total Number of Patients in Each Arm and the Number of Patients with Metastatic Pancreatic Cancer (MPC) is Shown in Parentheses. Median Progression Free Survival (PFS) in Months with the 95% Confidence Interval is Shown along with Median Overall Survival (OS) in Months with 95% Confidence Interval in Parentheses. The Hazard Ratio (HR) and its 95% Confidence Interval is also Shown with the Referent Group Fixed at 1.0 and Shaded. Note that for the NAPOLI-1 Trial, nal-IRI Monotherapy was Compared with a Distinct FF Subgroup, but the Results are Very Similar to the FF Subgroup Used as Comparator for the Combination Arm which is Shown in the Table above.

an important part of the microenvironment. The use of syngeneic mice permits transfer of neoplastic tissue from germline modified mice into wild-type mice with an intact immune system addresses these issues but can only be used to study pancreatic cancers from mice [71]. More recent models using 3-D tissue culture techniques of patient derived pancreatic tumors, organoids, can be used to model pancreatic cancer [72] and for drug screening [73,74].

Beyond metastatic PDAC, new effective therapies are also useful in the adjuvant and neoadjuvant setting. Adjuvant chemotherapy with gemcitabine [12] or FF [11] has been shown to be superior to surgery alone, but relapses remain common. How newer agents, alone or in combination, might fare in the adjuvant and neoadjuvant setting is currently being tested in clinical trials [75]. Meta-analysis of small neoadjuvant chemotherapy trials did not show a convincing benefit, but none of the trials used (nab)-paclitaxel or nal-IRI [76]. A small, single institution report indicates that the combination gemcitabine with (nab)-paclitaxel can be safely used in the neoadjuvant setting, but the benefits compared to surgery alone remain to be tested in a larger randomized trial [77]. The use of nal-IRI in combination with FF or OFF in the frontline setting is currently being investigated as a Phase II, randomized, open-label trial (NCT02551991). Substitution of irinotecan in FOLFIRINOX with nab-paclitaxel (FOLFOX-A) is also being tested in metastatic pancreatic cancer (NCT02080221). Perhaps the use of newer, more effective, systemic chemotherapy agents can change the landscape of neoadjuvant chemotherapy and hopefully upset the balance of incidence and mortality in PDAC.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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