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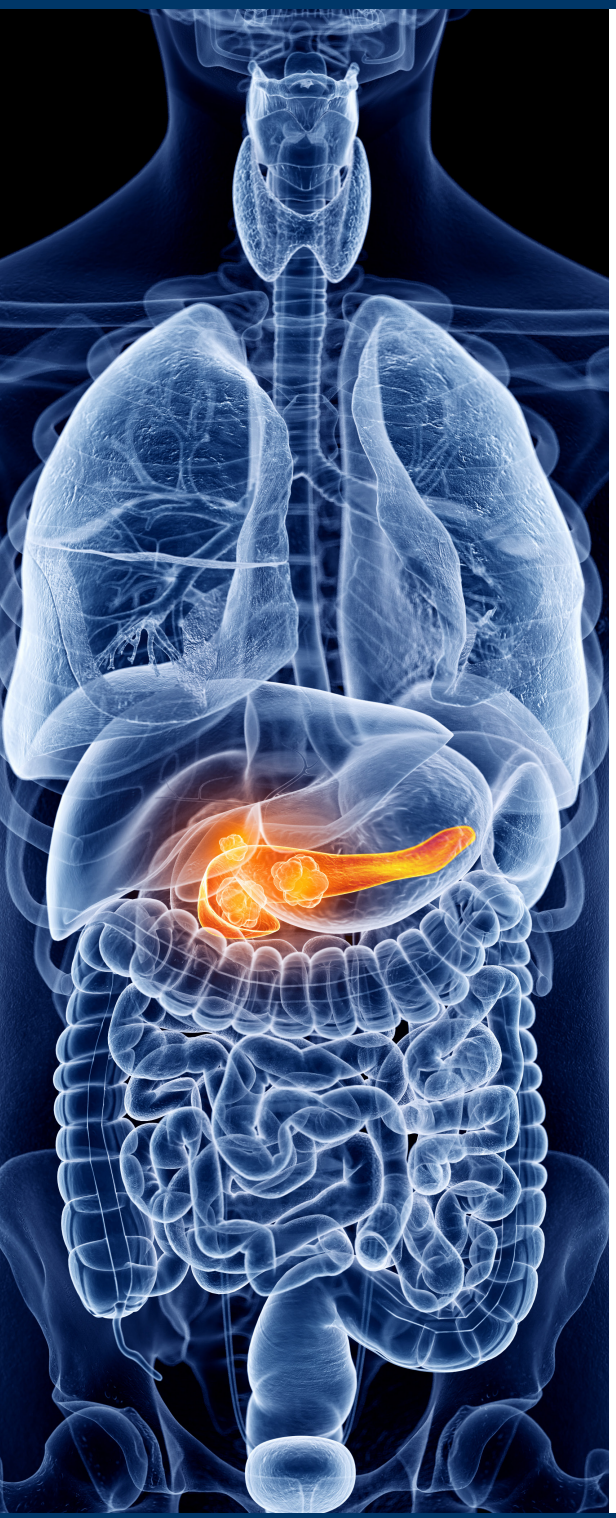

Integrating Novel Targeted Treatment Strategies to Advance Pancreatic Cancer Care

Introduction

***American Journal of Hematology/Oncology®*:** How is pancreatic cancer typically classified? What has been the historical approach to treating pancreatic cancer, and how is it changing?

Tanios Bekaii-Saab, MD, FACP: When we refer to pancreatic cancer, typically we refer to adenocarcinoma of the pancreas. So, whenever we use the term *pancreatic cancer*, it typically relates to that. There are other forms of pancreatic cancer that include pancreatic neuroendocrine tumors; then the rare tumors, including acinar cell sarcomas; and even lymphoma that have been described in the pancreas. Overwhelmingly, pancreatic cancer relates to adenocarcinoma of the pancreas.

In terms of the historical approach to treating pancreatic cancer and how it's changing, in 1997, we had the first drug approval for pancreatic cancer, and that was gemcitabine (Gemzar). It really was the only agent available to us for quite a while. In the mid-2000s, we had an addition, a drug called erlotinib (Tarceva). Erlotinib is a tyrosine kinase inhibitor that targets *EGFR* and when added to gemcitabine seems to improve outcomes versus gemcitabine alone. This essentially has very modestly improved outcomes at the expense of significant cost and toxicity. It never really became a true standard and ultimately disappeared from our armamentarium.

In 2010, a study was positive with folinic acid (leucovorin), 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) versus gemcitabine in the first-line setting, and led to adopting FOLFIRINOX for selected patients, specifically younger and higher-performing patients. And then ultimately, gemcitabine with nanoparticle albumin-bound paclitaxel (nab-paclitaxel) showed improvement over gemcitabine alone. This was after 20 to 30-plus phase III studies of gemcitabine plus "drug X" or "drug Y" failed to show an improvement. Gemcitabine plus nab-paclitaxel showed improvement in outcome versus gemcitabine alone and has led to a new standard for pancreatic cancer.

Note: Portions of this transcript have been edited for clarity and style.

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Activity Overview
Oncology Briefings™ is an online interactive monograph and print supplement that includes an overview of novel chemotherapeutic and targeted therapies for the treatment of patients with metastatic pancreatic cancer. Discussion includes pharmacodynamic and pharmacokinetic rationales behind novel treatment strategies, clinical data leading to new approvals, and treatment-related adverse events to monitor. A national thought leader interprets presented data and provides key take-home points and clinical pearls for practice to place the content into clear perspective. Audio sidebars and tables provide supporting evidence for this activity.

Target Audience
This educational initiative is directed toward medical oncologists, endocrinologists, radiation oncologists, and surgeons who treat patients with pancreatic cancer. Nurse practitioners, nurses, physician assistants, pharmacists, researchers, fellows, and other healthcare professionals interested in the treatment of pancreatic cancer are also invited to participate.

Learning Objectives
Upon completion of this activity, participants should be better prepared to:

- Describe pharmacodynamic and pharmacokinetic approaches to the management of advanced forms of pancreatic cancer
- Report clinical trial evidence on the efficacy of liposomal irinotecan and other novel treatments for the management of metastatic pancreatic cancer
- Place clinical trial findings on novel targeted approaches into the context of evolving treatment paradigms in the field of advanced pancreatic cancer management
- Detail differential toxicity profiles and approaches in multiple lines of therapy to mitigate the impact of treatment-related adverse events in the care of patients with metastatic pancreatic cancer

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Pancreatic cancer is the fourth-leading cause of cancer-related deaths in the United States, with incidence rates increasing.[1] More than 53,000 new cases of pancreatic cancer were estimated to be diagnosed in the United States alone in 2017, with over 43,000 deaths expected.[2] The 5-year overall survival (OS) rate for all patients with pancreatic cancer across all stages is only 8.2%. For the 52% of patients with metastatic pancreatic cancer at diagnosis, the 5-year OS rate is falls to 2.7%.[1,2]

Pancreatic cancers comprise a heterogeneous group of both endocrine and exocrine malignancies; however, more than 90% of pancreatic malignancies are pancreatic ductal adenocarcinomas (PDACs).[1] The majority of patients with pancreatic cancer receive their diagnosis at an advanced stage, with only less than 10% of cases confined to local disease.[2] The incidence of PDAC and other pancreatic cancers increases with age; the median age at diagnosis is 70 years.[2]

Patients with pancreatic cancer can present with nonspecific symptoms, including fatigue and abdominal pain. For PDAC, more-specific symptoms include jaundice, new-onset diabetes, and weight loss. Other conditions, including thromboembolism, often do not present until after the patient has developed metastatic disease.[3,4]

Chemotherapy remains the primary treatment for patients with advanced pancreatic cancer.[1] Burris and colleagues demonstrated the efficacy of gemcitabine monotherapy for these patients compared with 5-fluorouracil (5-FU) in 1997.[5] A total of 23.8% of patients experienced some form of clinical benefit on gemcitabine treatment, including symptom alleviation and a modest survival benefit. The 12-month OS rate was 18% for patients receiving gemcitabine compared with 2% for patients receiving 5-FU.[5]

Depending on performance status (PS), first-line treatment options for patients with metastatic disease include a combination of folinic acid (leucovorin [LV]), 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX); gemcitabine in combination with albumin-bound paclitaxel; and for select patients with borderline-low PS, gemcitabine monotherapy.[6] Gemcitabine in combination with erlotinib is no longer a recommended option.[6]

Although gemcitabine monotherapy has been the historical standard, recent advances in chemotherapy have modestly transformed the pancreatic cancer treatment landscape.[6] FOLFIRINOX became an option based on results from the phase III PRODIGE study out of France.[7] Further advancements include: the September 2013 approval of nanoparticle albumin-bound (nab)-paclitaxel in combination with gemcitabine as a first-line treatment option, following the results of the phase III MPACT trial[8]; the October 2015 approval of nanoliposomal irinotecan (nal-IRI) in combination with 5-FU and LV for the treatment of patients with metastatic pancreatic cancer following progression on gemcitabine-based therapy, based on the results of the phase III NAPOLI-1 trial[9]; the continued investigations into the role of PARP inhibitors and PD-1 checkpoint inhibition in patients with microsatellite instability-high (MSI-H) pancreatic cancers[6]; and the ongoing investigations into novel agents such as napabucasin and pegvorhyaluronidase alfa (PEGPH20).[10,11]

Novel Chemotherapy Strategies

Liposomal Irinotecan

How does liposomal irinotecan work? What is the mechanism and rationale behind its use?

Liposomal irinotecan is essentially a nanoliposomal formulation that includes close to 80,000 molecules of irinotecan in every nanoliposomal element. The goal with nanoliposomal formulations is largely to allow more prolonged exposure to the agent so that the patient technically gets a higher dose of the drug. The concept behind liposomal formulations is that the drug leaks mainly into the vasculature areas that are compromised, such as around the tumor. This is where you get a longer residence time. They are very distorted blood vessels, and release of active chemotherapeutics is directly into the tumor, with very low systemic leakage.

Indeed, if you look at the kinetics of the drug in early human studies, it seems that it has a very low systemic leakage rate, meaning most of the drug remains intact until it hits the tumor. Before that, it circulates for quite a while. It can stay around in the circulation for about a week while it continuously releases the drug.

Theoretically, the goal with this formulation is to increase the level of exposure at the tumor level. Because you're technically giving a higher concentrated dose of the drug, you hope that the low systemic leakage rate prevents change in the toxicity profile. Indeed, when you look at this agent, the toxicity profile looks very similar to what you would expect from irinotecan, except for 1 difference: alopecia is significantly lower with the liposomal formulation.

To understand the utility of novel chemotherapeutic strategies for the treatment of pancreatic cancer, one must understand the pharmacologic rationale behind

liposomal-based drug delivery systems. Liposomes were first described in 1965 by Bangham and colleagues, who detailed the similarities between the liquid crystals and the cell membrane.[12] Liposomes are generally spherical vesicles made up of lipid bilayers with an internal aqueous cavity, in which molecules, including chemotherapy drugs, can be sequestered from external solvents.[13] Drug sequestration in liposomes allows for increased retention in vivo.[13]

Irinotecan is a cytotoxic topoisomerase I inhibitor that demonstrated efficacy for patients with metastatic pancreatic cancer in the second-line setting, as a monotherapy and in combination with other agents.[14] However, when metabolized, irinotecan is associated with heterogeneous dose-limiting toxicities, particularly neutropenia and diarrhea.[15] These limitations led to the development of liposomal formulations that could improve efficacy and distribution of the drug while minimizing toxicity.[16,17]

Pharmacokinetic studies have shown that the liposomal irinotecan formulation remains in circulation for a longer period ($t_{1/2}$ = 10.7 hours) compared with free irinotecan ($t_{1/2}$ = 0.27 hours). Further, the release of irinotecan from the liposome itself increased the half-life of drug release up to 56.8 hours.[17]

Liposomal irinotecan was approved for use in patients with metastatic pancreatic cancer in late 2015. Can you talk about the NAPOLI-1 trial that led to this approval?
In 2015, we had the next approval, based on the NAPOLI-1 study with liposomal irinotecan, in patients who had failed prior gemcitabine therapy, and so it was approved for second- and third-line therapies. NAPOLI-1 was designed to look at 5-fluorouracil [5-FU] plus nanoliposomal irinotecan [nal-IRI] versus nal-IRI alone. It ultimately showed a significant improvement in outcome with the combination of nal-IRI plus 5-FU.

This led to an additional option for us in the second- and third-line settings following gemcitabine failure, after which we did not have any options except the folinic acid (leucovorin), 5-FU, and oxaliplatin (FOLFOX) regimen, based on German data that were positive but that were confounded by negative data from Canada. A third study with oxaliplatin plus a fluoropyrimidine from Asia also did not look too promising. And so, for the longest time, we mainly used oxaliplatin-based regimens based on scattered data. That was until we had this phase III study that changed the standard to a nal-IRI–based therapy following gemcitabine plus nab-paclitaxel failure.

Liposomal irinotecan was investigated in the phase III NAPOLI-1 trial (NCT01494506).[14] In this study, 417 patients were randomized 1:1:1 to receive nal-IRI monotherapy (n = 151), 5-FU plus LV (n = 147), or a combination of the 3 (n = 117). Patients in the nal-IRI monotherapy arm received 120 mg/m^2 (equivalent to 100 mg/m^2 of free irinotecan) every 3 weeks. Patients in the 5-FU/LV arm received 2000-mg/m^2 5-FU plus 200-mg/m^2 LV in a 6-week cycle. Patients in the nal-IRI/5-FU/LV arm received 80-mg/m^2 nal-IRI (equivalent to 70 mg/m^2 of free irinotecan) plus 2400-mg/m^2 5-FU and 400-mg/m^2 LV every 2 weeks.[14]

TABLE 1. Grade 3-4 Adverse Events With nal-IRI in Gemcitabine-Refractory Metastatic Pancreatic Cancer[14]

Adverse Event	Combination (n = 117) No. of Patients (%)	Monotherapy (n = 147) No. of Patients (%)	5-FU/LV Control (n = 134) No. of Patients (%)
Diarrhea	15 (13)	31 (21)	6 (4)
Vomiting	13 (11)	20 (14)	4 (3)
Nausea	9 (8)	8 (5)	4 (3)
Decreased appetite	5 (4)	13 (19)	3 (2)
Fatigue	16 (14)	9 (6)	5 (4)
Neutropenia	32 (27)	22 (15)	2 (1)
Anemia	11 (9)	16 (11)	9 (7)
Hypokalemia	4 (3)	17 (12)	3 (2)

5-FU indicates 5-fluorouracil; LV, leucovorin; nal-IRI, nanoliposomal irinotecan; No., number.

Median OS for patients receiving nal-IRI/5-FU/LV was 6.1 months (95% CI, 4.8-8.9) compared with 4.2 months (95% CI, 3.3-5.3) in the 5-FU/LV group. The hazard ratio (HR) was 0.67 (95% CI, 0.49-0.92; *P* =.012). Median OS was similar in patients who received nal-IRI monotherapy and the combination with 5-FU/LV: 4.9 months (95% CI, 4.2-5.6) and 4.2 months (95% CI, 3.6-4.9), respectively (HR, 0.99; 95% CI, 0.77-1.28; *P* = .94).[14]

These data led to the October 2015 approval of nal-IRI in combination with 5-FU and LV for the treatment of patients with metastatic pancreatic cancer with disease progression following gemcitabine-based therapy.[9]

In the NAPOLI-1 trial, approximately 30% of patients treated with liposomal irinotecan, either as monotherapy or a combination, experienced adverse events (AEs) requiring a dose reduction.[14] This compared with only 4% of patients treated with 5-FU/LV requiring dose reductions. At a lower dose in combination therapy, liposomal irinotecan showed a more tolerable toxicity profile.[14]

Grade ≥3 AEs from NAPOLI-1 are noted in **Table 1**.[14] Strategies to reduce these adverse effects include dose reduction, medication interruption, antidiarrheal agents, and anticholinergic agents.[18]

Nanoparticle Albumin-Bound Paclitaxel

Can you discuss the results of the pivotal MPACT trial investigating nab-paclitaxel and gemcitabine? How does paclitaxel differ from free paclitaxel?

The MPACT trial led to the approval of nab-paclitaxel and gemcitabine, as discussed, as first-line therapy for patients with metastatic pancreatic cancer. About 60% to 70% of patients in the United States become exposed to nab-paclitaxel and gemcitabine in the first-line treatment of patients with metastatic pancreatic cancer.

So, what is the difference between nab-paclitaxel and regular paclitaxel? The difference, really, is in the delivery. Nab-paclitaxel is nanoparticle albumin bound. It's specifically an albumin-bound formulation of paclitaxel that theoretically incurs 2 advantages. One advantage is that you can give it over a shorter amount of time. Plus, because you don't have to use Cremophor EL [now known as Kolliphor EL] formulations, the risk of hypersensitivity or allergic reactions to the carrier has been eliminated with the nanoparticle albumin-bound formulation.

The pancreatic stroma is so dense, it makes it very difficult for chemotherapy to integrate into the stroma and reach the cancer site. The other advantage, at least theoretically, is the formulation itself; with the help of a protein called secreted protein acidic and rich in cysteine [SPARC], it supposedly has higher access to the tumor. Unfortunately, in the larger studies, when they looked at the effects of SPARC protein expression, it didn't seem to correlate with improvement in outcome. So I think it remains relatively unknown whether the albumin-bound formulation will actually improve that aspect versus free paclitaxel. We don't have any data in pancreatic cancer that compare nab-paclitaxel with free paclitaxel. The same is true for nal-IRI versus standard irinotecan. But these are the agents that were tested, and the results were positive.

The nab-paclitaxel formulation is designed to deliver paclitaxel to tumors via interaction with albumin receptors that mediate drug transport.[19] In 2005, Gradishar and colleagues demonstrated the clinical benefit of nab-paclitaxel over solvent-based paclitaxel in patients with metastatic breast cancer.[19] Nab-paclitaxel was also demonstrated to be efficacious in patients with non–small cell lung cancer by Socinski and colleagues in 2012.[20]

Following the success of this formulation in other cancers, nab-paclitaxel was investigated in combination with gemcitabine for patients with metastatic pancreatic cancer in the phase III MPACT trial (NCT00844649).[21] In this trial, 861 patients were randomized to receive 125-mg/m^2 nab-paclitaxel plus 1000-mg/m^2 gemcitabine weekly for 3 of 4 weeks or gemcitabine alone weekly for 7 of 8 weeks. Following the first cycle of 8 weeks, during all subsequent cycles, treatment was administered weekly for 3 of 4 weeks.[21]

TABLE 2 Grade 3/4 Adverse Events With nab-Paclitaxel and Gemcitabine in Metastatic Pancreatic Cancer[21,22]

Adverse Event	nab-Paclitaxel Combination (n = 421)	Gemcitabine Monotherapy (n = 402)
	No. of Patients (%)	No. of Patients (%)
Neutropenia	153 (38)	103 (27)
Leukopenia	124 (31)	63 (16)
Thrombocytopenia	52 (13)	36 (9)
Anemia	53 (13)	48 (12)
Fatigue	70 (17)	27 (7)
Peripheral neuropathy	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Any	326 (77)	205 (51)
AEs leading to death	18 (4)	18 (4)

AE indicates adverse event; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; No., number.

Patients receiving nab-paclitaxel had an improved median OS of 8.5 months compared with 6.7 months for patients receiving gemcitabine alone (HR, 0.72, 95% CI, 0.62-0.83; P <.001). Progression-free survival (PFS) was also higher for patients receiving the nab-paclitaxel combination than gemcitabine alone: 5.5 months versus 3.7 months, respectively.[21]

In the MPACT trial, approximately 77% of patients receiving the nab-paclitaxel combination experienced at least 1 grade ≥3 AE compared with 51% of patients receiving gemcitabine monotherapy. The number of patients experiencing any AE was greater (326, 77%) in the nab-paclitaxel-plus-gemcitabine arm compared with the gemcitabine-alone arm (205, 51%).[22] The nab-paclitaxel combination was associated with high rates of leukopenia, neutropenia, diarrhea, fatigue, and peripheral neuropathy.[21] Patients receiving the combination also experienced measurable rates of anemia (any grade) or thrombocytopenia, although not significantly higher than the proportion of patients receiving gemcitabine alone.[21] Grade ≥3 AEs from MPACT are noted in **Table 2**.[21,22]

Recently published data on a modified regimen of biweekly nab-paclitaxel (125 mg/m^2) plus gemcitabine (1000 mg/m^2) administered on days 1 and 15 suggested an acceptable toxicity profile and relative efficacy in pancreatic

cancer.[23] The modified regimen has been widely adopted in selected patients with advanced disease.

How do you decide between nab-paclitaxel and FOLFIRINOX for your patients with metastatic pancreatic cancer? How does the approval of liposomal irinotecan change your approach?

There are 2 ways that the combination of gemcitabine and nab-paclitaxel is typically administered. The standard way comes from the pivotal MPACT trial, which gave us weekly gemcitabine/nab-paclitaxel 3 weeks in a row with a 1-week break. And there's a modification that is utilized in about 30% to 40% of practices in the United States, specifically in patients who are low performing, but quite a sizable number of patients. That's the biweekly gemcitabine-and-nab-paclitaxel formulation, which is based mostly on a retrospective study that looked at institutional experience with the regimen in close to 60 patients. It showed that you may keep an essentially similar efficacy profile for the biweekly regimen compared with the weekly regimen, while significantly cutting down on the toxicities. The majority of patients remains on the weekly regimen.

We mentioned also that there was another study in the first-line setting, FOLFIRINOX versus gemcitabine. That was a French-only study, so it was French sites, mostly centers of excellence, with a highly selected patient population. Patients had to be less than age 76 years, and so were primarily more highly performing patients. The outcomes with this regimen versus gemcitabine were quite significant, almost a doubling of survival with an improvement in progression-free survival [PFS]. Historically, survival that is seen with FOLFIRINOX is considered superior to nab-paclitaxel with gemcitabine. However, when we look at more modern studies, mostly US-based studies, we see survival that is approximately the same between the 2 regimens—gemcitabine/nab-paclitaxel, and FOLFIRINOX—despite the fact that patients who go on FOLFIRINOX are more highly selected. This raises the question, "Is a doublet inferior to a triplet in this setting?" And because there have never been any direct comparisons, most of the data we have relate to indirect comparisons.

Some of these will depend on looking at the demographics of the study. So, the gemcitabine/nab-paclitaxel study, the MPACT study, was essentially a worldwide study with a large cohort from Eastern Europe with less access to second-line or salvage therapies. That is certainly a limitation. In some parts of the world, care is less optimal than in the centers of excellence in France, where patients were randomized to FOLFIRINOX versus gemcitabine. That's 1 factor.

The other element that's interesting is that there was one study from the US Oncology Network that looked at real-world surrogate markers. These were mostly surrogate markers of PFS and overall survival (OS) for patients who received gemcitabine/nab-paclitaxel and FOLFIRINOX through the network. Intriguingly, what this study showed is that there's not much of a difference between one backbone and the other, placing in doubt whether we really need to intensify treatment—in other words, give a 3-drug regimen versus a 2-drug regimen in the first line.

Now, the fact that we do have a second-line option for patients with gemcitabine-based regimens, nal-IRI plus 5-fluorouracil (5-FU), which tends to have nonoverlapping toxicities, brings an interesting concept. In a disease where we never thought we'd have options that work through multiple lines of therapy, we have 2 studies in the first line and the second line that seem to carry some improvement. Then, the concept of sequencing starts rising again, similar to the same concept in different cancers. In lung cancer, breast cancer, and colon cancer, we prefer sequencing strategies versus what I call the whole kitchen sink approach, which is pretty much what FOLFIRINOX is. My bias is actually in favor of starting with gemcitabine/nab-paclitaxel and then to follow patients with nal-IRI plus 5-FU.

What genetic or patient factors affect your choice of chemotherapy?

There are certainly cohorts of patients who may benefit from the addition of a platinum. Those are the patients who have established *BRCA* or *PALB* germline or somatic mutations, mutations that do respond to topoisomerases and platinums. FOLFIRINOX may be reasonable for those patients. I would argue that gemcitabine/cisplatin also has some really good data in that group of patients, so a doublet could suffice with cisplatin.

I think that the options right now are a little bit different. It's good to have options. We have nab-paclitaxel, gemcitabine, and FOLFIRINOX. They seem to be on equal footing, I think, if you use them correctly and in the correct patients. And then, access to second-line regimens perhaps would favor more

of a 2-drug approach in the first line and a 2-drug approach in the second line, rather than a 3-drug approach in the first line, whereby there are no significant data to tell us or to inform us about what to do in the salvage setting.

What's arising is similar to that of other cancers: trying to understand which subgroups of patients are most likely to benefit from certain therapies. Pancreatic cancers are mostly *KRAS*-mutated, *KRAS*-driven tumors for more than 90% of patients in the metastatic setting. But what we find is that there are a very small percentage of patients, about 0.5%, who actually have microsatellite instability–high (MSI-H) features. This is the rare patient, usually in the setting of Lynch syndrome; however, these patients tend to respond quite significantly with PD-1 inhibitors. In fact, I have personal experience with a couple of patients who have had significant responses, including a complete response in 1 patient who had actually failed traditional chemotherapy.

So, this is certainly exciting. Unfortunately, it's an incredibly uncommon event, but with the approval of pembrolizumab for all cancers with MSI-H disease, I tend to check all of my patients with pancreatic cancer for MSI in hopes of finding that 1 in 200 or 1 in 500 patient. So, in large practices such as ours, this may make sense because we have the capacity to do it. I understand that certain practices may have more challenges, and perhaps will have difficulty, as well, in screening all patients for MSI-H disease.

Physicians must consider a patient's PS when selecting a chemotherapy regimen, as well as consider second-line options. First-line treatment recommendations include clinical trials, FOLFIRINOX, and nab-paclitaxel in combination with gemcitabine.[6]

In general, the choice of second-line therapy for metastatic pancreatic cancer depends on the first-line treatment, the patient's PS, present comorbidities, and residual toxicities from frontline treatment. The recent addition of liposomal irinotecan as an option for second-line therapy in metastatic pancreatic cancer adds to the treatment armamentarium and provides an option for patients who are refractory to first-line gemcitabine therapy. Recommendations for second-line therapy for advanced disease that has failed prior gemcitabine-based therapy include nal-IRI plus 5-FU and LV (preferred), FOLFIRINOX; LV, 5-FU, and oxaliplatin (FOLFOX); and capecitabine plus oxaliplatin (less preferred).[6,24] Referral to a clinical trial is preferred for the majority of patients with PDAC.[6,24]

How do you manage treatment-related toxicities in your patients across treatment strategies? What key factors do you look out for?

Any time you intensify your treatment regimen, the toxicities are going to be worse. Let's say we start with FOLFIRINOX, and what we expect is significant fatigue and significant drops in blood counts. In fact, what we do commonly in the United States is typically give all patients who are scheduled to receive FOLFIRINOX a growth factor support, as well, along with FOLFIRINOX. In Europe, it remains mostly FOLFIRINOX, and then for patients who actually end up with neutropenia, there is initiation of granulocyte colony-stimulating factor support. That ends up actually being quite a significant number of patients.

The other toxicities can include diarrhea and neuropathy from oxaliplatin. That actually limits exposure to oxaliplatin beyond 4 to 5 months. Most patients who start on FOLFIRINOX will end up on FOLFIRI or 5-fluorouracil [5-FU] alone after 4 to 5 months of therapy. Often, the toxicities that emanate from FOLFIRINOX carry over to the second line, making it very difficult to apply second-line regimens unless the patient's performance status remains stellar and the toxicity is minimal.

With gemcitabine/nab-paclitaxel, although it's a doublet, it's not necessarily a regimen that has a low toxicity profile. And the large majority of the toxicities are hematologic. Because of the weekly administration, oftentimes on day 8 or day 15, but more commonly on day 8, the doublet gets skipped. In fact, the results of one study suggested that in more than 40% of patients who end up with dose reductions or modifications, their outcomes did not seem to be compromised. There was a suggestion that their outcomes may be slightly better than of those who actually stayed with a weekly dose. This could be an effect of the fact that patients get longer exposure and end up with more doses, but this was not clear from that paper. I think the gist of it is that dose reductions don't seem to affect outcomes—dose intensity per se does not seem to affect the outcome.

So, with gemcitabine/nab-paclitaxel, in addition to the hematologic toxicities for the weekly regimen, there's also neuropathy. The risk for neuropathy is about 17% at grade 3. Most patients actually end up having some dose modifications or dropping the nab-paclitaxel after 4 to 5 months of therapy. So that certainly is limiting. As I mentioned before, the

biweekly regimen seems to cut down significantly on the risk of both hematologic toxicity and neuropathy. The risk of neuropathy drops down to 2% with a biweekly regimen, which tends to be favored in our institution.

The one thing about gemcitabine/nab-paclitaxel is that it also allows us to utilize nal-IRI plus 5-FU in the second line because that's where we have data. Again, the NAPOLI-1 study had only about 13% of the patients receive prior nab-paclitaxel, but all patients had prior exposure to gemcitabine. The other thing that is important to keep in mind with nal-IRI plus 5-FU is that there are very few overlapping toxicities with gemcitabine and nab-paclitaxel, unlike FOLFOX, which has become less favored because of its questionable efficacy. However, FOLFOX also tends to have overlapping toxicity with nab-paclitaxel; nal-IRI plus 5-FU does not, for the most part. And so, it fits well into that sequencing strategy. Nanoliposomal irinotecan and 5-FU have a very similar toxicity profile to FOLFIRI—mostly some gastrointestinal [GI] toxicities and some neutropenia. As I mentioned before, alopecia tends to be less of a problem with the nanoliposomal formulation versus traditional irinotecan.

Emerging Targeted Therapies

PARP Inhibition

Where do PARP inhibitors stand in the management of pancreatic cancer?

The other target that I think is incredibly interesting is the one that we referred to a little bit, where platinums may actually have a role, but also topoisomerase inhibitors such as irinotecan and nal-IRI. Those are patients with *BRCA*-driven tumors—*BRCA* and *PALB*. Both germline [and] somatic mutations in *BRCA* seem to do well with platinum-based therapies as well as the emerging PARP inhibitors. PARP inhibitors seem to play an important role in this subgroup of patients, and this continues to evolve.

A number of studies are looking at the role of PARP inhibitors in pancreatic cancer selected for *BRCA* or *PALB*. The 2 agents right now that seem to be the most promising are olaparib and rucaparib. Both have single-agent activity that is close to 20% in patients who are heavily pretreated and have received prior therapy. Again, single-agent activity of close to 20% of pancreatic cancers with selected patients. Some of these responses actually tend to last for more than a year, with some even crossing beyond that point.

I think that that subgroup of patients seems to be a subgroup that may have exquisite sensitivity to PARP inhibitors. Strategies to improve on that with the addition of chemotherapy are underway—whether that's with a platinum or liposomal irinotecan or irinotecan-based therapy.

Veliparib is another PARP inhibitor that is being looked at in pancreatic cancer. However, the response rate with this agent, even in selected patients, has been quite dismal. In fact, it's probably the only PARP inhibitor right now that does not seem to have an indication, including in diseases that are known to respond well to PARP inhibitors. So unfortunately, I think veliparib is an unlikely candidate for a PARP inhibitor to continue development in pancreatic cancer. There are other PARP inhibitors that are also being looked at, but I think right now that among the 3, only rucaparib and olaparib seem to have a path moving forward; I don't think veliparib will have any path moving forward in pancreatic cancer.

PARP inhibitors have established clinical efficacy and demonstrated improvement in PFS in multiple cancer types, including ovarian and breast cancers associated with germline *BRCA1/2* mutations, or the phenotype referred to as BRCAness.[25] The underlying biology of PARP inhibitors also suggests that treatment may prove beneficial in other commonly *BRCA*-mutated cancers, including prostate and pancreatic cancers. In a multitumor phase II study investigating olaparib, an objective response rate (ORR) of 21.7% (95% CI, 7.5%-43.7%) was demonstrated in patients with pancreatic cancer.[25] A phase II investigation in rucaparib, another PARP inhibitor, showed an ORR of 16% in patients with metastatic pancreatic cancer with at least 1 prior line of therapy.[26,27]

Investigations continue for both agents. Rucaparib is currently being investigated in a phase II study (NCT03140670) for patients with *BRCA*- or *PALB*-mutated pancreatic cancer that has not progressed on platinum therapy,[28] as well as in another phase II study (NCT03337087) in combination with nal-IRI, 5-FU, and LV in patients with metastatic pancreatic and other cancers.[29] Olaparib is currently under investigation in the placebo-controlled phase III POLO trial (NCT02184195) for patients with germline *BRCA*-mutated pancreatic cancer that has not progressed on platinum-based chemotherapy,[30] as well as 2 phase II trials investigating PARP inhibition in patients with pancreatic cancer that displays BRCAness (NCT02511223; NCT02677038).[31,32]

STAT3 Inhibition

What about the STAT3 inhibitor napabucasin? Can you discuss its clinical development so far?
The question is, of course, what's next? We've talked about traditional chemotherapy. We've talked about microsatellite instability-high cancers, where we know PD-1 inhibitors seem to make a difference. We've talked about *BRCA*-mutated cancers, where homologous recombination–deficient patients seem to be moving in the direction of PARP inhibitors, with or without chemotherapies. So what other emerging therapies seem to be very promising in this disease?

Two therapies right now are being explored in phase III trials. One is an agent called napabucasin, and another one is pegvorhyaluronidase alpha. Napabucasin is essentially a cancer cell stemness inhibitor that technically targets STAT3 as well as the beta-catenin pathway and has been found—at least in preclinical settings—to inhibit cancer cells that have acquired stemness or stem cell properties. Essentially, what that means is that those cells are very resistant to chemotherapy and to radiation therapy, and these cells tend to be like seed cells—the cells that ultimately continue to produce new cancer cells and metastasize.

The agent is oral and has been looked at in pancreatic cancer along with gemcitabine and nab-paclitaxel before moving to phase III. The results of the study with the most updated data were last presented at the ESMO Gastrointestinal meeting. It was an oral presentation with napabucasin plus gemcitabine/nab-paclitaxel, a phase IB trial. A little more than 60 patients were included in the study, and the response rate in the evaluable patients was 55% in a disease where you would not expect the response rates with the gemcitabine/nab-paclitaxel combination to be higher than 30%, which was a significant outcome measure. Also, the progression-free survival as well as the overall survival looked very promising, at least in the early readout. Final readouts are being made. But the cumulative data suggest that this would be a very interesting combination to go forward with.

And now we have CanStem 111P, which is a phase III study looking at gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel plus napabucasin, already underway around the world and in the United States. This study will help us to better understand the role of this agent plus gemcitabine/nab-paclitaxel. If the results of the phase Ib exploratory study hold, there may be a good path for this agent to become a part of our standard of care. But, again, we won't know until the final results of the study, which is currently underway.

Napabucasin, a first-in-class cancer stemness inhibitor, is currently under development for patients with metastatic pancreatic cancer. A STAT3 inhibitor, napabucasin is able to inhibit gene transcription in cancer stem cells, slowing the growth of cancer. At the 2017 ESMO Congress on Gastrointestinal Cancer, results of a phase Ib/II study of napabucasin in combination with nab-paclitaxel and gemcitabine in 66 patients with metastatic PDAC were reported. The disease control rate was 93% and the ORR was 55%, including 2 complete responses.[33]

Further investigation into the role of napabucasin in pancreatic cancer is currently underway in the phase III CanStem111P trial (NCT02993731),[29] which is recruiting participants. This trial will be comparing the combination of napabucasin plus nab-paclitaxel and gemcitabine with nab-paclitaxel and gemcitabine alone. CanStem111P is estimated to reach its primary completion date in December 2020.[34]

PEGPH20

PEGPH20 has been shown to increase response and progression-free survival (PFS) in patients with high levels of hyaluronic acid (HA). Can you discuss its current role and clinical development?
The other agent that also seems to be interesting is PEGPH20, which is essentially a hyaluronidase inhibitor. PEGPH20 technically disrupts the stroma around the tumor and allows increased access of chemotherapy to the cancer site. That's the whole concept of it. The primary analysis combining this agent with gemcitabine/nab-paclitaxel versus gemcitabine/nab-paclitaxel alone showed a very modest improvement with the combination. And then, when patients were selected for HA, the PFS and the response rate seemed to improve significantly—especially PFS. The trial was small but exploratory, and the difference was quite significant. The response rate was slightly increased, and the overall survival was about the same, at least statistically.

This led to the phase III study that is currently underway randomizing patients to receive gemcitabine/nab-paclitaxel plus or minus PEGPH20 based on selection for high levels of HA. There was a small hiccup in the development of this agent with a SWOG study that looked at FOLFIRINOX plus or minus PEGPH20. That study was actually stopped prematurely for what was considered lack of benefit from adding PEGPH20 to FOLFIRINOX. However, this current study was not selected for high levels

of HA. Certainly, the fact that it did not show any improvement has been a slight setback, but I don't think that should stop us from continuing to move forward with completing the phase III study with its intent for patients with high HA. And, again, we're eagerly awaiting more results from the FOLFIRINOX study as well as the completion of the phase III study.

TABLE 3. Ongoing Clinical Trials in Pancreatic Cancer

Intervention	Phase	NCT No. (Name)	Primary Completion
nal-IRI + 5-FU + leucovorin ± oxaliplatin vs nab-paclitaxel + gemcitabine	II	NCT02551991	October 2018
Olaparib vs placebo	III	NCT02184195 (POLO)	May 2018
Olaparib (single arm)	II	NCT02511223	September 2017
Olaparib (single arm)	II	NCT02677038	November 2019
Rucaparib + nal-IRI + 5-FU + leucovorin	I/II	NCT03337087	December 2021
Rucaparib (single arm)	II	NCT03140670	July 2021
PEGPH20 (vs placebo) + nab-paclitaxel + gemcitabine	III	NCT02715804 (HALO-109-301)	October 2018
Napabucasin (vs placebo) + nab-paclitaxel + gemcitabine	III	NCT02993731 (CanStem111P)	December 2020
Ibrutinib (vs placebo) + nab-paclitaxel + gemcitabine	II/III	NCT02436668 (RESOLVE)	March 2018
Modified FOLFIRI + veliparib vs FOLFIRI	II	NCT02890355	May 2019

5-FU indicates 5-fluorouracil; FOLFIRI, folinic acid (leucovorin), 5-FU, irinotecan, and oxaliplatin; nab-paclitaxel, nanoparticle albumin-bound paclitaxel; nal-IRI, nanoliposomal irinotecan; NCT, National Clinical Trial; PEGPH20, pegvorhyaluronidase alpha.

PEGPH20 is also currently being explored as a treatment for patients with metastatic pancreatic cancer following promising results. A pegylated recombinant form of human hyaluronidase, PEGPH20 works to prevent HA accumulation in the tumor microenvironment, reducing tumor pressure and vascular compression, and increasing drug delivery of other anticancer agents.[11] In the phase II HALO-109-202 study (NCT01839487), patients receiving PEGPH20 in combination with nab-paclitaxel and gemcitabine had an ORR of 46% compared with 34% for nab-paclitaxel and gemcitabine alone. In the exploratory group, PFS for patients with high levels of hyaluronan was 9.2 months for patients receiving the PEGPH20 combination compared with 5.2 months for patients in the control group. Median OS was higher for patients receiving the hyaluronidase compared with the control group: 11.5 months versus 8.5 months, respectively.[11]

The phase III HALO-109-301 (NCT02715804) study is further investigating this combination, and is currently recruiting participants. HALO-109-301 is estimated to reach its primary completion date in December 2019.[35]

A summary of selected ongoing trials in pancreatic cancer is listed in **Table 3**.

Conclusion

The number of agents available for the treatment and management of pancreatic cancer has greatly expanded in the recent years. Novel chemotherapy formulations such as nab-paclitaxel have created additional treatment options in the first-line setting. Another advancement, liposomal irinotecan, further expands options for patients in the second-line setting. Additional agents, including PARP inhibitors, checkpoint inhibitors, tumor stem cell inhibitors, and pegylated hyaluronidase, are under investigation with the hope to get them incorporated into the pancreatic cancer treatment armamentarium.

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