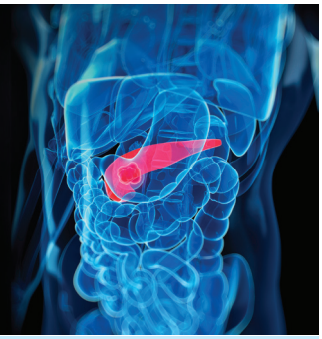
EXPERT perspectives

Advances in the Management of Pancreatic Cancer: From Bench to Bedside



OVERVIEW

In this program, Eileen M. O'Reilly, MD, reviews the molecular pathogenesis and genetics of pancreatic cancer, and outcomes for different subsets of patients; talks about identifying patients who should be referred for management to a high-volume treatment center; and discusses the importance of clinical trial participation that takes into account the patient treatment goals, as well as identifying patient subgroups that may differentially benefit from certain types of therapies – ie, moving toward precision medicine in this disease.

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Content Areas

- Molecular pathogenesis and genetics of PDAC
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CE STATEMENT

Target Audience

The target audience is oncologists and other health care providers who care for patients with pancreatic cancer.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Review the outcomes for different subsets of patients with pancreatic cancer (knowledge)
- Identify patients who should be referred for management at a high-volume treatment center (knowledge)
- Apply the NCCN guidelines to develop treatment plans (competence/performance)
- Develop a personal policy for discussing clinical trial participation with patients that takes into account the low enrollment into trials, the need for trial participation, and patient treatment goals (performance)

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Epidemiology: Molecular Pathogenesis Genetics of PDAC

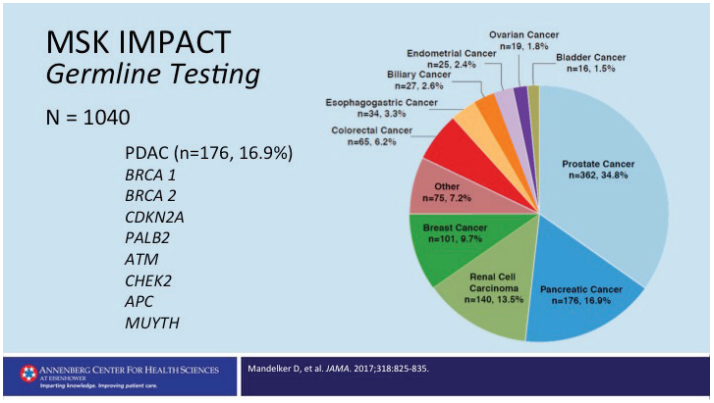
Pancreatic cancer poses a number of challenges, not least of all is that the incidence of this disease is on the rise. It's anticipated that this year in the US there will be over 55,000 people diagnosed with this cancer. It ranks disproportionately high on the list of leading causes of cancer-related mortality relative to its incidence, and there's been a steady—about a half to 1%—increase in the frequency of this disease over the last number of decades. If we take into account all-comers diagnosed with this disease, the 5-year overall survival (OS) is about 8%; but it is of note that OS has been slowly but steadily increasing.

A common question is, why is this cancer so challenging? There are many factors that are put forward. We know that the microenvironment in the whole stromal context is very important with this disease, and it provides a physical barrier to drug delivery—it's relatively avascular, and it's hypoxic—so it can be considered a hostile microenvironment. Also, the genetics of PDAC are complex in that we see a number of frequent tumor suppressor genes and oncogenes that are mutated, none of which are effectively targetable in 2018. However, there are a number of lower frequency genetic events, some of which are targetable in this disease.

Arguably, we do not have validated biomarkers for routine treatment decision-making, although during the course of this review, we'll touch upon some that have become and are increasingly integrated into practice. And I think it's fair to say that, while our current therapies may work well for a proportion of patients, there's an inherent primary and acquired treatment resistance to the best available agents that we have in practice.

Looking at the molecular pathogenesis of PDAC, this has now been a well-described pathway for development of this disease where normal ductal epithelial cells undergo progressive neoplastic change to pancreatic intraepithelial neoplasia (PanIN) 1, PanIN 2, ductal carcinoma in situ, and ultimately invasive cancer. Timelines for this may be protracted over several decades, and as this process happens, there's an accumulation of genetic changes that are characteristic of each PanIN time point. And it's also important to know that PanIN 1 is common as we all get older, and probably the committal step in terms of development of invasive disease comes up at a level of PanIN 2.

What about the genetics of pancreatic cancer? We know that at least 10%, and that's probably a conservative figure, of this disease is associated with a genetic predisposition, and in some there are a number of single gene mutations that are well described. So, for example, hereditary breast and ovary cancer syndrome, via 2 breast cancer susceptibility genes (BRCA1 and BRCA2), contributes to the risk of this disease. The Lynch syndrome genes that are associated with stomach, endometrial, and urothelial malignancies, account for a small proportion of the incidence of this malignancy. And then there is a group of individuals where we see 2 and sometimes 3 relatives in a family where we do not know what the genetic link is, but presumably there is a genetic link that just has not been identified yet for these individuals. And that's actually the biggest group, that have a potential familial predisposition to develop this cancer.



This is an analysis from ~1,000 patients who underwent initially somatic profiling in pancreatic cancer, and then this was an evaluation of the paired germline genetic analysis that was done across a variety of cancers at Memorial Sloan Kettering. In this first pass of 176 patients with PDAC, we identified that about 16% had a germline genetic mutation, with BRCA1, BRCA2 being most common, the next most common was CDKN2A, and then PALB2, ATM, and a number of other lower-frequency events.

We did a further and deeper analysis on this, and, of importance, about half of these germline mutations occur in genes that are associated with DNA damage repair. The potential implication of that, for the individual affected, is that there may be therapeutic opportunities targeting these gene mutations, and we'll review this in the section on therapeutics and emerging advances in a later stage of disease.

So, what to do for high-risk families? These are families where a number of individuals have a confirmed diagnosis of PDAC. So, there are a few healthy lifestyle recommendations that are made. For example, we counsel people not to smoke, to have a healthy, balanced diet, and to remain as active as possible. And for healthy family members of these families where there are several individuals that have been diagnosed with PDAC, we recommend enrollment on screening registries and potential consideration of trials. And these family members may also benefit from counseling by genetics counselors in terms of evaluating their individual risk of this disease.

This is a very active area, and to sum up here with regard to the genetics and epidemiology for pancreatic cancer, we know a lot about the development of this disease. Identifying individuals of high risk is a challenge, although there are subsets of individuals that may be identified. Healthy lifestyle recommendations are important for families where we see multiple members with PDAC. And for each individual diagnosed with this disease, we recommend, now, routine genetic testing, both on the blood, with regard to the family germline mutations, and with regard to the tumor.

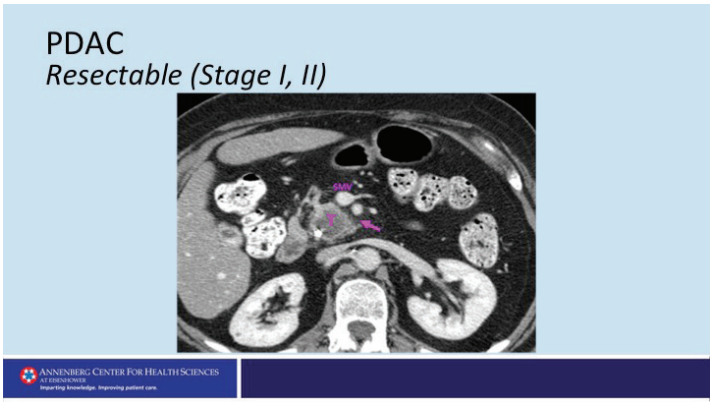
We have covered here the genetics and the development of PDAC. In terms of the carcinogenesis process, we've discussed some of the major genes that are mutated in this

disease and the cardinal ones being KRAS, P53, SMAD4, and CDKN2A, none of which are effectively targetable at this time.

We reviewed that it's important to recognize that pancreatic cancer is a genetic disease and that about 10%—maybe 15%—of individuals have an underlying genetic connection in their family, some of which we have identified as single gene mutations, much of which we do not know at this current time. And for individuals and families at risk for this disease, we recommend consideration of enrollment in high-risk registries. We recommend healthy lifestyle approaches in terms of no smoking, being active, and attention to diet.

Localized PDAC Adjuvant Therapy Neoadjuvant Therapy

This is an example of what a resectable pancreas cancer looks like. If you look at the T, that's the tumor, it's a hypovascular lesion. There's a stent in place there. And in this graphic, you'll see that the superior mesenteric vessels are clear of the tumor. There's a fat line, so there's a good probability that if this individual went directly to the operating room, that a complete removal would be able to be done.

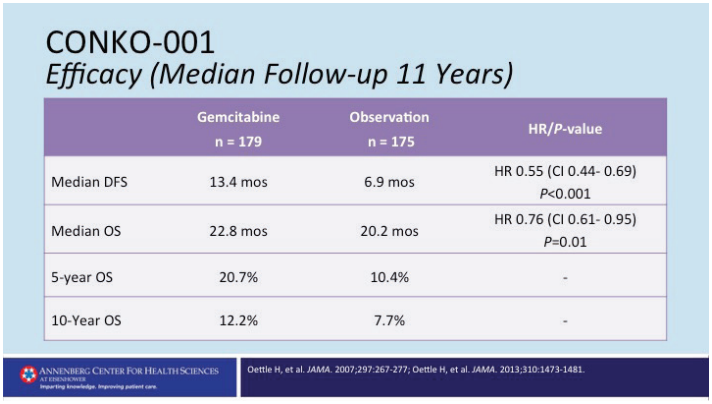


With regard to staging of localized PDAC, we have the AJCC classification, but of greater utility is the breaking up of PDAC into the spectrum of resectable disease and locally advanced, and unresectable, which is characterized by T4 tumors with arterial involvement, where it isn't possible to do a complete or a zero oncologic resection. And then that group of tumors in the middle, which are about 15% of people with PDAC presentation called borderline resectable disease, where there are venous involvements but not encasements, and to a lesser extent, limited arterial involvement. And the designation of borderline resectable means that an individual technically could go to the operating room tomorrow, but there's a high probability of having a margin-positive resection, so we don't recommend that. And increasingly, this group of patients is recommended neoadjuvant therapy.

It is important to emphasize the role of high-volume treatment centers with improved diagnostic management and complex multidisciplinary decision-making. We know that surgical outcomes are optimized when patients are treated in centers where there's a high level of expertise in looking after patients with PDAC, and that includes not only the surgical care, but the postoperative care, management of complications, and the optimal use of systemic therapy, radiation therapy where it's indicated, and integration of targeted opportunities where they exist for individuals.

Looking at resectable and borderline disease, for patients who have operable PDAC, the traditional approach is upfront surgery followed by adjuvant systemic therapy. If there's suspicion of more advanced disease, for example, if an individual has a very elevated CA 19-9 level or a distal site—so a body or tail location—then often it will be recommended to do a laparoscopy to rule out subradiological disease before committing to a complete resection.

An area of evolution, in terms of approach, is to recommend neoadjuvant therapy for patients with resectable PDAC. We don't have randomized trial data to indicate that this is a superior approach, but there's been a move in that direction by surgeons and medical oncologists for patients with resectable cancer. We have some studies that will mature out over the next year or so that will further inform the data to support this approach in this population. And we talked about an upfront systemic therapy for resectable disease often including chemoradiation, and subsequently surgical resection is the paradigm that's undertaken.

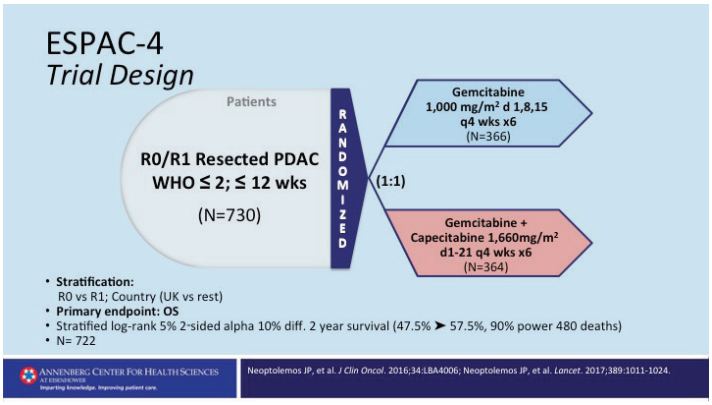


Adjuvant therapy is a standard of care essentially for all patients who undergo resection, and I'm talking about now patients who go directly to surgery. A traditional approach was evaluating gemcitabine, and the data to support this comes from the CONKO-001 trial looking at gemcitabine compared to observation for resected PDAC. These are the data that were reported now a number of years ago that showed that there was a significant improvement in disease-free survival (DFS) for patients who received gemcitabine compared to observation, supported by a more modest improvement in median overall survival (OS), likely related to the fact that a lot of patients who were allocated to the observation arm went on to receive gemcitabine as their therapy in the advanced disease setting.

For many years, that was the standard of care. We also have data supporting the value of fluorouracil and leucovorin. This trial had 2 components. One of the analyses compared 5-flurouracil (5-FU) and leucovorin (LV) given in the old Mayo Clinic style (every 4 weeks) compared to no chemotherapy. As you can see, there was a clearly superior statistical difference in outcome. And a subsequent trial compared

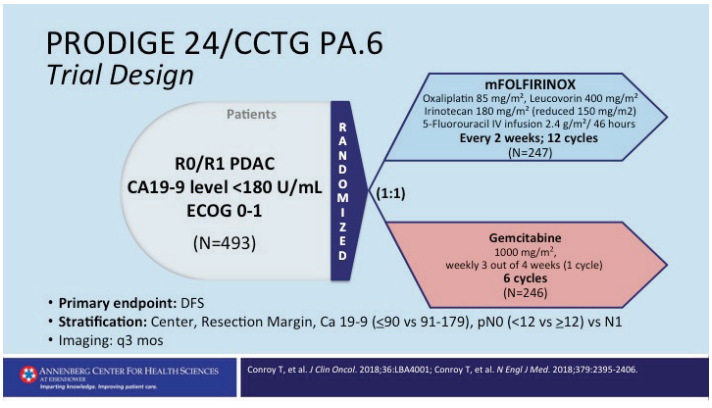
5-FU/LV to gemcitabine, that was ESPAC-3, and showed that these were similar.

I'm going to focus on the more recent studies that have led to practice change. The first of these is ESPAC-4. These data were presented a couple of years ago, and now fully reported in *The Lancet*. Essentially, the trial looked at the combination of gemcitabine and capecitabine compared to gemcitabine in a large cohort of patients, approximately 730. This study was conducted primarily in the UK and some European countries, with a primary endpoint of overall survival.



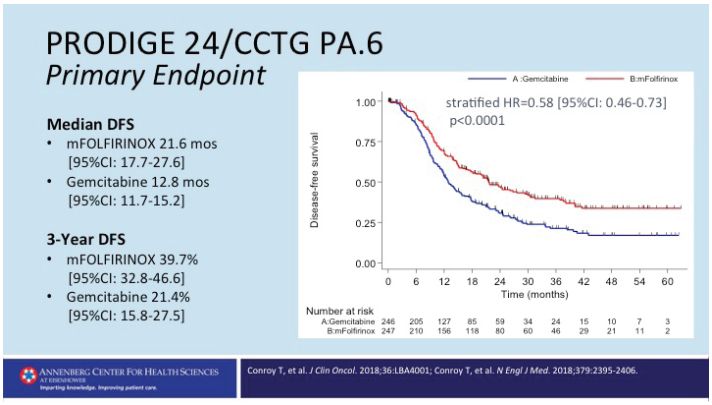
There was a statistically significant improvement in OS for the gemcitabine-capecitabine combination compared to gemcitabine on its own. And for the period of 2016 and '17 and early part of 2018, gemcitabine and capecitabine has been, for many, the go-to regimen for patients with resected PDAC.

However, we have significant data that's led to a major practice change in 2018. These data were presented by Dr. Conroy and colleagues at ASCO in the spring of 2018. The trial compared modified FOLFIRINOX to gemcitabine. Again, this was a population that went directly to surgery. Patients



were stratified based on their R0 or R1, so margin positive vs negative resection status. The CA 19-9 level had to be less than 180 at the time of enrollment. Patients had to have a good performance status, and primary endpoint here was a DFS, and patients underwent imaging every 3 months.

A few points about the chemotherapy. It started at full dosing of FOLFIRINOX. However, during the conduct of the study, it was noted that there was a significant rate of grade 3 diarrhea that led to an upfront reduction of the dose of irinotecan to 150 milligrams per meter squared, and this was instituted after about a third or so of patients were enrolled.



Here are the key data: primary endpoints, median DFS, modified FOLFIRINOX was 21.6 months compared to gemcitabine, which was 12.8 months. And I'll make the point here that the gemcitabine population did, for the DFS endpoint, as we would have expected, from multiple prior studies—and we've looked at some of the CONKO data and the ESPAC data, so that number is very familiar. Hazard ratio here was very significant at .58 and *P* value less than .0001. So, these are important outcomes.

There was an OS of almost 4½ years for patients who received modified FOLFIRINOX compared to those who received gemcitabine. So, point to note here that some of the impact in terms of OS comes from what patients received at the time of disease recurrence, and for those on the 5-FU arm, it was gemcitabine-based regimens. For those on the gemcitabine arm, it was 5-FU based regimens. For those with modified FOLFIRINOX, they received gemcitabine-based regimens and vice versa for the gemcitabine alone arm.

That's the best outcome we've seen in any trial in any setting in PDAC. I'll also note that for the gemcitabine-treated population, the survival here for ECOG 0 to 1 patients is significant, and that survival also exceeds any prior study in the adjuvant setting. And, of course, this is attributed in part to patient selection. So, making the point again that these were fit patients, performance status is 0 to 1, low CA 19-9, and have undergone a successful resection, all of which contributes to improved outcome.

So what data are pending here? The RTOG 0848 study has completed enrollment. This trial will evaluate the addition of adjuvant chemoradiation after patients have received either gemcitabine or a gemcitabine-based combination in the adjuvant setting, and we look forward to seeing those data in the not-too-distant future. And the APACT trial, which evaluates gemcitabine with or without nab-paclitaxel, in a resected patient population, very similar to the design of the modified FOLFIRINOX trial. This trial will likely mature out in 2019, and it's possible this will add to the standard of care choices for patients receiving adjuvant therapy after successful resection.

Here are the key points with regard to adjuvant therapy. It's now a recommended consideration for all patients who are well enough to receive postoperative treatments.

Adjuvant Phase 3 Trials
Pending Data

Sponsor	Trial	N
RTOG 8048 NCT01013649	Gemcitabine/Combination +/- ChemoRT Erlotinib randomization removed Primary: OS	952
APACT NCT01964430	Gemcitabine +/- Nab-Paclitaxel Primary: DFS **(accrual complete; pending 2019)**	800
Italy GIP-2 NCT02355119	FOLFOXIRI vs Gemcitabine Primary: DFS	310

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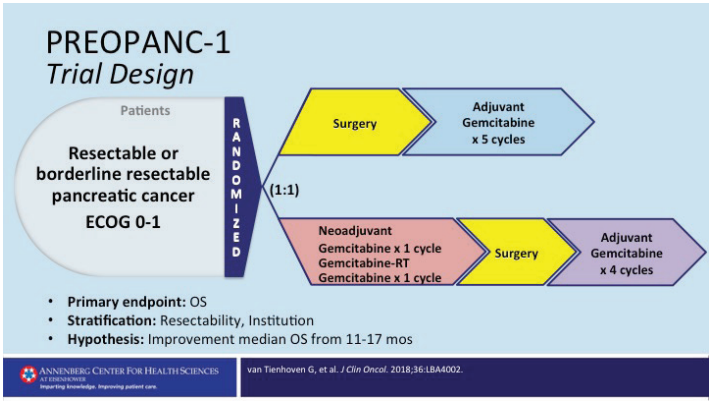
Traditionally, it's been gemcitabine, or where gemcitabine wasn't feasible, a fluoropyrimidine-based approach. In the mid-2000s, gemcitabine and capecitabine, and now I think FOLFIRINOX or modified FOLFIRINOX, displaces all of the other considerations. Having said this, there will be consideration for patients who have less robust performance status to use less intense combinations such as gemcitabine, capecitabine, or, indeed, single-agent gemcitabine. With regard to the role of chemoradiation, I think we have to wait for data regarding the RTOG 0848 study, to identify whether there are subsets of patients in which we should routinely recommend adjuvant chemoradiation.

A couple of comments on neoadjuvant therapy. It's a "standard approach" in the study of borderline resectable PDAC and stems from the high risk of systemic failure; the ability to avoid a surgery for patients who present with systemic disease; we also know that a significant group of people who do undergo surgery are not well enough to be able to receive adjuvant therapy in a timely way, and that means that theoretically, neoadjuvant therapy may get more modalities of treatment, be it systemic therapy, be it radiation or surgery, into more people, and that in and of itself could improve outcomes; and there's some data, certainly when radiation's included, that margin-negative resection rates are higher and lymph node retrieval rates and lymph node positivity rates are lower. I think with modern cytotoxic regimens, there's evidence that we can truly downstage some patients.

The con of course is that we may lose the ability to successfully resect patients. That, in my opinion, speaks to biology and probably not the treatments per se, and that an individual who demonstrates early disease progression probably would not have benefited from an upfront surgical approach in the first place.

Speaking of recent data, the PREOPANC-1 trial was presented at ASCO this year, and this looked at a neoadjuvant chemoradiation approach compared to a traditional surgery and adjuvant gemcitabine approach. And I'll just point out here that the treatment was essentially single-agent systemic therapy, so not what we recommend or use. But the point to note is that it really does support the notion that a neoadjuvant paradigm may have value for patients. So, in this trial, and preliminary analysis, there was a clear hint that patients who receive neoadjuvant therapy had an improvement in outcomes. So, this question



really needs to be asked and answered with modern-day combination cytotoxics—those studies are being planned at this time—and similarly for DFS.

And just to sum up, with regard to neoadjuvant and adjuvant therapy, we're actually awaiting a lot of studies that are on the relatively-speaking smaller side, mostly phase 2s, one phase 3 here, that will potentially inform this question for patients with borderline resectable disease and with patients with resectable disease. And these studies are here for your reference.

Neoadjuvant/Adjuvant Trials
Pending Data

Study	Duration	N	Treatment Arms	Endpoint
NEOPAC NCT01521702	2009-2014	310	Neoadj GemOxaliplatin + Adjuvant GemAdjuvant Gemcitabine	DFS
NCT01150630 Phase 2 (3) PACT-15	2010-1016	88	Adjuvant Gemcitabine (control) **23%**[2] Adjuvant PEXG **50%**[1] **Neoadjuvant/adjuvant PEXG 66%**[1]	Ph 2 Event-Free 1-Yr (Ph 3 OS)
NEPAFOX Phase 2-3 NCT02172976	2014-2020	126	Resectable, Borderline resectable Neoadj/Adj FOLFIRINOX Adjuvant Gemcitabine	OS 24 months
SWOG S1505 NCT02562716	2015-2018	150	Neoadj/adj FOLFIRINOX/FOLFOX Neoadj/Adj Gem/nab-Paclitaxel	OS 24 months
NEONAX Phase 2 NCT02047513	2015-2019	166	Perioperative Gem/nab-Paclitaxel Adjuvant Gem/nab-Paclitaxel	DFS 18 months
HEAT NCT01077427	2012-2017	336	Adjuvant Gemcitabine Adjuvant Gem+Cisplatin+Hyperthermia	OS 24 months

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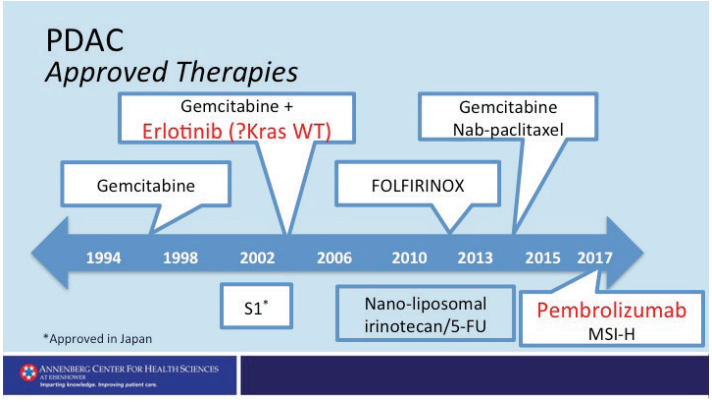
1. Reni M, et al. *Lancet Gastroenterol Hepatol*. 2018;3:413-423.

Summing up now with regard to where we are with treatments for localized disease, for resectable PDAC. The main approaches are upfront surgery, followed by adjuvant therapy, and that adjuvant therapy for a fit patient is modified FOLFIRINOX. For patients that are less robust, gemcitabine-capecitabine, or single-agent gemcitabine. For patients who have borderline resectable disease, with venous involvement or limited arterial involvement, an increasing strategy for neoadjuvant therapy with chemotherapy and/or chemoradiation. We have studies underway from one of the North America cooperative group, the Alliance, evaluating the potential benefit of adding radiation to this group.

And for resectable disease on its own, neoadjuvant therapy remains a concept that's in active development, and we're awaiting definitive, high-level data to indicate whether or not this will ultimately prove to be superior to upfront surgery and adjuvant therapy. And the possibility is that it will be based on the notion, putting aside the specifics of the treatment, that you get more modalities of treatment into a greater number of patients.

Advanced PDAC Standard Therapy Developments

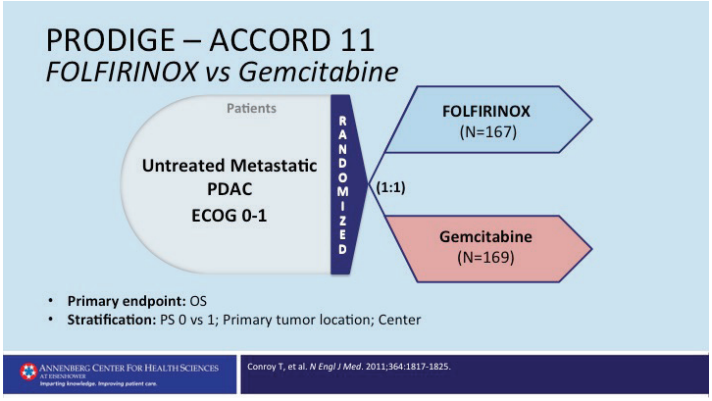
This is the landscape of therapeutics that are available for PDAC. You'll see it's dominated by cytotoxics, and more recently by gemcitabine/nab-paclitaxel and FOLFIRINOX.



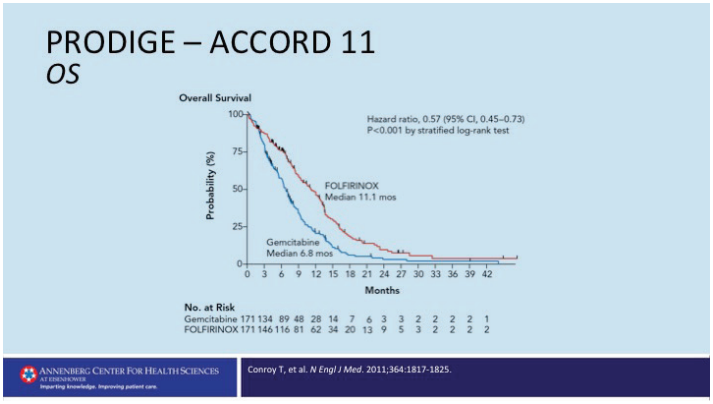
There are 2 areas highlighted in red, and these represent targeted agents. Although, of note, erlotinib was approved in combination with gemcitabine for unselected patients, we now know that it may have a role for about the 5% of patients that are KRAS wild type. And pembrolizumab received an FDA disease agnostic approval in 2017 for patients with mismatch repair deficiency, and that's about 1% of people with PDAC.

One of the studies that led to the use of routine cytotoxics in PDAC was this older study from about 20 years ago, looking at gemcitabine compared to 5-FU and demonstrating a clearly superior outcome for gemcitabine. And that launched a whole series of trials comparing new drugs to gemcitabine and adding new drugs to gemcitabine.

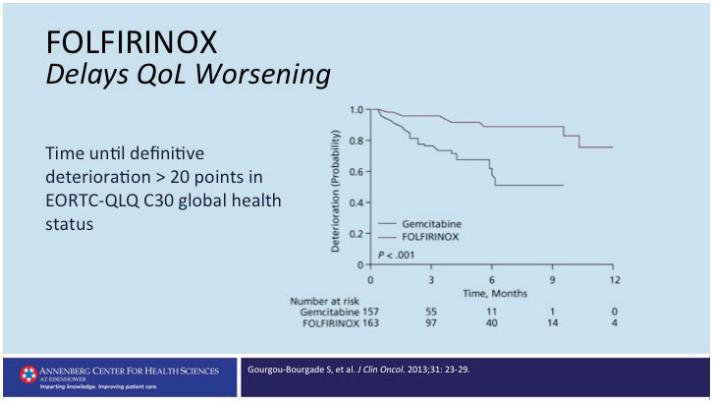
And I'm going to move to the key recent developments. This is the landmark study evaluating FOLFIRINOX. These data were initially presented in 2010. This trial evaluated FOLFIRINOX compared to a single-agent gemcitabine in patients with good performance status, metastatic PDAC.



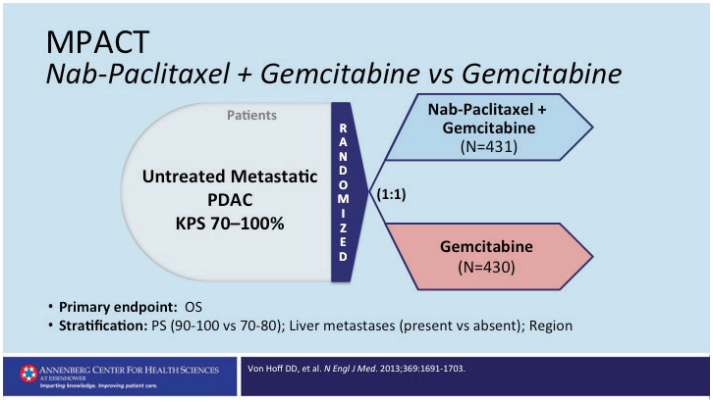
As you can see, there was a nice difference in outcomes for patients who received FOLFIRINOX, a hazard ratio of .57, compelling *P* value, and this has led to this being integrated as a standard of care, now essentially in every setting of PDAC.

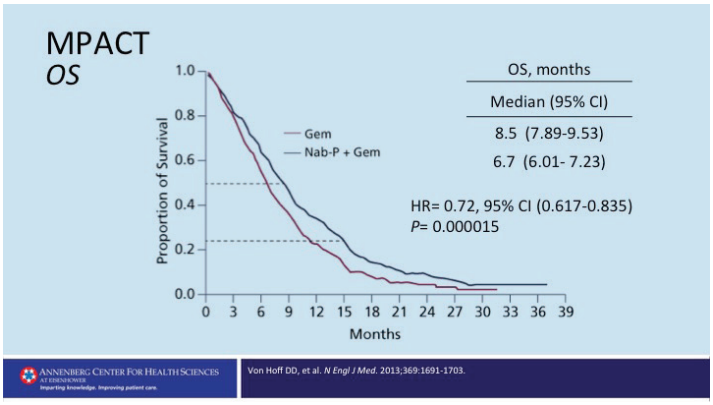


The other point of interest I think is an important one. We know that this disease induces a significant quality of life detriment for patients, but we also see in practice that when we treat this disease successfully, and when patients respond, they undoubtedly feel better, they're eating better, putting on weight, more active, their pain is decreased. And this is captured here in the secondary analysis from that study showing that despite the inherent relative toxicity of this regimen, if disease is responding and people are feeling better, their quality of life, as interpreted by the individual, is better for longer.



The other major regimen in the advanced disease space is gemcitabine and nab-paclitaxel. This is the study that led to its FDA approval, comparison being single-agent gemcitabine. Make a note that compared to the FOLFIRINOX trial, this included a broader group of patients with performance status spanning from 70% to 100%, and it had no age limit, in contrast to the FOLFIRINOX population. These are the outcomes: statistically significant improvement for

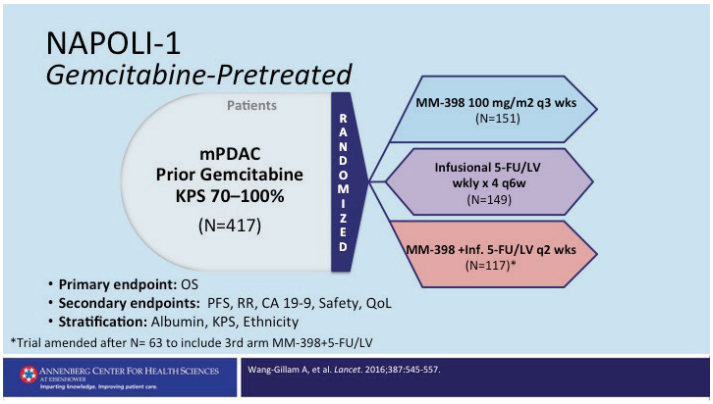




gemcitabine and nab-paclitaxel hazard a ratio of .72 and compelling *P* value.

Summing up, with regard to frontline therapy choices for advanced disease, we do not have clear evidence to indicate that one approach is better than the other. There has been no head-to-head comparison data that have been presented in terms of prospective analysis, as yet. But part of this discussion I think relates to age and relates to performance status, it relates to comorbidities and certainly relates to patient preference. So, for example, the need for mediports and infusional therapy with FOLFIRINOX, and the concerns of alopecia for nab-paclitaxel and gemcitabine. And it's also probably fair to note that gemcitabine and nab-paclitaxel may be applicable to a broader group of patients as it's served as a platform for adding novel agents. So, we'll come to that in the new therapeutics module where we discuss emerging developments.

A couple of comments on second-line therapies for PDAC. Traditionally, oxaliplatin-fluoropyrimidine combinations have been used. We have 2 trials to draw upon. They have discordant conclusions. CONKO-003 supporting the use of oxaliplatin, infusional 5-FU, while the PANCREOX study coming to the conclusion that a fluoropyrimidine infusion was better. Hard to know what to make of that, and there are limitations to both of these studies. We have NAPOLI-1 trial, which evaluated nanoliposomal irinotecan compared to infusional 5-FU and leucovorin. This particular trial showed that there was a clear survival advantage to nanoliposomal irinotecan and 5-FU compared to 5-FU on its own.



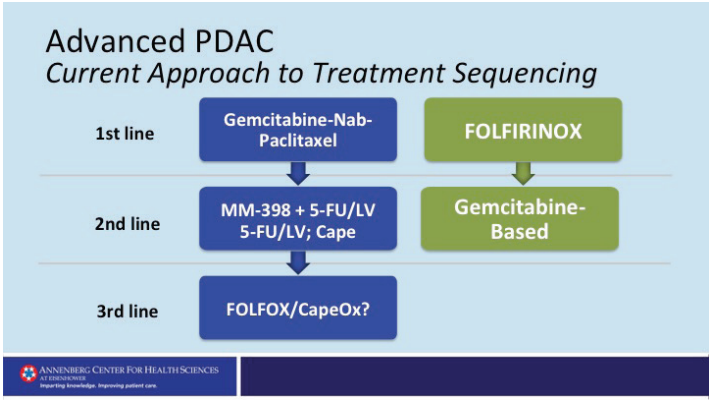
Summing up with regard to second-line therapies for PDAC, the regimen for those who've received prior gemcitabine in a frontline or in an adjuvant or neoadjuvant setting, would be nanoliposomal irinotecan and 5-FU. Alternatively, oxaliplatin-fluoropyrimidine combinations may have a role, and there's a big need for clinical trials and new therapies in this second-line setting.

Summing up with regard to advance disease, and we haven't focused on this, but just to point out key prognostic factors are the stage of disease, stage III locally advanced vs metastatic, performance status of course. We have 2 good regimens, FOLFIRINOX or gemcitabine and nab-paclitaxel. For those who have a less robust performance status, either single-agent therapy or some of the older combinations may have a role.

And then pointing out that supportive care and integration of symptom-directed management is critical to optimizing outcomes for patients with this disease. We know that patients can develop obstructive processes in the GI tract very commonly, biliary obstruction in the sequelae of cholangitis and occluded stents or duodenal obstructions, also known as gastric outlet obstruction, and that can be palliated often with endoscopic stenting and more rarely surgical bypasses.

Pain is a substantive issue in this disease. Generalized abdominal pain, back pain in particular, and a whole variety of strategies are part of routine care for these patients. Nutritional consideration and addressing issues of pancreatic insufficiency is key. Thromboembolic complications occur pretty frequently, and some patients will present with pulmonary emboli or DVT, and as the disease process evolves, thromboembolic sequelae occur and probably in up to 50% of patients at some point during the trajectory of their disease. This will need to be addressed.

There are psychosocial issues for patients in the family associated, understandably, with a disease with an ultimately limiting prognosis in terms of anxiety, depression, and other consequences. So just to emphasize, again, how important addressing these considerations as optimally as we can is critical to maximizing the outcome for a particular individual.

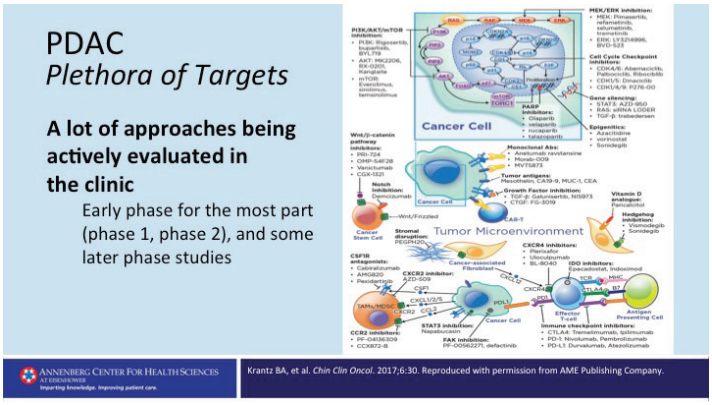


Leaving you with this schema for how one might think about sequencing therapies for patients with newly diagnosed advanced PDAC. One approach for patients who received gemcitabine and nab-paclitaxel-based therapy would be, at the time of progression, nanoliposomal irinotecan, 5-FU, and potentially subsequently FOLFOX. For those who receive a fluoropyrimidine-based regimen upfront, gemcitabine-based treatment is the logical go-to, and kind of overarching here to all is the consideration of clinical trials.

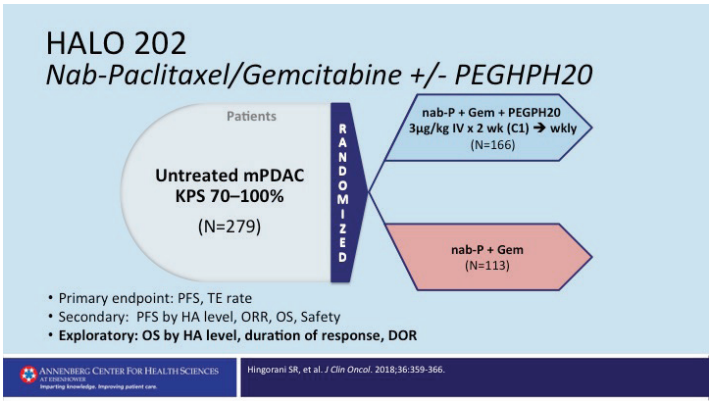
Advanced PDAC Novel Treatment Strategies

Moving now to new therapeutic approaches for PDAC, and the nice news is there's a lot on the horizon. And some of the strategies that we'll discuss look at stroma modulation, look at targeting genetic subgroups, immune-based approaches, and then there are a lot of opportunities with regard to key signaling pathways in PDAC, radioimmune therapy strategies, emerging metabolic therapies for PDAC, some of which are now in late-stage trial development.

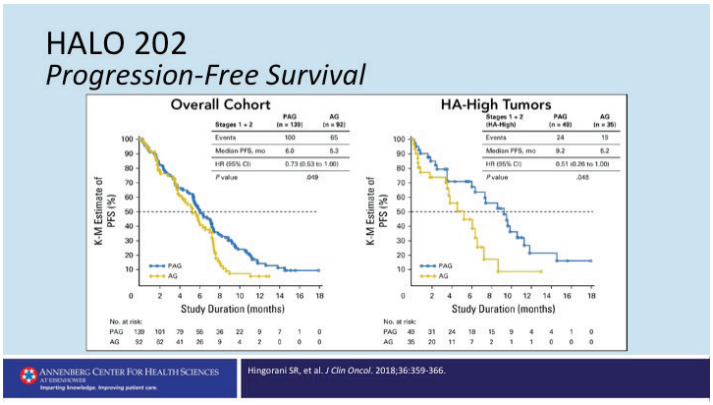
This slide is adapted from a publication and summarizes some of the major approaches that are in development. These are early phase, for the most part, in terms of phase 1, phase 2, and some later phase studies impact. And I think this is where a lot of excitement comes because there's a lot of approaches being actively evaluated in the clinic.



Moving to the stroma and the microenvironment targeting for PDAC, and just a reminder again that this stroma is characterized again by a relative absence of epithelial malignant cells and a predominant presence of stroma, which is composed of hyaluronan and glycosaminoglycans, and this provides a physical barrier, may inhibit drug delivery. A pegylated hyaluronidase enzyme has been shown to degrade the stroma, to alter the physiology and dynamics from the vascular perspective, and to facilitate drug delivery. And this approach has been taken to late stage clinical development in PDAC following early promising signals.

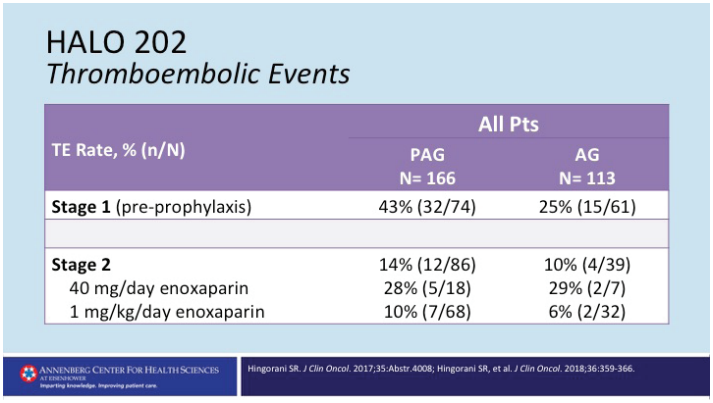


These data were fully published earlier this year looking at the addition of pegylated PEGPH20, combined with gemcitabine and nab-paclitaxel and compared to gemcitabine and nab-paclitaxel for patients with untreated advanced disease. And looking, here, at progression-free survival and looking at thromboembolic outcomes, and then there was secondary analysis by hyaluronan level as adjudicated by tissue immunohistochemical analysis from a baseline biopsy or archival tissue.



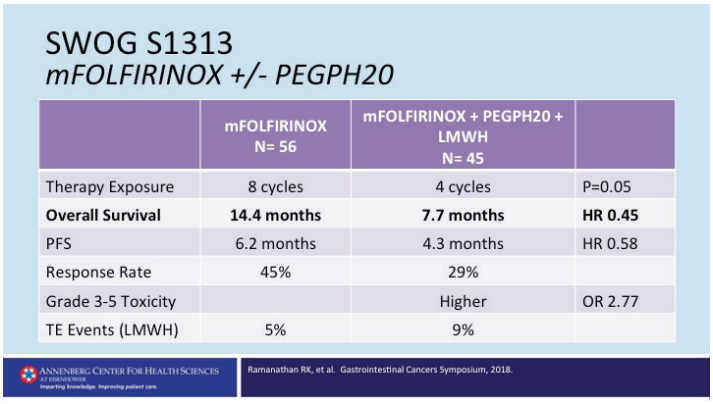
And looking at the principal outcome of progression-free survival, you see for the overall cohorts, there was an improved outcome, but I want to draw your attention to the subgroups of patients who had an elevated level of hyaluronan. This group of patients appeared to have particularly promising potential advantage for the addition of PEGPH20 to standard therapy, and we will see how this translates going forward.

During the conduct of the study, it was paused because of, early on, an excess of thromboembolic events that were noted in the triplet's combination arm. This resulted in a primary prophylaxis strategy where patients were initiated on low molecular weight heparin, and you'll see for the stage II patients, though after the hold and reopening of the study, if you look at the bottom line here, you'll see that thromboembolic event rates were sort of neutralized with the addition of low molecular weight heparin. And this has now become standard practice for studies that are underweight with this particular combination.



The key study for which we'll hope to see results some time later in 2019 is the HALO-301 trial. This study is being conducted in a biomarker-selected subgroup of patients with elevated levels of hyaluronan and looking at primary outcome of overall survival. And this study will enroll, in view of its recently updated statistical analysis, approximately 500 patients.

I want to draw your attention to an evaluation of modified FOLFIRINOX with PEGPH20. This was a randomized phase 1B, a randomized phase 2 [trial] that was conducted by the SWOG Cooperative Group, and it yielded some surprising results. Firstly, the control arm did well, and did better maybe than even the original phase 3 had suggested, and that's important as this was across a swath of community and academic sites. That part was good.

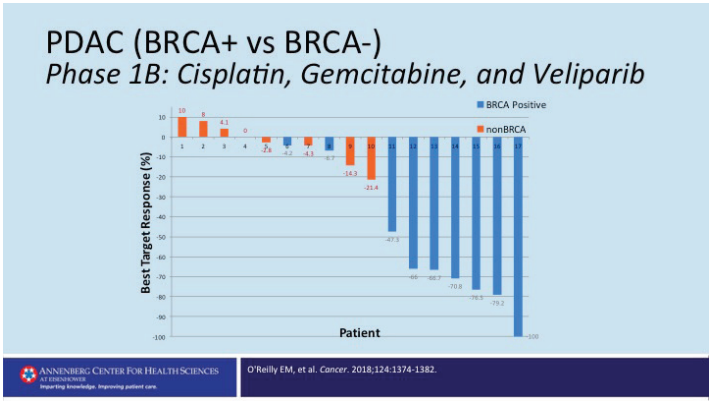


The part that was disappointing, and unexpected, was that for the group of patients who received modified FOLFIRINOX and PEGPH20, their outcome was inferior to standard therapy alone, with a median survival of 7.7 months. Unclear whether this was related to the higher rates of toxicity, which were present for this particular combination. Also, this was not a biomarker-selected group, and we're hoping that there may be some retrospective analyses that will be able to further inform the observations of the study. But the key kind of take-home point here is PEGPH20 and FOLFIRINOX do not go together at this juncture.

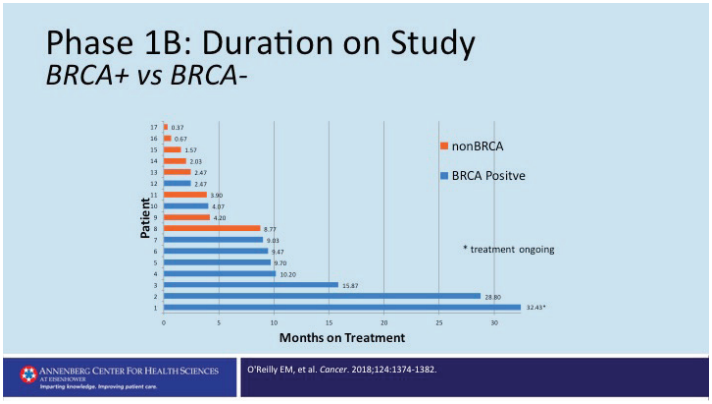
Moving now to genetic targeting of PDAC. We've known for a while that there's a subset of patients who have defects in DNA repair and may benefit from selected targeting of a DNA damage response/repair pathway. And the concept behind this in BRCA-deficient cells is the concept of synthetic lethality, where individuals with BRCA-driven malignancies have an ineffective ability to repair DNA damage, and alternative mechanisms which are much more unstable and lead to cell death and depletion, lead to potentially higher therapeutic advantage in BRCA-deficient cells for some platinum and potentially PARP inhibitor strategies.

Bruton's tyrosine kinase (BTK) is a key enzyme in the B-cell receptor pathway. While the BTK inhibitors (BTKi) such as ibrutinib and acalabrutinib are currently indicated for the treatment of patients with various B-cell malignancies, because BTK signaling appears to play multiple roles in pancreatic adenocarcinoma (PDAC) and its inflammatory stroma, the role of BTKi has also been investigated in preclinical and clinical settings of PDAC.

The largest clinical trial (RESOLVE), evaluated ibrutinib in combination with nab-paclitaxel and gemcitabine vs nab-paclitaxel, gemcitabine and placebo, as the first-line therapy in patients with metastatic PDAC.[3] Recently, however, it has been reported that the study did not meet its primary and secondary endpoint of improving progression-free survival and overall survival, respectively.



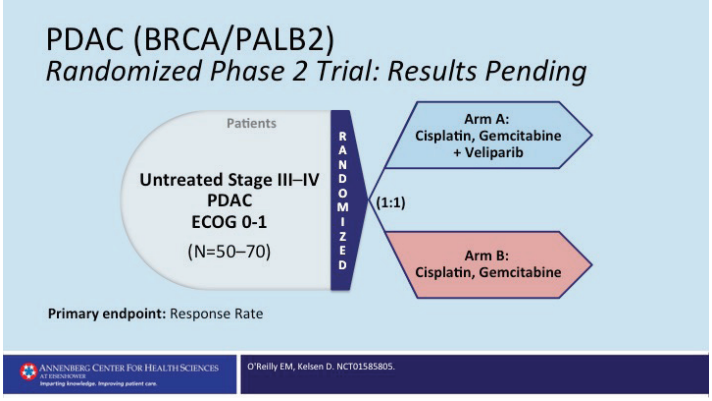
This is an example of a study... This was a prospective multicenter small trial in 2 cohorts of patients, those who had a germline BRCA mutation and those that did not. For those who did have a germline BRCA mutation, frontline therapy with platinum and PARP combined, we saw significant responses. We saw no objective responses in the non-BRCA mutation group. Similarly, some of these responses were very durable, going on for a number of years.



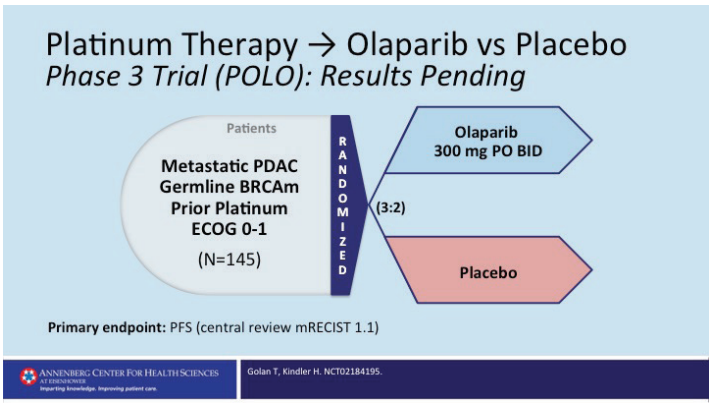
And again, in this small subset—a caveat to note that it was prospective and multicenter—we saw approximately a doubling of survival for patients who received platinum-based therapy as their initial treatment strategy compared to those that did not have a germline BRCA mutation. It's sort of unclear how much of this is predictive vs prognostic effect, but our understanding is that it is primarily a predictive effect of platinum in the BRCA-mutated subgroup.

And that's led to a series of studies. This particular trial has just completed recruitment and will evaluate platinum and PARP inhibitor upfront as opposed to platinum-based therapy on its own for germline BRCA and PALB2 mutated individuals with advanced PDAC. And a very important study we hope will read out in 2019 evaluates a maintenance approach of using a PARP inhibitor following platinum stabilization for patients with, again, a germline mutated PDAC. The study builds on themes of PARP inhibitors in ovary cancer and in breast cancer where significant benefits have been identified, and we hope that this will be also seen in PDAC.

Moving to the issue of immune therapies and genetic profiling in PDAC. So firstly, do checkpoint inhibitors work? We have some older data. This particular study looks at ipilimumab, the anti-CTLA-4. There was 1 individual who had a delayed response. A second presentation looked at durvalumab in

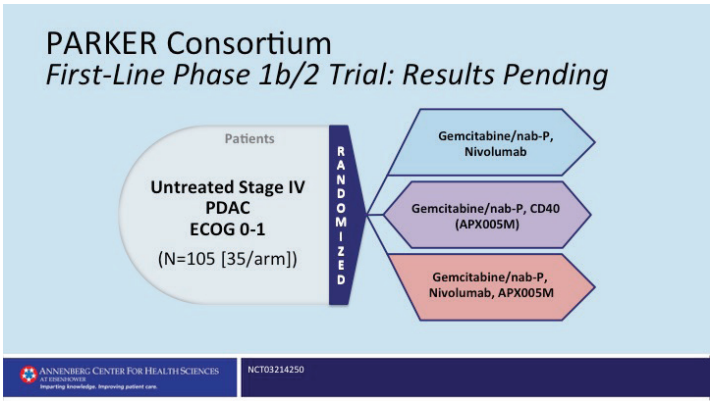


a multi-arm, multi-disease cohorts. This was single-agent therapy. This evaluated checkpoint inhibitor for patients with pretreated disease and showed that a small number of patients, about 7% in this trial, had an objective response.



Single-agent checkpoints have some limited activity. We know that patients with MSI-high mismatch repair-deficient disease are those who certainly stand to potentially benefit from checkpoint inhibitors, but for most people with advanced PDAC, single-agent checkpoint inhibitors are insufficient, and that leads to a variety of combination approaches. So, "Okay, 1 checkpoint is insufficient. What about 2?" This trial suggests to us that 2 does not move the bar in a meaningful way for patients unselected with advanced PDAC.

But I think a very interesting strategy that's being assessed now across a number of platform studies, and this is an example of Parker Institute Consortium trial, is looking at combination chemo and immunotherapy in a frontline setting with patients with untreated advanced PDAC. This particular study is looking at nivolumab or CD40 or the combination of both nivolumab and the agonistic antibody CD40 with frontline therapy. And this has completed phase IB testing and is actively accruing in a randomized phase 2 setting.

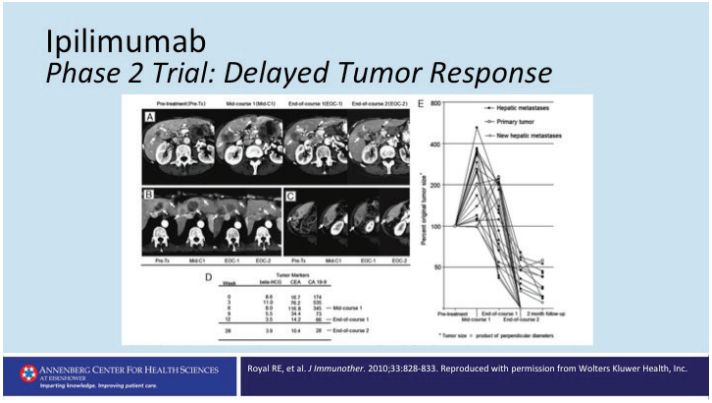


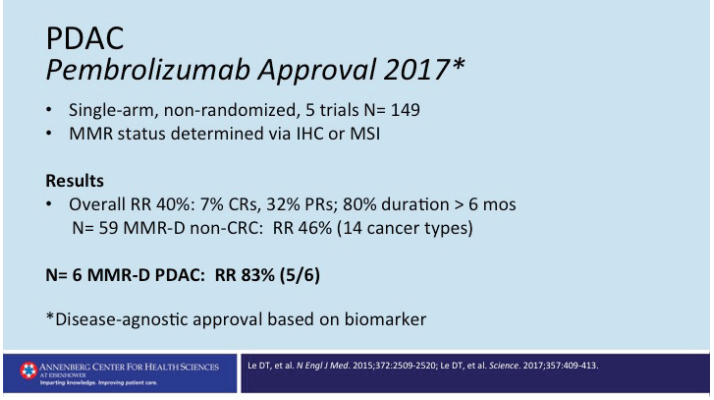
Given the technological advances facilitating genetic subtyping of PDAC, the relevant question has become whether mutational signatures can be used to develop personalized therapy for patients with this cancer? Recent data strongly suggest that, indeed, mutational signatures may be used to guide personalized treatment approaches for a subset of patients with PDAC.

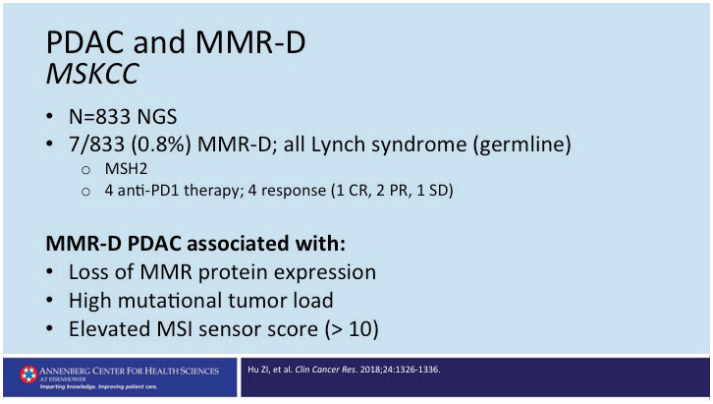
Next, the issue of mismatch repair testing in PDAC. We know there are a variety of ways to do it. Classic ways are using IHC to look for loss of protein expression or for PCR analysis looking for microsatellite. Increasingly, and I would say in particular in PDAC, because of some of these antigens that next generation sequencing brings in terms of tissue conservation and learning about other therapeutic opportunities, we have ways of assessing mutation load and bioinformatics analysis to evaluate MSIsensor score.

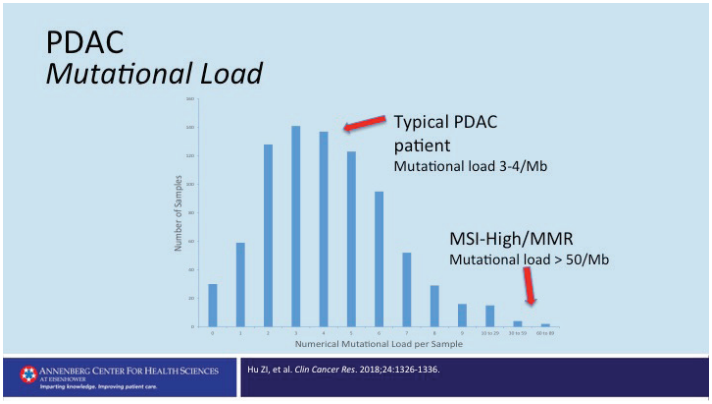
Here's a reminder regarding pembrolizumab approval, and these are the data that supported that approval. Remember, these were nonrandomized studies. But there are 6 patients in the 5-pool trials that led to approval. Sorry, 6 patients with PDAC in the 5 studies, and there was a high response rate identified in this particular population.

And our group chose to evaluate this in some detail and confirm that mismatch repair-deficient PDAC is rare. We saw it in about 1% of patients, and in this analysis of an ultimately large cohort, all of these patients had an underlying Lynch syndrome, so they had a germline mutation and associated mismatch repair-deficiency gene. We saw that these patients









had loss of protein expression, high mutation load, and an elevated MSIsensor score.

Looking at this graphically, you'll see that typical individual PDAC has 3 to 4 mutations per megabase, but those with mismatch repair deficiency, and again, in this analysis, all germline Lynch syndrome, had a high mutational load. And there's a group of individuals here which have a more intermediate mutational load for which we're currently learning whether or not this might be a possible subgroup for which immune-based strategies may have a role.

To sum it up, here, with regard to what's happening in advanced disease, I just want to make note that there are a lot of very interesting approaches underway. I think we're working hard to identify biomarkers for this disease. We now have a couple that we do use for clinical decision-making. So BRCA in terms of germline and selected somatic mutations confirms potential sensitivity to platinum agents and experimentally to PARP inhibitors, so we look hard to know those patients. We recommend consideration of somatic testing for all patients for the rare but important findings of fusion events or other targetable or off-label considerations and for possible clinical trial involvement consideration.

I think there are a number of very promising strategies in terms of modulating the microenvironments, in terms of DNA damage repair targeting in PDAC, and the future hope that immune therapy can be integrated into a broader group of people with PDAC; for now, it's unequivocally "yes" for the small group with mismatch repair-deficient disease—it's about 1%. But there's a lot of trials now trying to reverse the inherence and new resistance in the microenvironment in PDAC and to make this disease more susceptible to the benefits for immune therapies. And I think it's very fair to say that with all of these exciting approaches in the clinic, we are truly optimistic that change is coming in this disease.

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