“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

Brad Power
July 24, 2024

“It's exciting times in pancreas cancer. Having been in this field for a while and seeing a lot of things sadly not materialize, the field is poised for change.” – Eileen O’Reilly, MD

“The way we do genetic testing has really evolved to be practical, feasible, and timely. We now do what's called ‘point of care’ testing. At the time of diagnosis, and essentially at the first meeting for most of the new people that we will encounter, we will recommend getting germline and somatic testing underway, using a variety of educational tools.” – Eileen O’Reilly, MD

“Traditionally and currently, the main standards of treatment for almost all stages of disease are chemotherapy-based, and that has been improved and refined but imperfect, and multi-agent cytotoxic chemotherapy are in all our guidelines for advanced disease, for post-operative preventive therapy, and for treatment of localized and advanced disease. But increasingly the focus is shifting to subgroups of patients who can benefit from targeted therapeutics (e.g., KRAS, BRCA).” – Eileen O’Reilly, MD

Meeting Summary

Patients who are diagnosed with pancreatic cancer and do an online search about their prospects are confronted with a poor prognosis and dire statistics. If they then search for standard treatment options, they find a limited menu of treatment options that benefit only a small percentage of patients. However, improvements in supportive care, chemotherapy, molecular diagnostics and associated targeted therapies are enabling some patients to live longer and better, while immunotherapies are increasingly making progress. The pace of change is increasing exponentially. New tests and treatments are being approved and on the horizon which offer new hope for pancreatic cancer patients and caregivers.

Eileen O'Reilly, MD, is uniquely qualified to discuss recently announced regulatory approvals and research results in pancreatic cancer. Her research includes integration of molecular and genetic-based therapies for pancreas cancer along with development of adjuvant and neoadjuvant therapies and identification of biomarkers for therapy selection. Dr. O’Reilly received her medical degree at Trinity College in Ireland. She completed her postgraduate training in Ireland and subsequent Hematology/Oncology Fellowship training at Memorial Sloan Kettering. Dr. O’Reilly is a clinical scientist whose research focus involves integration of molecular and genetic-based therapies for pancreas cancer along with development of adjuvant and neoadjuvant treatments and identification of biomarkers for therapy selection. Dr. O’Reilly teaches and mentors junior faculty, oncology fellows, residents and medical/other students and has numerous teaching and other awards. Dr. O’Reilly is the principal investigator of multiple phase I, II, and III trials in pancreas cancer and has authored/co-authored about 400 articles, editorials, and book chapters and has an H-index of 93. She serves as an Associate Editor for the Journal of Clinical Oncology and Senior Editor for several other journals and has served on multiple grant review panels including, for the American Society of Clinical Oncology (ASCO),

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American Association of Cancer Research (AACR), NIH, DOD, and various international entities. She is the principal investigator of the MSK Pancreas Specialized Program in Oncology Research Excellence (SPORE), an NCI-funded team science grant. Dr. O’Reilly is the recipient of numerous awards including the Burkitt Medal (TCD) in 2022, and Giants of Cancer Care GI Oncology, 2023. Dr. O’Reilly’s other responsibilities include Chair of the Human Research Protection Program and Institutional Review & Privacy Board (IRB). Nationally, Dr. O’Reilly is Co-Chair of the NCI Alliance Co-Operative Group Gastrointestinal Cancers Committee and serves on the NCI Gastrointestinal Cancers Steering Committee (GISC) and serves in leadership roles in several advocacy organizations including National Pancreas Foundation, Hirshberg Foundation and Pancreas Cancer Action Network.

Why should you keep up-to-date on the latest treatments for pancreatic cancer?

Traditionally and currently, the main standards of treatment for almost all stages of pancreatic cancer are chemotherapy-based. That has been improved and refined, but it is imperfect.

However, what was best six months or a year ago may be old news. The pace of change is increasing exponentially. New tests and treatments are being approved and on the horizon which offer new hope for pancreatic cancer patients and caregivers. Increasingly the focus is shifting to subgroups.

What are the latest improvements in testing for pancreatic cancer that are available today and in the near future?

- Genetic testing and liquid biopsies for early detection are improving. Our ability to detect targets has progressed even from a couple of years ago. One of the greatest uses right now of liquid biopsies (from a blood draw) is being able to understand whether you have a KRAS mutation or not.
- Around 12% of people have a hereditary predisposition to pancreatic cancer, which can be identified through genetic testing.
- You should get “point of care” genetic testing (hereditary testing on your normal cells and testing on your tumor cells) at your first meeting, accompanied by educational videos to explain the test and its results.
- Although early detection of pancreatic cancer through tests may be expensive or infeasible today, using AI on medical records, and finding patients with certain kinds of diabetes, are identifying selected groups of patients who may benefit from screening tests. We are on the cusp of identifying pancreatic cancer with a lead time prior to clinical presentation, when, sadly, a lot of people are quite sick.
- Early research suggests immune response may predict outcomes in a pancreatic cancer vaccine trial.

What are the challenges in improving tests and treatments for pancreatic cancer?

- It can be difficult to get high-quality tissue from the pancreas for testing.

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- It is difficult to detect pancreatic cancer early from a liquid biopsy (blood draw) due to the lack of circulating tumor DNA in the blood.
- Pancreatic cancer has strong immune system suppression.

What are the latest improvements in treatments for pancreatic cancer that are available today?

- KRAS inhibitors, including emerging combinations with chemotherapy and immunotherapy
- If you have homologous repair deficiency or have ineffective DNA repair (courtesy of a BRCA1, BRCA2 PALB2, and some other gene alterations), then there are chemotherapeutics, PARP inhibitors, and an emerging role for immunotherapy-based combinations.

What are new treatments for pancreatic cancer that are being studied and may be available in the near future?

- About 15%, maybe 20%, of pancreatic cancer patients have deletion of a gene called “MTAP”, which is associated with other genes, which may have a treatment implication.
- Immunotherapy approaches for pancreatic cancer (e.g., personalized neoantigen vaccines, CD40 agonists which activate the immune system, CD73 inhibitors which target immune system suppression)
- Additional RAS-targeted drugs, such as RMC-6236, including in combinations

How can you learn more and engage in choosing among the latest pancreatic cancer treatments?

- Get a second opinion from the big academic centers; usually, they will have a good sense of what's happening and where the field is headed and what trials are most relevant, and what might be an approximate horizon for access
- See our discussion with John Strickler, MD, on KRAS treatments.
- Check out PanCAN and other pancreatic cancer advocacy organizations
- Get a free second opinion from Cancer Commons
- Check out clinical trial resources and search tools at Massive Bio and myTomorrows, free services which review your medical records and make recommendations on suitable clinical trials for you, tailored to specifics, including what might be practical geographically
- Get germline and somatic testing at your diagnosis
- Research the importance of diabetes, weight changes, and other atypical symptoms as potential early warning signs

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Meeting Notes

KEYWORDS

pancreas cancer, people, disease, k ras, targeting, mutation, treatment, question, immunotherapy, part, pancreas, drugs, setting, chemotherapy, terms, therapeutics, important, tumor, early, field

SPEAKERS

Eileen O’Reilly (71%), Brad Power (9%), Rick Davis (5%), Gitte Pedersen (5%), Jill Rosen (3%), Roger Royse (3%), Francesca Paradiso (2%), Kathi Peterson (2%), Allen Morris (1%)

CHAT CONTRIBUTORS

Rick Davis, Robyn Caldwell, Allen Morris, Ellen Miller, Saed Sayad, David Plunkett, Roger Royse, Gitte Pedersen, Rob Weker

SUMMARY

Pancreatic cancer treatments can be tailored to individual patients based on their unique genetic profiles and immune systems. Emerging targets and therapies for pancreatic cancer include KRAS inhibitors, vaccines, and small molecule inhibitors. Genetic testing and liquid biopsies for early detection are improving, though there are challenges, such as the need for high-quality tissue and the difficulties in detecting targets due to the lack of circulating tumor DNA in the blood. Further research is needed to overcome technical challenges and improve early detection and treatment strategies.

OUTLINE

Pancreatic cancer research and treatment advancements, including targeted therapies and immunotherapies

- Dr. Eileen O'Reilly discusses pancreatic cancer research and future developments.
- There have been recent announcements of targeted therapies for KRAS-mutated tumors and homologous repair deficient subgroups.
- Genetic testing is evolving, including point-of-care testing and timely results.
- Researchers are exploring new treatments for pancreas cancer, including PARP inhibitors and high-dose therapy, with promising results in early trials.

Emerging areas of targeted therapies and immunotherapies in pancreatic cancer

- KRAS mutations provide potential treatment targets, including combination with chemotherapy and immunotherapy.
- Immunotherapy approaches for pancreatic cancer include personalized neoantigen vaccines and CD40 agonists.

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- Early research signals suggest immune response may predict outcome in pancreas cancer vaccine trial.
- Researchers explore personalized neoantigen vaccine approach for pancreas cancer, showing oncologic signal in early phase study.

Challenges and potential solutions for early detection and monitoring of pancreatic cancer, including liquid biopsies and blood-based biomarkers.

- Challenges in obtaining high-quality tissue and DNA for liquid biopsies in pancreas cancer, including difficulty in detecting tumor shedding and obtaining usable biopsy samples.
- Early detection of pancreatic cancer through blood tests is challenging due to lack of circulating tumor DNA.
- Speaker discusses potential for blood-based biomarkers in early detection of pancreas cancer, particularly in high-risk groups such as those with a family history or diabetes diagnosis over age 50.

Pancreatic cancer biomarkers and clinical trials for new treatments.

- Roger Royse luckily detected his pancreatic cancer early, despite subtle symptoms that were overlooked by his primary care physician.
- Dr. O'Reilly discusses RMC 6236, a pancreas cancer drug in phase 2 trials, with potential to move to phase 3 soon.
- She also mentions ongoing phase 1 and phase 1b combinations for pancreas cancer, with more opportunities for access to these drugs.
- She discusses the rarity of KRAS Q61 mutation in pancreatic cancer, with only 5% of cases having this mutation.
- Speaker 5 asks about clinical trials for KRAS Q61 mutation, expressing interest in potentially enrolling in a study despite being in stage four cancer and having already undergone chemotherapy for years.
- Dr. O'Reilly discusses the most common gene mutations in pancreatic cancer, including G12D, G12V, and G12R, and their response to current drugs.
- Advocacy organizations and clinical trial search platforms like Massive Bio and myTomorrows can help patients find relevant clinical trials tailored to their specific needs.

Using AI and models to predict pancreatic cancer treatment response.

- Gitte Pedersen asks Dr. O’Reilly about the potential link between pancreatic microbiome and treatment resistance, as well as the availability of tests to guide chemotherapy delivery to the pancreas.
- Dr. O’Reilly discusses potential for microbiome analysis to predict cancer treatment response.
- Researchers are using AI and EMR data to identify pancreatic cancer patients 12 months prior to diagnosis.

Early detection and treatment of pancreatic cancer, with a focus on AI tools and community clinics.

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- Dr. O'Reilly highlights the potential of AI tools in early detection of pancreatic cancer, citing examples of successful implementation in health systems.
- Rick Davis questions the choice of treatment for patients in community settings, where healthcare providers may not be aware of the importance of ATR2 expression.
- Dr. O’Reilly discusses adenocarcinoma of the pancreas, including prognosis and treatment options.
- Comprehensive cancer centers are best for optimal care.

Cancer treatment options for a patient with a KRAS mutation.

- Dr. O’Reilly discusses concerns about using an older drug combination for a patient with KRAS mutation.
- She mentions that high expression of the signal is more modest than expected in pancreatic cancer, suggesting that other factors may be at play.
- In phase 1 trials, the extent of prior treatments is less restrictive compared to phase three trials, which typically require only one line of prior chemotherapy.

Immunotherapy for pancreatic cancer, including genetic profiling and liquid biopsy.

- Understanding the genetic profile of tumor and immunotherapy approaches are key considerations for patients with pancreatic cancer.
- Key takeaway: Loss of second gene copy predicts benefit from BRCA-targeted therapy.
- Francesca Paradiso discusses using PBMCs for immunoprofiling to predict outcomes in immunotherapy.
- Dr. O'Reilly believes there is a subset of pancreas cancer patients who may benefit from immunotherapies, and the immune environment is important for these agents.

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TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

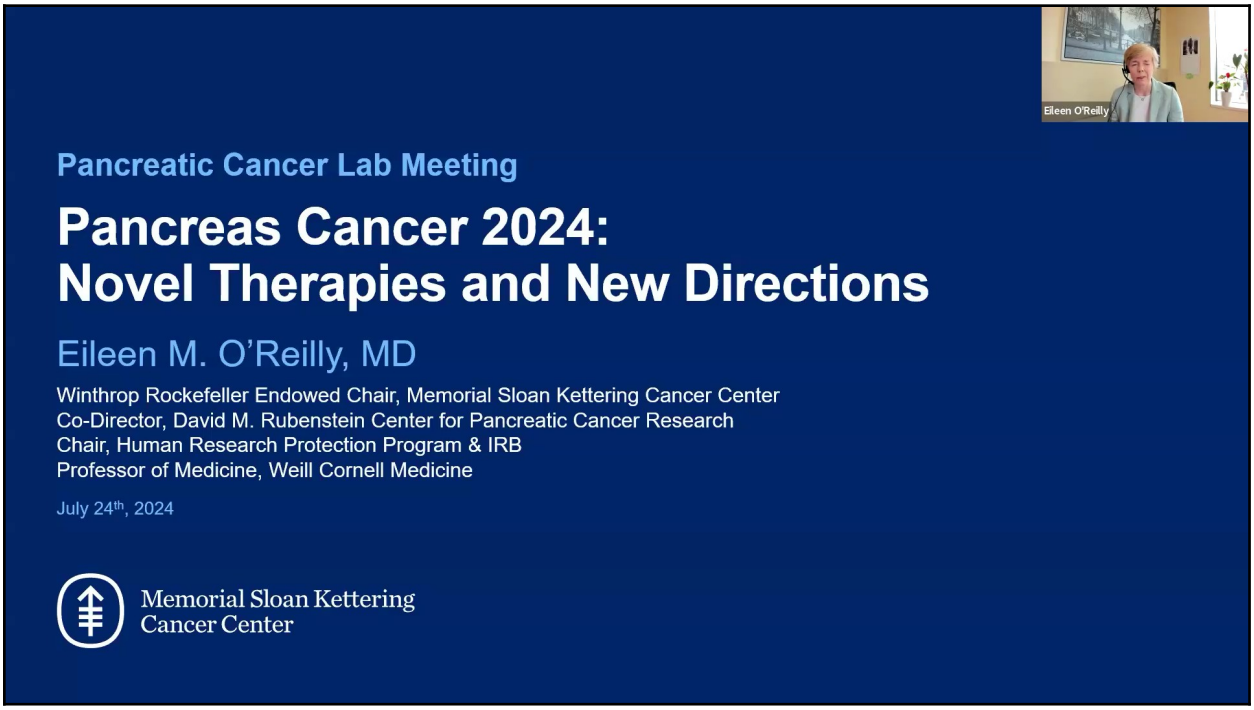
Today we're honored to have Dr. Eileen O'Reilly with us. She's with Memorial Sloan Kettering and a leader in research and clinical care in pancreatic cancer and other cancers that are associated.

This is not medical advice. This is for information purposes only for you to take to your medical team.

The Cancer Patient Lab is a patient-led volunteer community, and we would welcome any donations you might be inspired to make through our website.

Dr. O'Reilly has a bio with titles and history that is about a mile long. If I read it, it might take several minutes. But she is an expert in pancreatic and other cancers, as we mentioned. And there's an Irish connection, back in her origins.

Eileen O'Reilly 1:53
Thanks for the introduction and for the invitation to be here. It’s wonderful to meet you all. I think I recognize some names and people. Hopefully we'll have a good discussion. I've been asked to give a 15 minute or so presentation, which I'll do, and it's really just to set the scene for questions.



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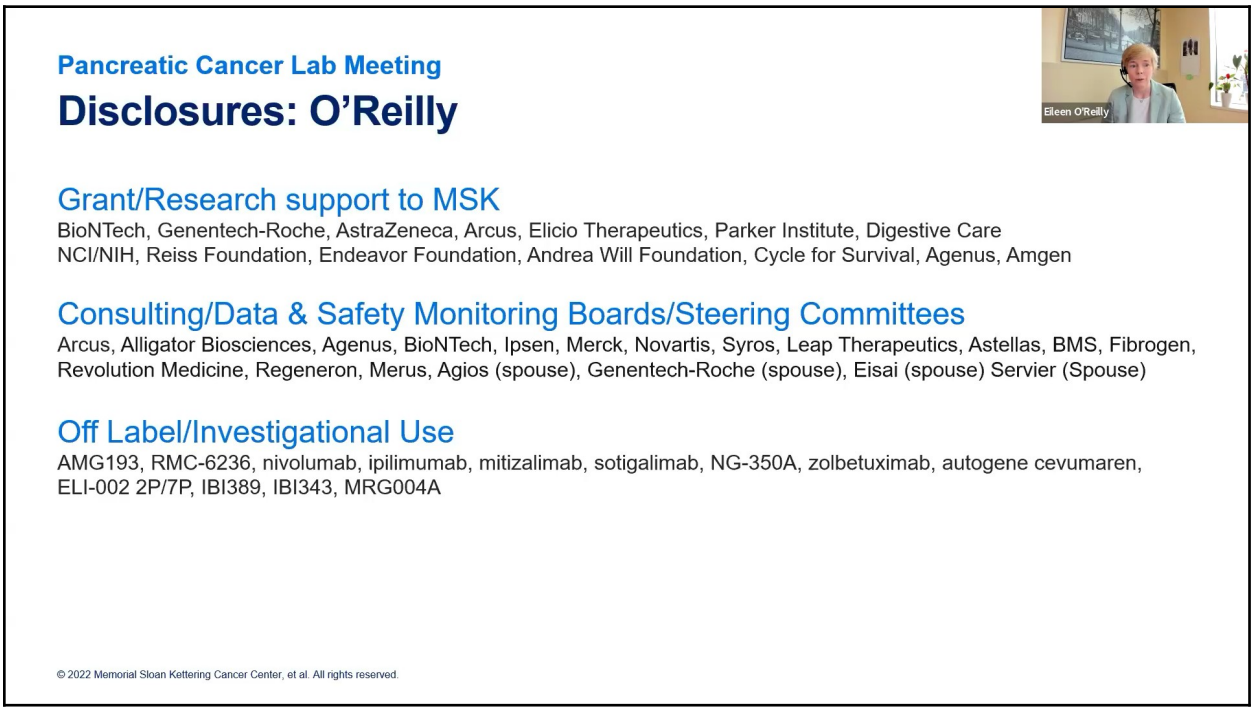
The title is Pancreas Cancer in 2024. This is a high level view or snapshots of where we are and what's happening. It's exciting times in pancreas cancer. Having been in this field for a while and seeing a lot of things sadly not materialize, the field is poised for change. I'll show you some of the things that we're hoping are going to contribute to that.



I need to acknowledge that I do a lot of research, a lot of consulting, Data and Safety Monitoring Board, steering committees, and I have various disclosures. Most of it is uncompensated and good to talk about, a lot of Investigational Use, just there for your reference.

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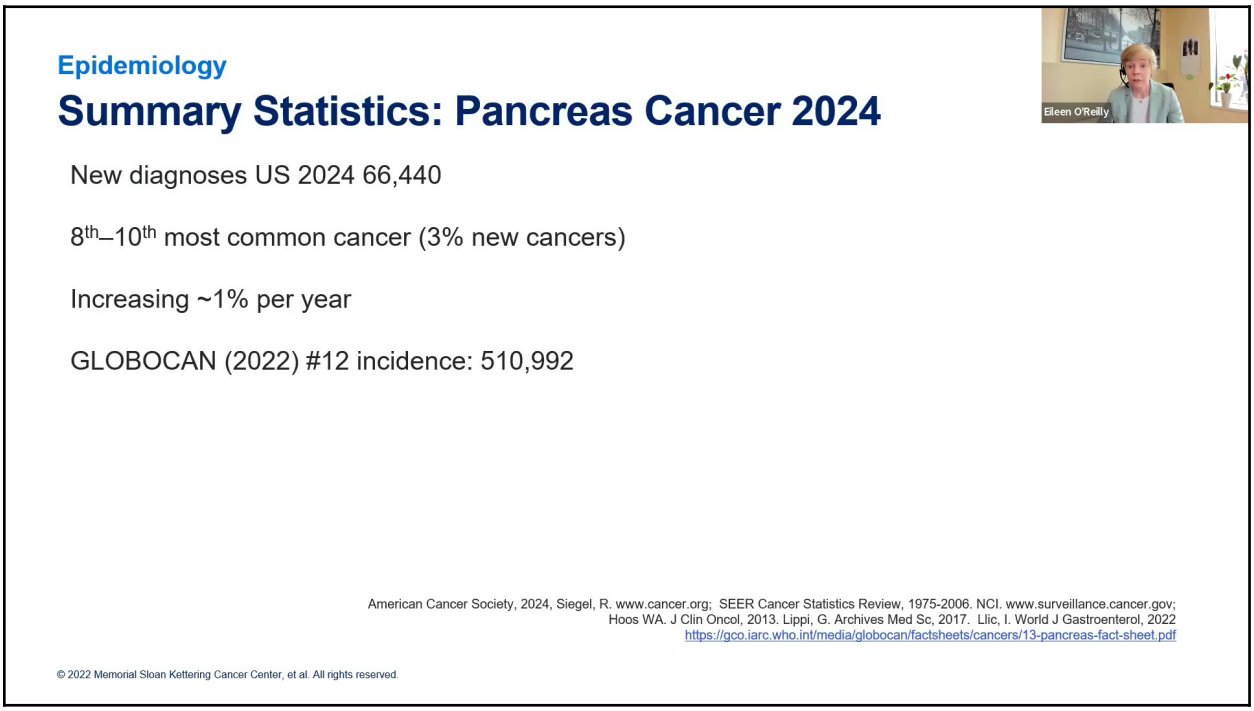
These are the topics:

- a very brief recap of the highlights in pancreas cancer,
- an overview of the current standards, one slide, and then,
- where the field is moving, which will be most of our focus today.



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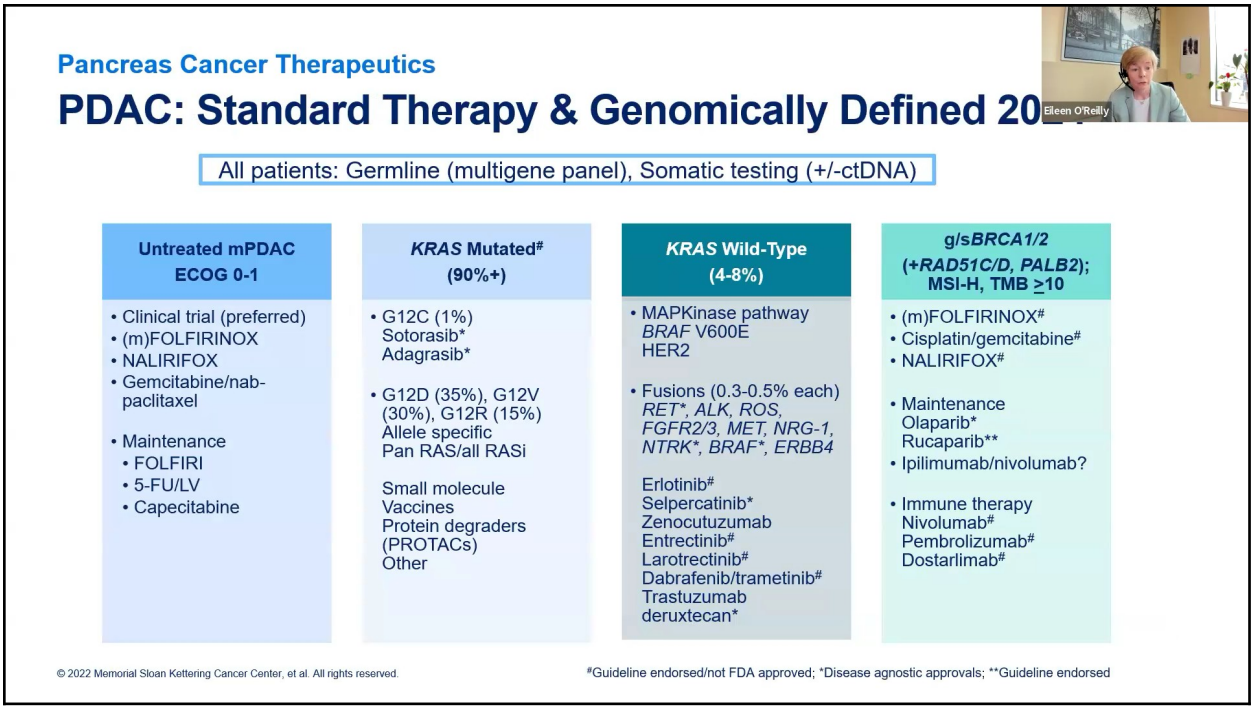
This disease is getting more common and is projected to become one of the leading diagnoses in coming decades, and it’s not clearly understood why. Our population is aging, that's part of it. But there are some fundamental other changes that are happening with this disease. Pretty steadily now for the last 25 years, it has been increasing at about a half to 1% per annum. That's significantly different from most other other solid organ cancers, where diseases have plateaued and incidence is starting to fall. This underscores that it's a big public health challenge, and it's a global challenge as this disease results in about a half a million diagnoses worldwide.



There is a lot of information on this slide, but I'll just pare it down.

Traditionally and currently, the main standards of treatment for almost all stages are chemotherapy-based, and that has been improved and refined but imperfect, and multi-agent cytotoxic chemotherapy are in all our guidelines for advanced disease, for post-operative preventive therapy, and for treatment of localized disease.

But increasingly the focus is shifting to the subgroups.

KRAS (the Kirsten rat sarcoma virus gene, which provides instructions for making a protein called K-Ras, part of a pathway that relays signals from outside the cell to the cell's nucleus to grow and divide or to mature and take on specialized functions) is essentially ubiquitous in pancreas cancer, a critical driver, a gene involved in growth and pathogenesis (the process of disease development) and metastasis (the spread of cancer cells from the place where they first formed to another part of the body) from this disease. We've known about this forever, but not been successfully able to target this with therapeutics.

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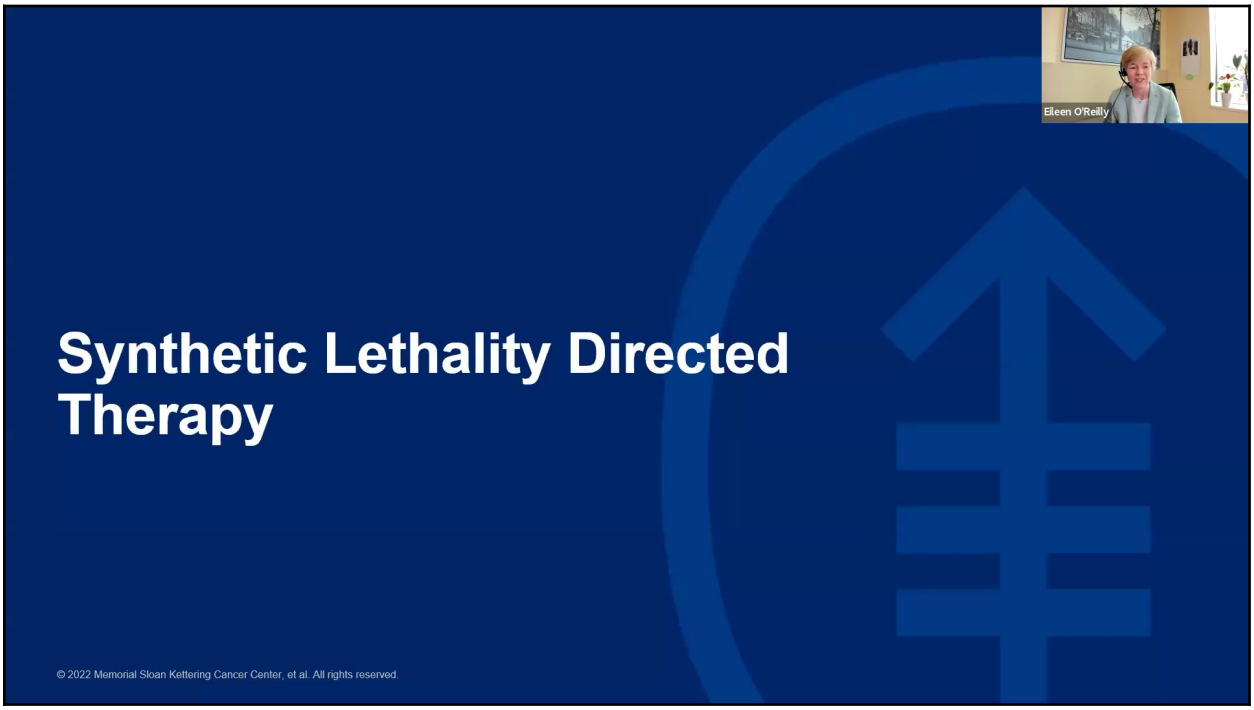
But equally important is that when we don't see a KRAS mutation, which is a relatively small subset of pancreas cancer, there are other findings in the tumor, genomically-based, for which there are a series of therapeutics that are in the clinic. We look hard to find those.

Then a well-defined subgroup is individuals who have homologous repair deficiency or have ineffective DNA repair, courtesy of a BRCA1, BRCA2, PALB2, and some other gene alterations. There we have chemotherapeutics, which have heightened advantages, PARP inhibitors, and an emerging role for immunotherapy-based combinations.



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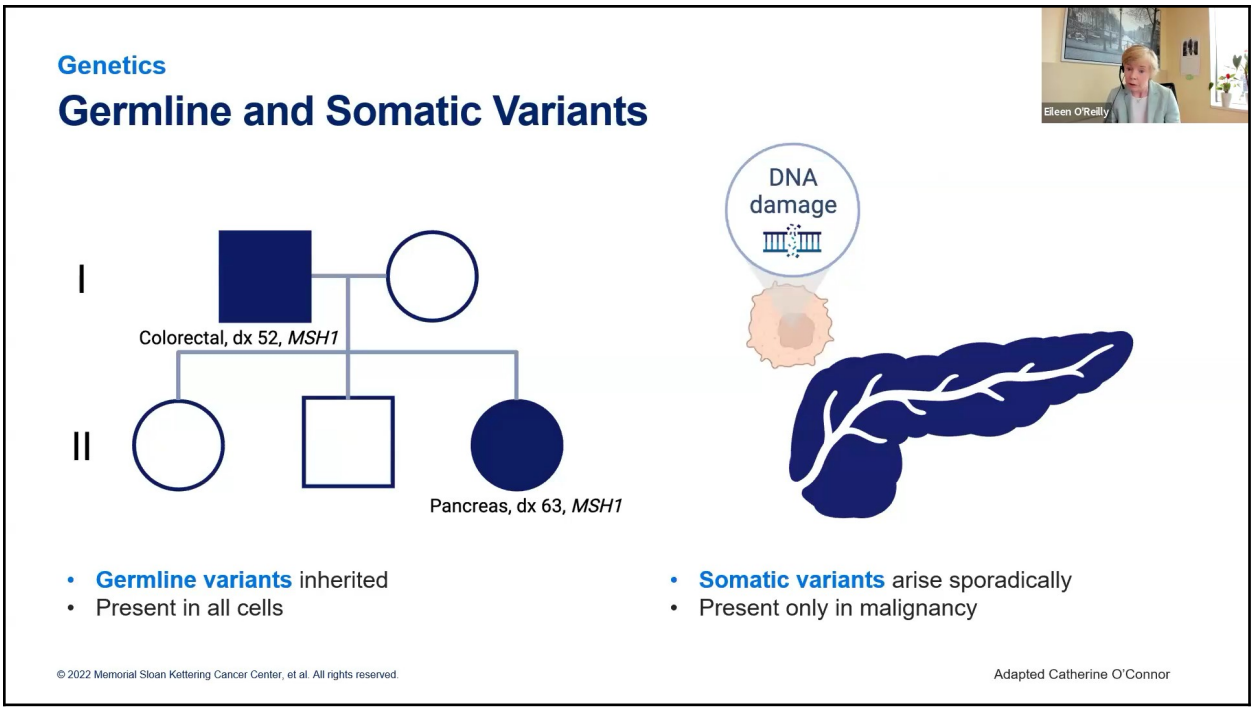
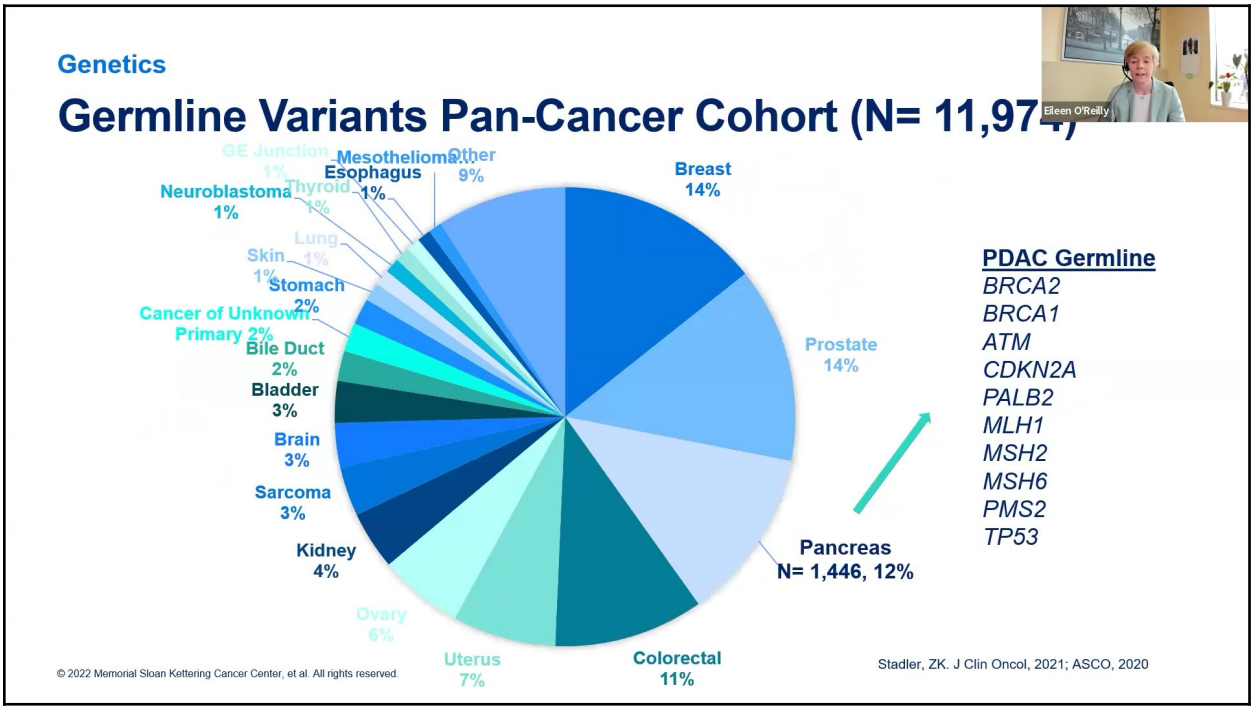


To level set, we're talking about germline and somatic variants; germline being inherited predisposition, somatic being for the purposes of our discussion restricted to the tumor and being a target that represents a unique opportunity in terms of a more favorable treatment index and safety profile in pancreas cancer.



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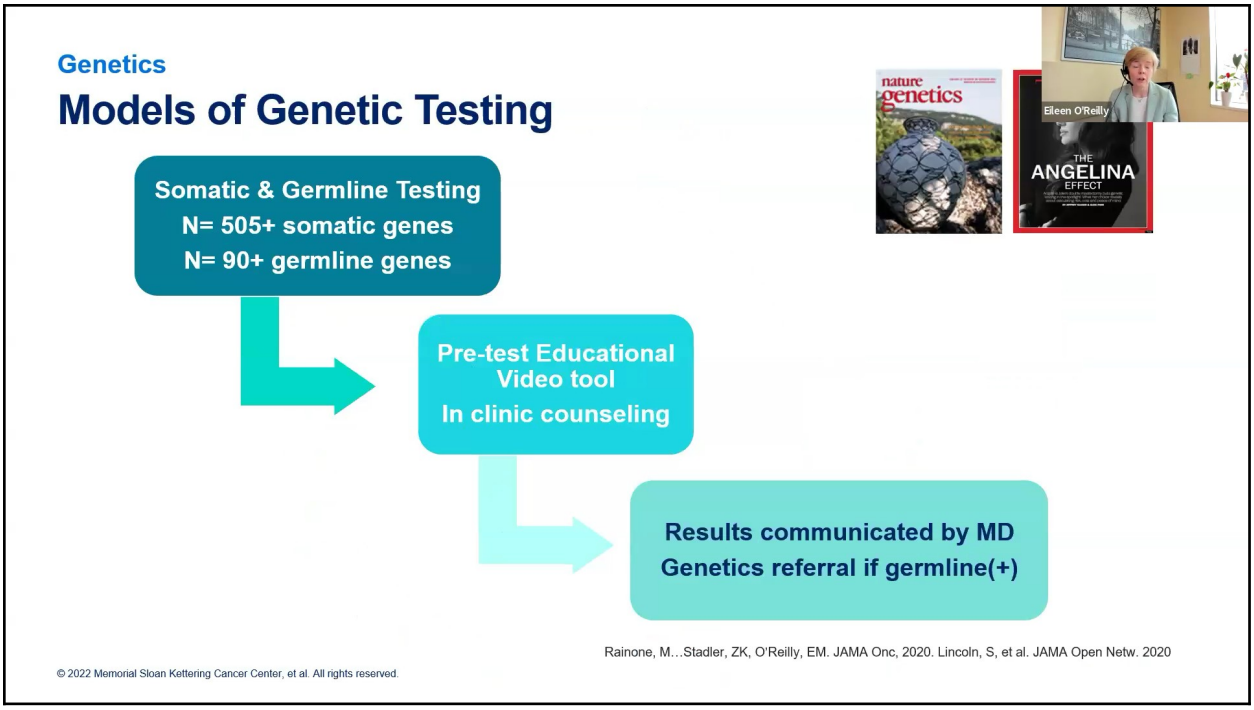
This is not unique to pancreas cancer. But we see about 10 or 11% or 12% of people with a genetic predisposition to pancreas cancer. Those genes are important from the potential of possible actionability or treatments. But they're also important for screening applications, and may be opportunities for early detection. That's always a good topic to discuss. I don't have any slides on that today. But perhaps we'll come back to that in the discussion.



The way we do genetic testing has really evolved to be practical, feasible, and timely. We now do what's called “point of care” testing. At the time of diagnosis, and essentially at the first meeting for most of the new people that we will encounter, we will recommend getting germline and somatic testing underway, using a variety of educational tools. Then on the back end, if there's a positive result on the germline finding just because of the criticality of that information to the person and their family, we'll hand that sequence to our genetics team. But for the most part, the rest is handled by the oncology team. That's really made this practical, scalable, and feasible, not to take away in any way from genetic expertise, but just making sure we get this information in a timely way to act on this disease, where timelines can be more challenged than in other malignancies.

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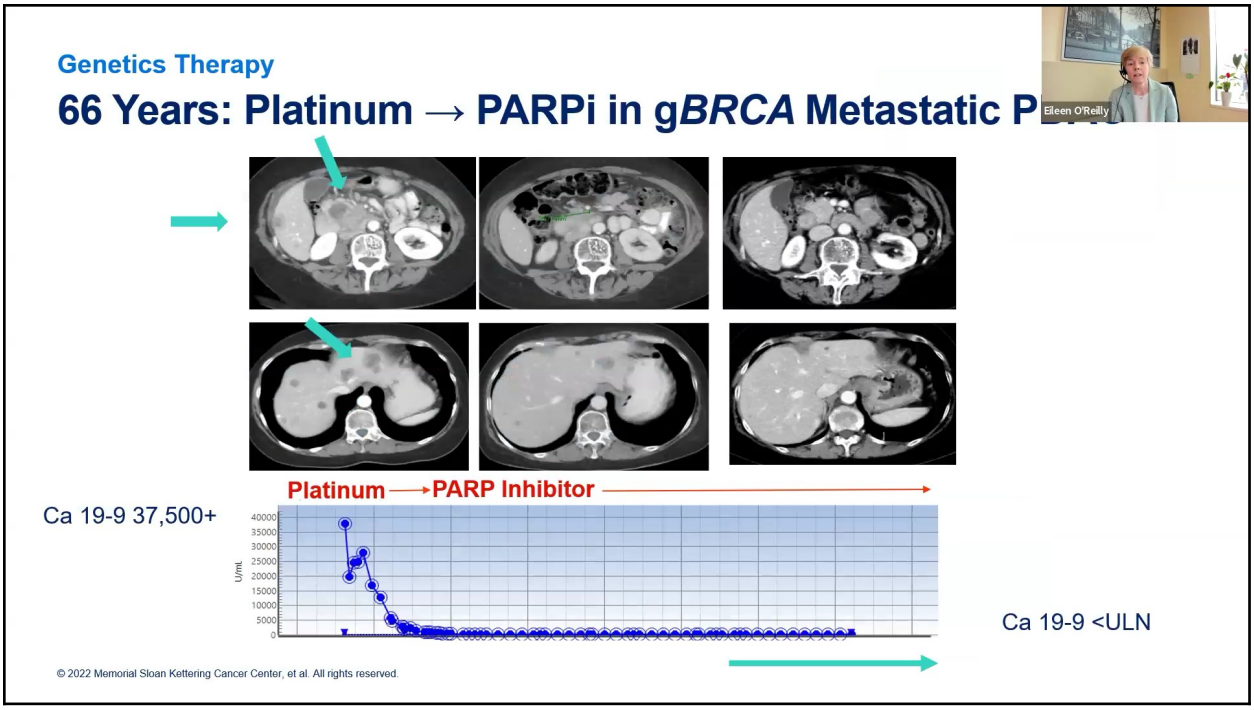

The importance of this is that there are profound examples, and this is one, of a subset of people who have alterations in DNA damage repair, where they particularly benefit from platinum-based treatments, and from this class of drugs and oral targeted group of medications called PARP inhibitors, where we can see these striking, durable responses. For privacy here, I've not put any dates on or anything. But this is measured in many years. We want that to be true for most people with this disease, and we're certainly not there yet. But the key point is we have to look, and if we find, we have to act on that information. That's easier said than done because of all of the complexities of this disease, but always what we're hoping for is that we'll find this unique target and be able to capitalize on this in terms of favorable outcomes.

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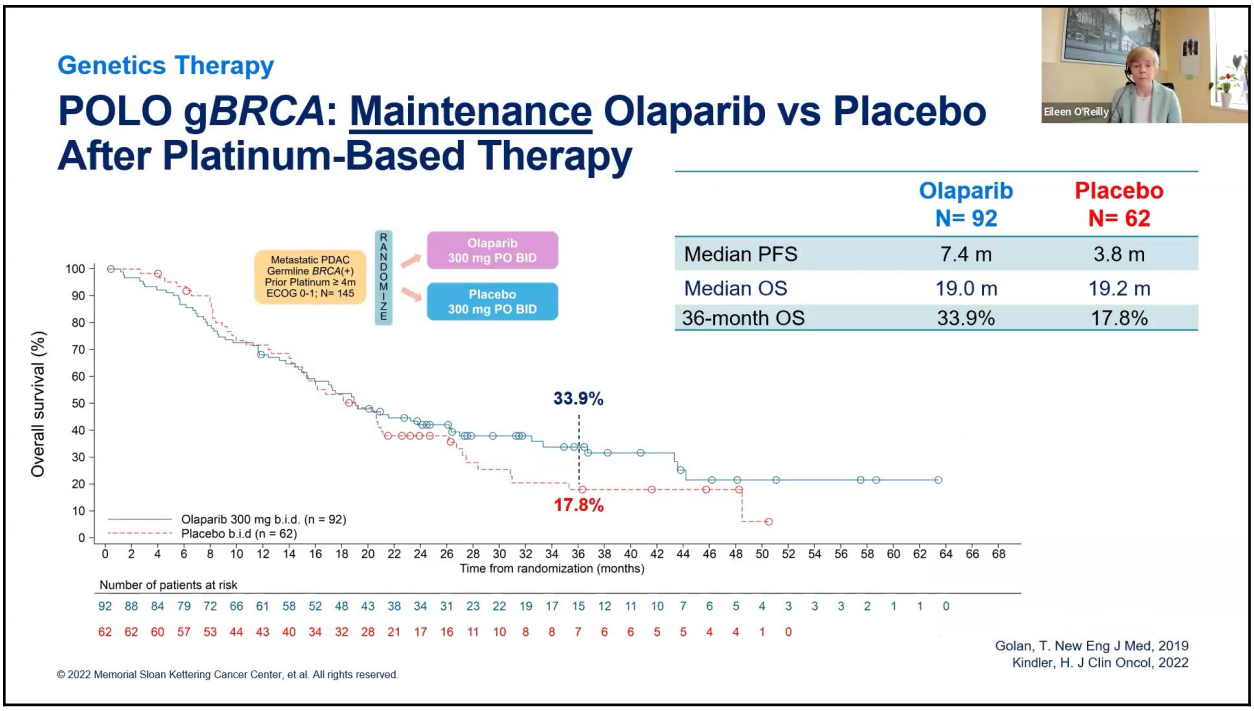
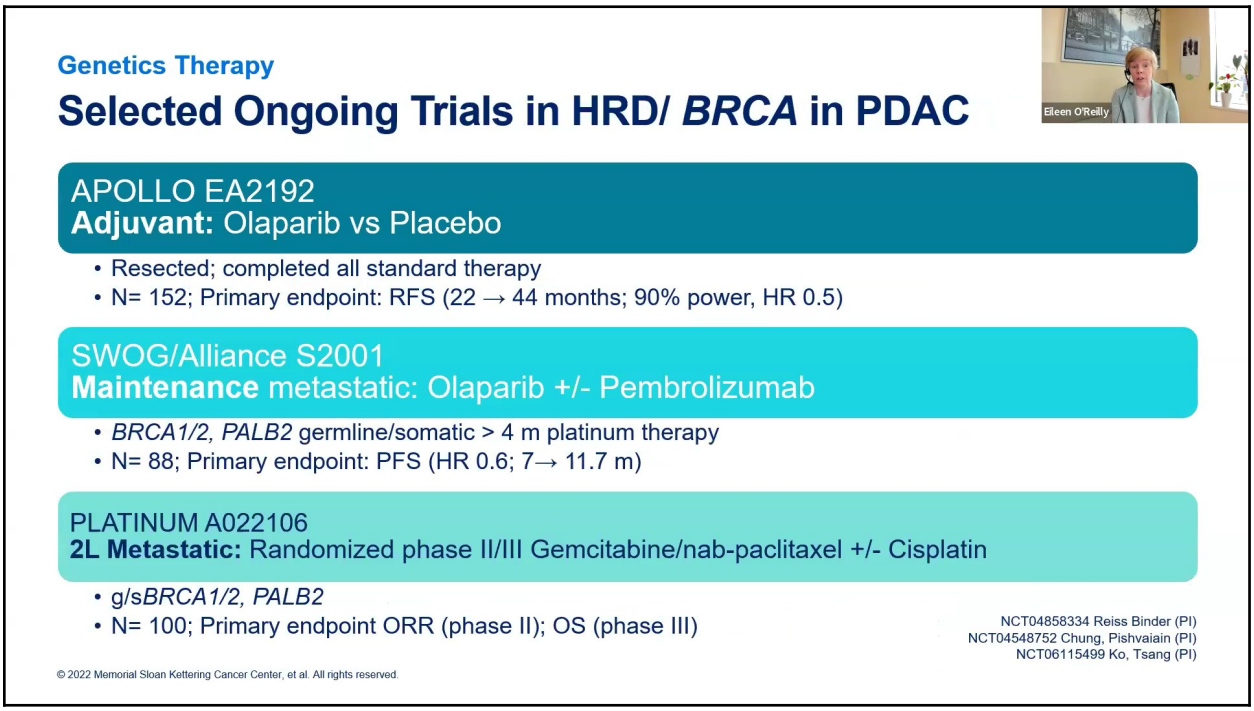


That's been underpinned by this large study, which looked at this class of drugs called PARP inhibitors, and ultimately led to FDA approval. The magnitude of benefit is real in pancreas cancer, although not as pronounced as it is in other diseases. There's a lot of work underway to see how we can scale that.



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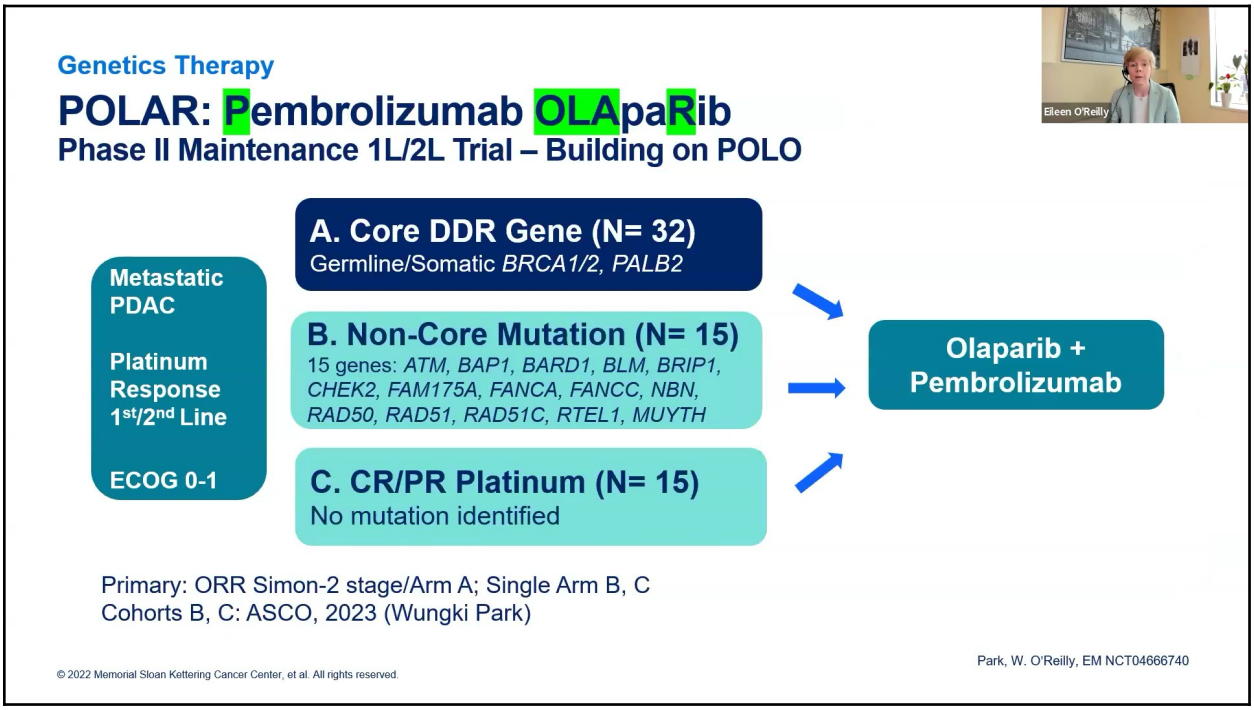
For example, bringing PARP inhibitors to an earlier stage disease setting. They were evaluated in metastatic disease, but looking at them in the postoperative setting, looking in combination with immunotherapy, individuals who have BRCA mutations have heightened levels of genomic instability and maybe more targets for the immune system, and roles in that regard.

Then we have this other study, which is looking at a different platinum, and also looking at high dose therapy and particular alkylating therapy, using autologous transplantation (uses healthy cells from your own body to replace cells that are not working properly) in the BRCA setting to see if there might be a role.



This is a study that will be read out this autumn, looking at immunotherapy and PARP inhibitors in selected groups of people with pancreas cancer. This is a theme that's going to be one to build on. Specifics will come a little bit later, in the autumn.

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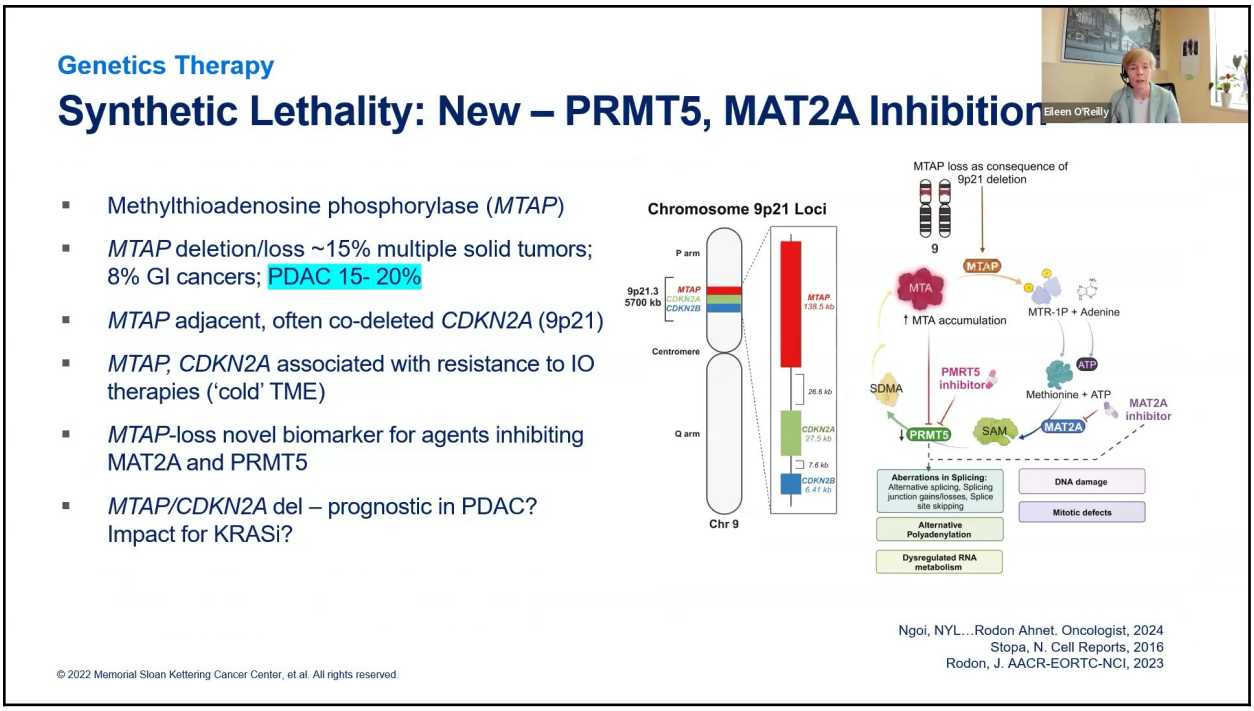
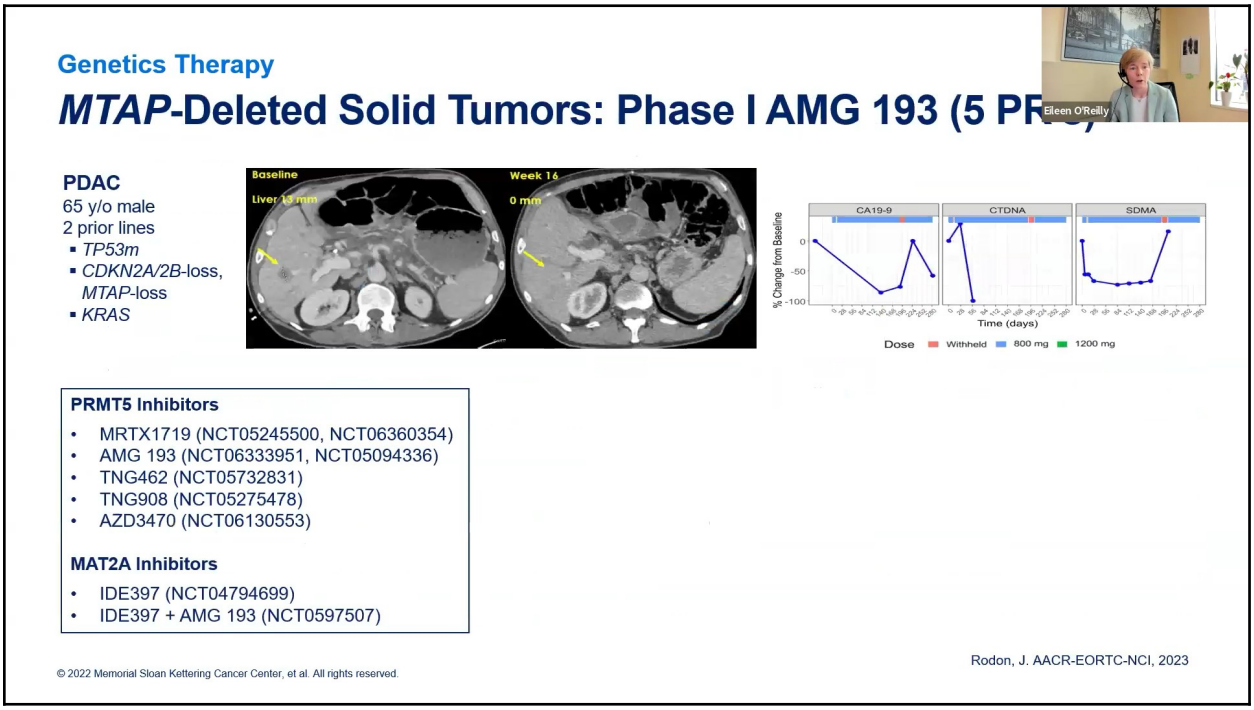


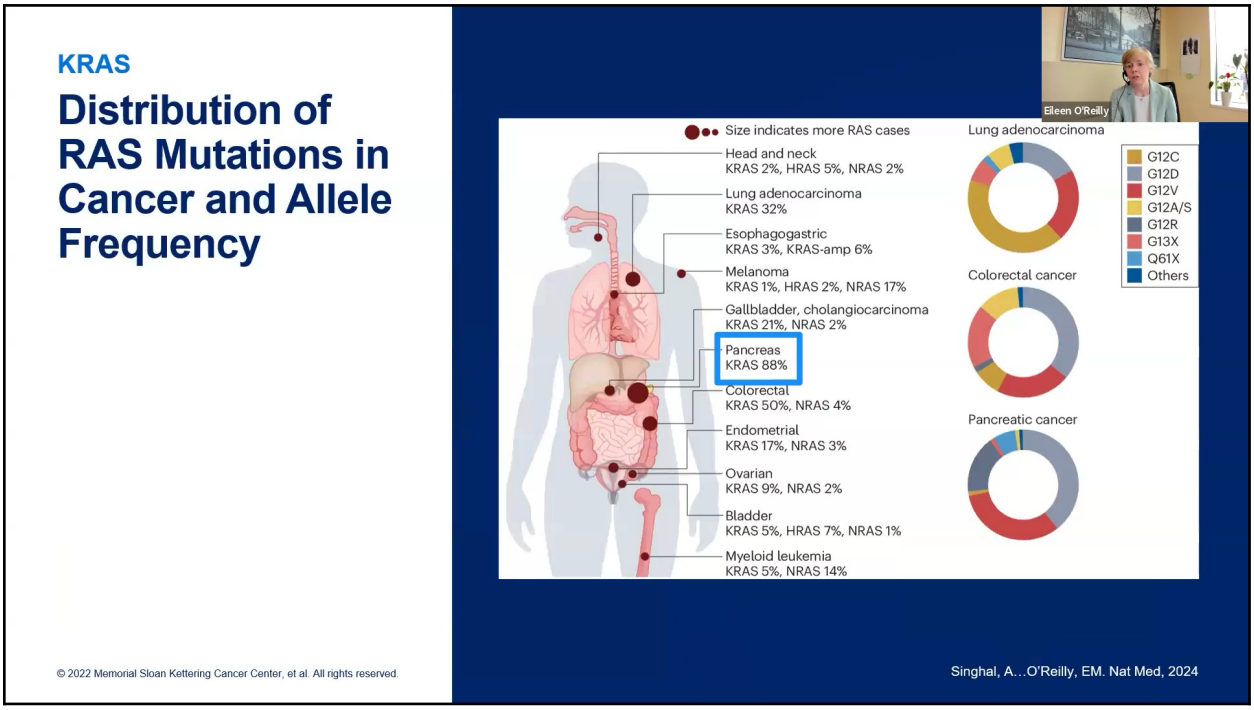


I'm going to pick up a couple of themes here, in terms of emerging areas, going to tumor-based genetics.

About 15%, maybe 20%, of people with pancreas cancer will see deletion of a gene called MTAP, which is associated with other genes in pancreas cancer. The importance is that there may again be a treatment implication. This is an example that was presented at a major meeting last year. This is an individual who had prior treatments, prior chemotherapy. When we see

responses to targeted therapy in the setting of previous chemotherapy treatments, it always tells us that we're probably onto something in this disease. That is being developed in combination with a variety of different agents.

Moving to KRAS-directed treatment.



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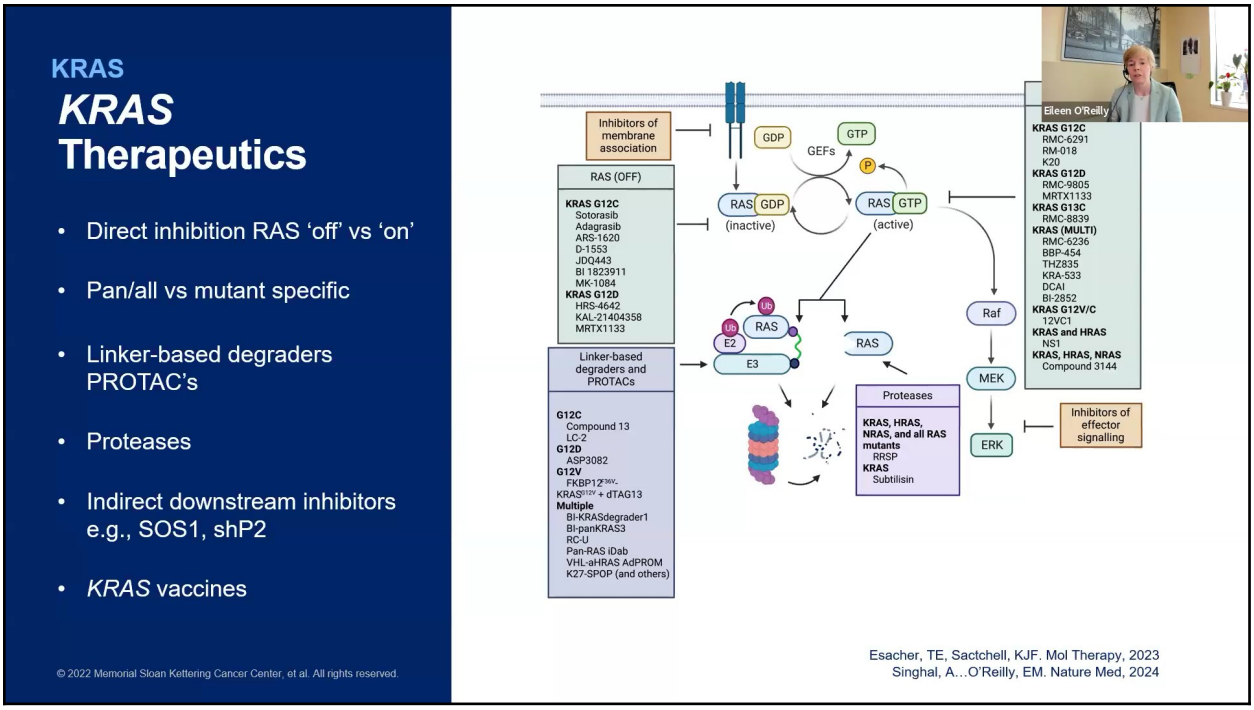
I know that you've had [a discussion with one of our colleagues in the field (Dr. John Strickler)] on this relatively recently. To illustrate the importance of KRAS, it really can't be overstated in pancreas cancer. It's present in the vast majority of people, and we think even 95-96% of people will see, if not KRAS itself, other alterations in that pathway, that lead to all the downstream consequences that are part of the disease process that we know.



Part of the excitement is that there are many therapeutics in the clinic, looking at targeting RAS directly, targeting it indirectly, targeting the downstream protein, and starting to use combinations.

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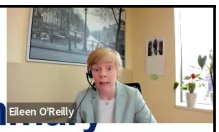
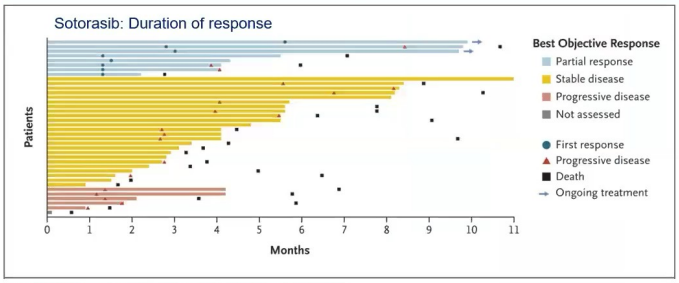
KRAS Therapy

KRAS G12C Inhibitors: Single Agents in PDAC Summary



	N	Response Rate	Disease Control	Median PFS	Median OS
Sotorasib (CodeBreaK 100)	38	21% (8/38)	84% (32/38)	4 m	6.9 m
Adagrasib (KRYSTAL-1)	21	33% (7/21)	81% (17/21)	5.4 m	8 m
Divarasib	7	43% (3/7)	100% (7/7)	-	-
Olamorasib (LY3537982)	12	42% (5/12)	92% (11/12)	-	-
Glecirasib (JAB-21822)	31	42%	93.5%	5.6 m	10.7 m

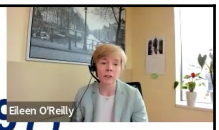


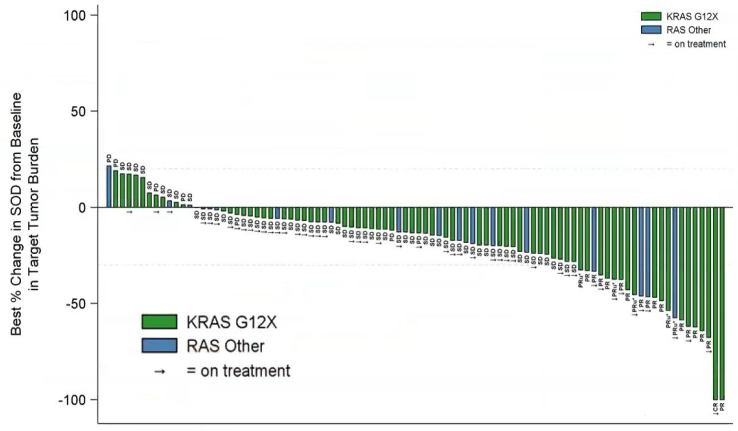
Stickler, J. New Engl J Med, 2023
Bekaii-Saab, T…Pant, S. J Clin Oncol, 2023
Sacher, A. New Engl J Med, 2023
Murciano-Goroff, Y. AACR, 2023
Li, J. GI Cancers Symposium, 2024

Some of these have shown an impact. KRAS G12C occurs in a small percentage of people with pancreas cancer, 1%. Reminder: this is not inherited; it's a somatic alteration. Here, proof of principle has been identified with multiple different agents. This plot on the bottom just shows the durability of the outcome for subsets of people over time. This is exciting.

KRAS Therapy

PDAC RMC-6236: Waterfall Response (N= 97)



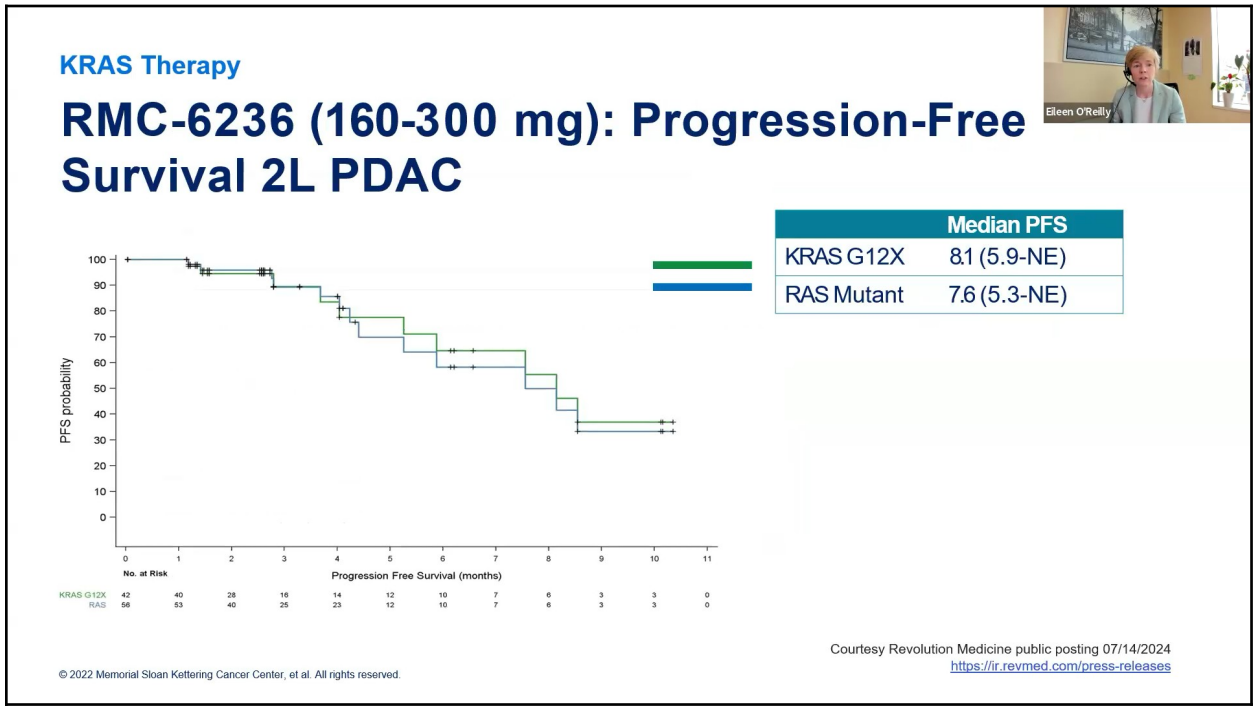


	Response Rate 14+ week	Disease Control 14+ week
KRAS G12X	20% (16/79)	87% (69/79)
RAS Mutant	21% (20/97)	88% (85/97)

Courtesy Revolution Medicine public posting 07/14/2024
https://ir.revmed.com/press-releases

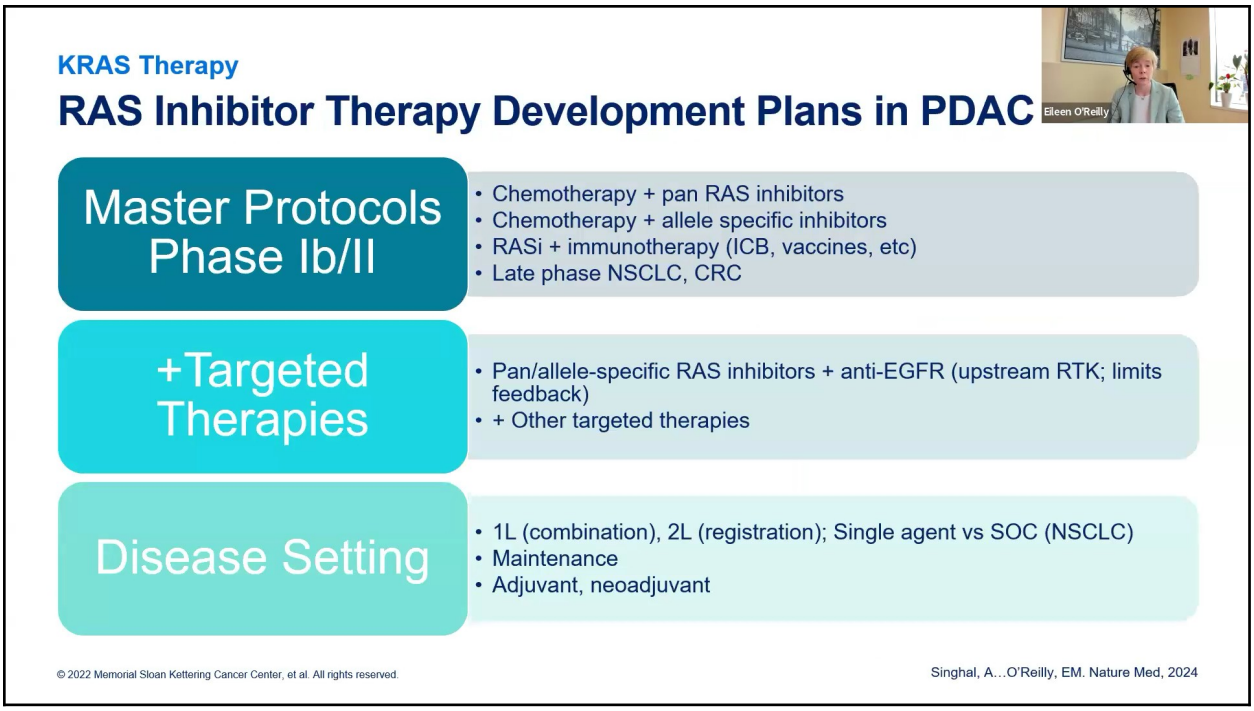
“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

But this is even more exciting because it impacts a larger proportion of people with this disease. This drug is a pan-RAS or all-RAS inhibitor. It's being looked at in pancreas, lung, colorectal, and other diseases with KRAS. This is data that was publicly shared last week, that speaks to the ability to shrink the cancer in the setting of previously treated pancreas cancer. What's happening is that this is moving to a phase 3 trial in previously treated pancreas cancer in people who've had one different one line of prior treatment, and compared to chemotherapy. While it's a targeted agent, it's actually relatively unselected in terms of the patient population that it will include because it covers all the major versions of KRAS that we see in pancreas cancer.



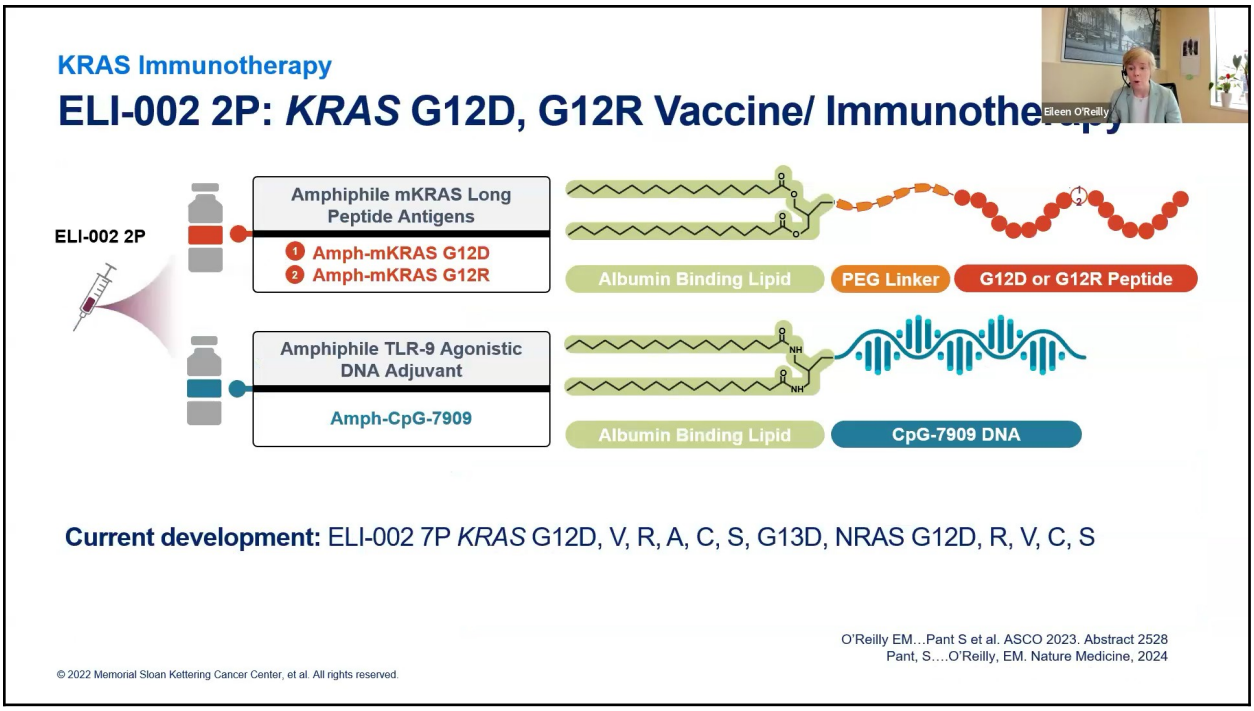
To show that very interesting signal with this disease.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

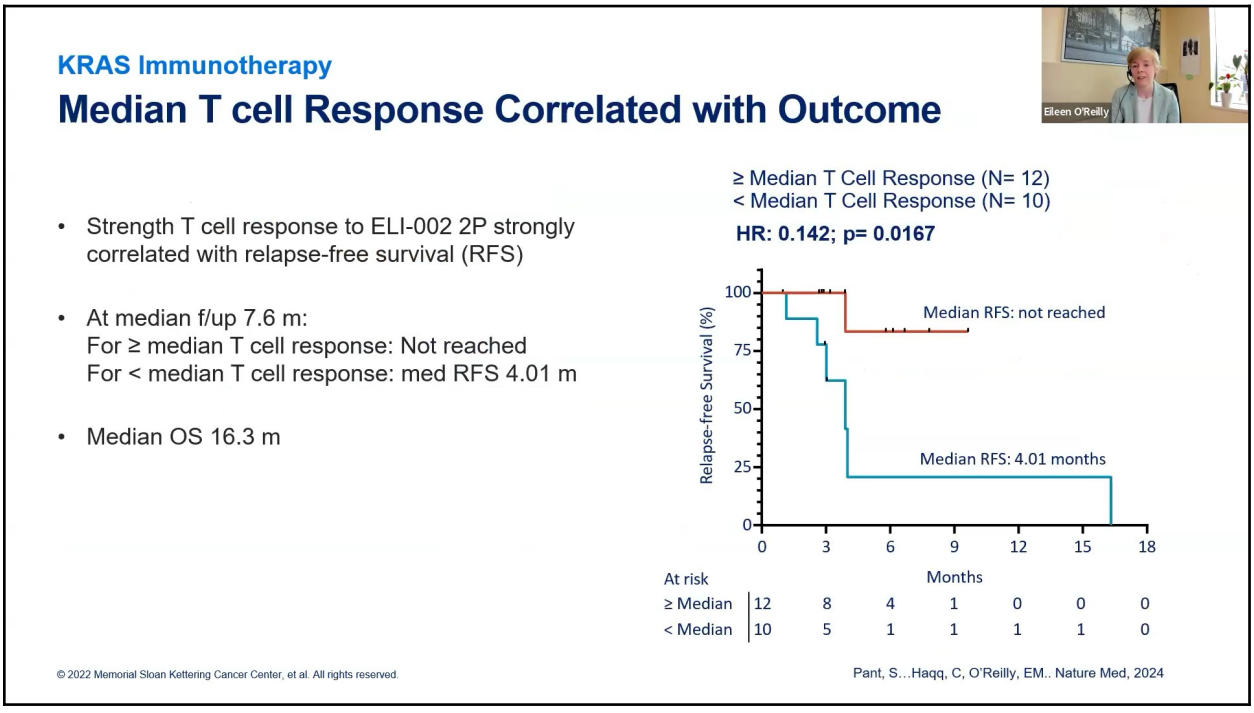


A lot is happening and alluding to the next steps of integrating RAS inhibitors with chemotherapy, in some malignancies, including in pancreas cancer, interested in exploring with immunotherapy, combining with targeted therapies and targeting narrow RAS-focused drugs with contrast drugs and bringing it into earlier stage disease where the impacts may be ultimately even more profound. All of this will have to be sorted out in the clinic in the next two to five years. There are a lot of questions here that are poised to be answered. A lot of them are going to see this moving forward.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

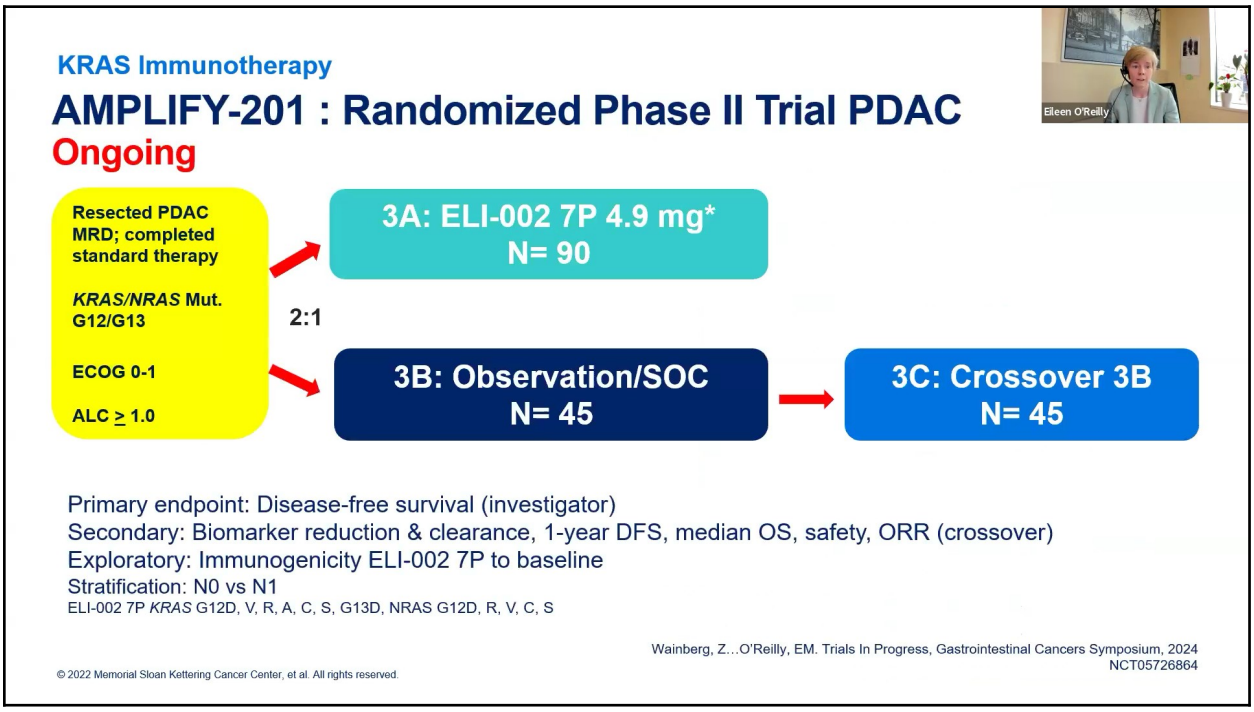


To again set the scene for our discussion, I wanted to highlight that another very interesting and exciting area is immunotherapy and vaccines in pancreas cancer. Vaccines have obviously had a long history in cancer in general, and in pancreas cancer. It's only recently with a few different approaches that we started to see a signal. This particular vaccine is looking at a platform delivery system that targets a protein activated in lymph nodes presented to the immune system and results in immune activation.



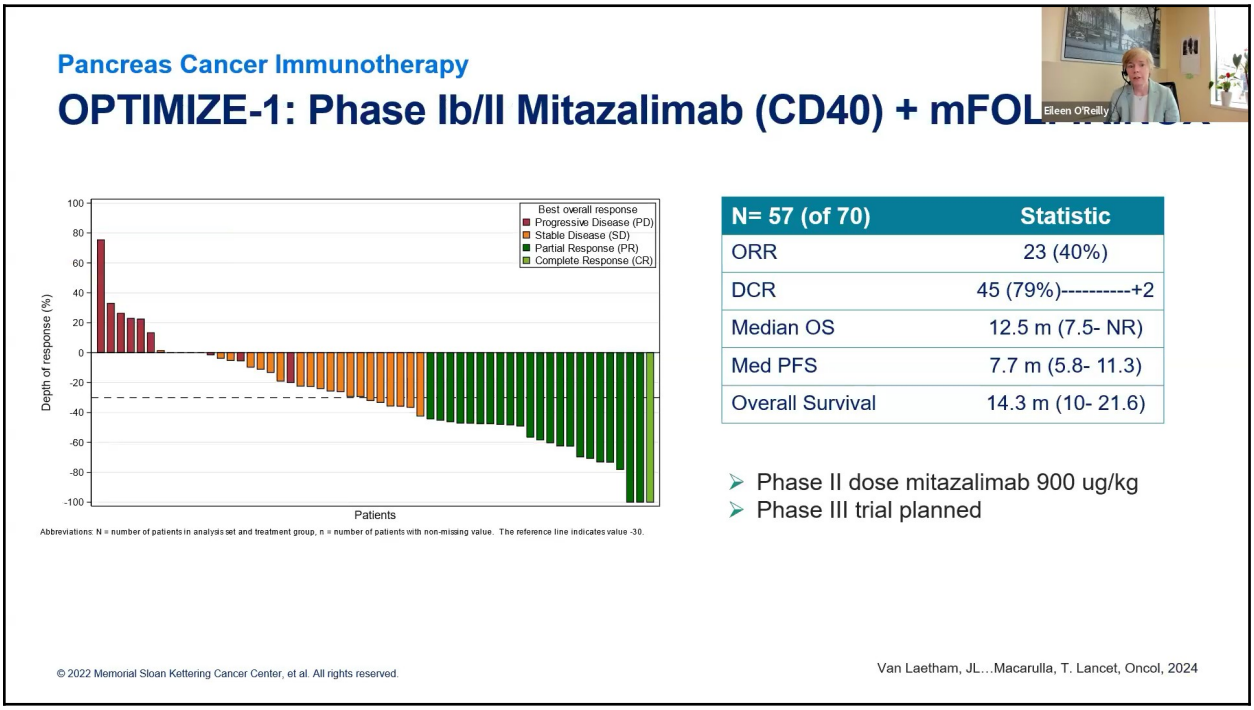
“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

Here the peptide or the target is KRAS with the early goal in pancreas cancer to see whether you could generate an immune response. Can that be done safely? And is that immune response associated with outcome? The early signal with this KRAS, off-the-shelf, non-customized, scalable vaccine is that it was feasible and doable. Early signals are suggesting that those who hadn't had an immune response relative to those that did not, that there may be a difference in their oncologic outcome.



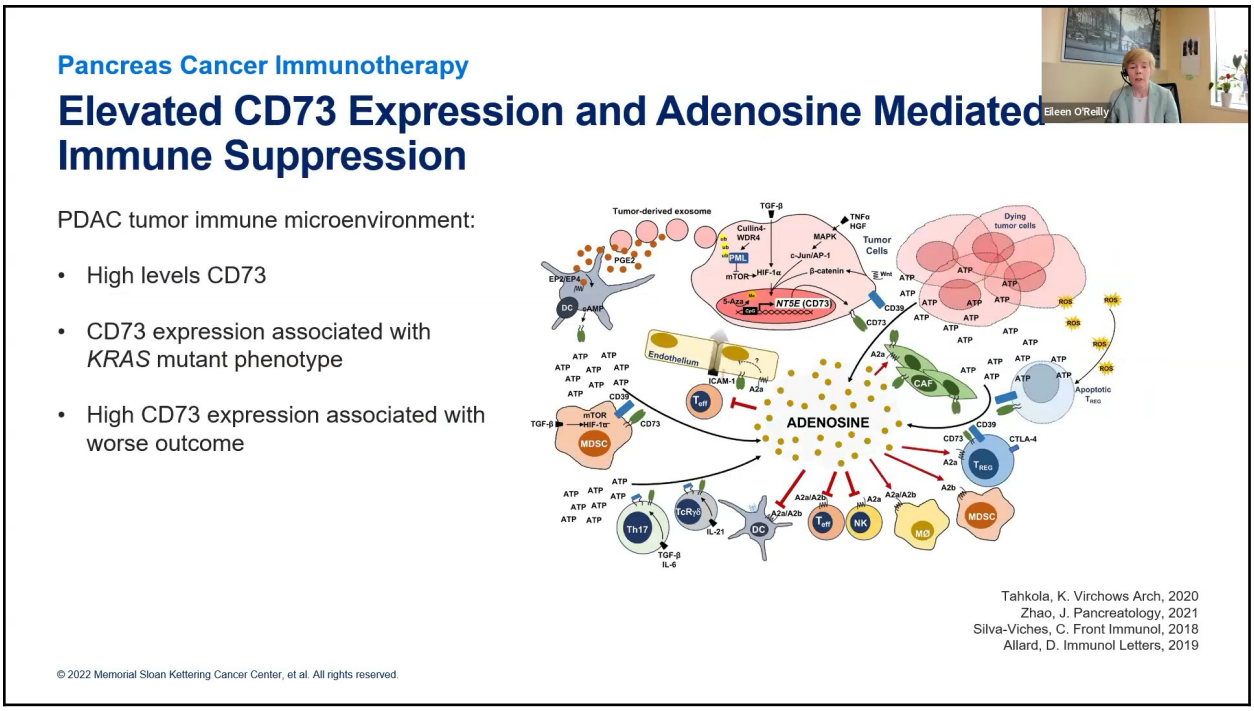
This led to this study, which is underway in pancreas cancer in the resected setting. People have completed all the treatments agnostic to what an individual has had, as long as they're free of disease, randomized to vaccine versus observation. In this setting observation would be the standard to see if this early signal translates into anticancer immunity and in terms of delayed recurrence. This is actively recruiting. We're looking forward to seeing the readout of this.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

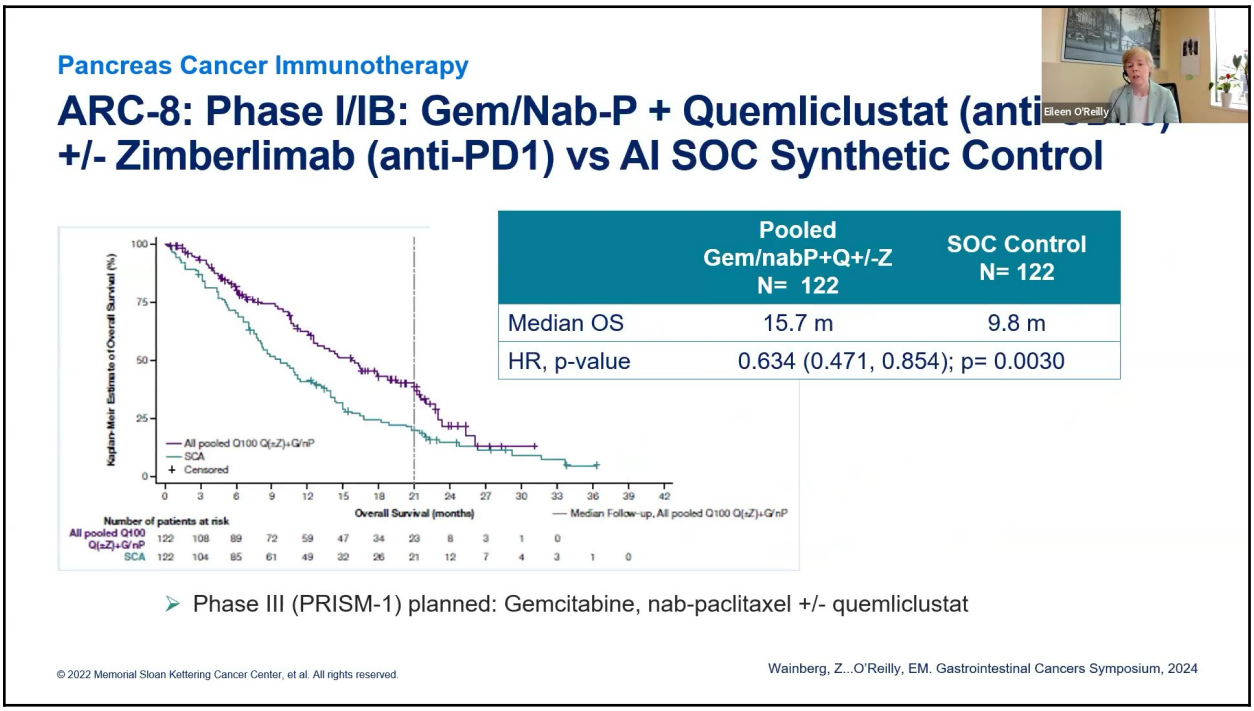


A couple of other things: other drugs to think about that are pathways or classes of drugs that are showing some potential in pancreas cancer is a class of drugs called CD40. It's an immune agonist that activates the immune system and has been combined with chemotherapy and showing nice added cancer shrinkage here in a mid-phase study. This is going to move to phase 3 in period of time.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

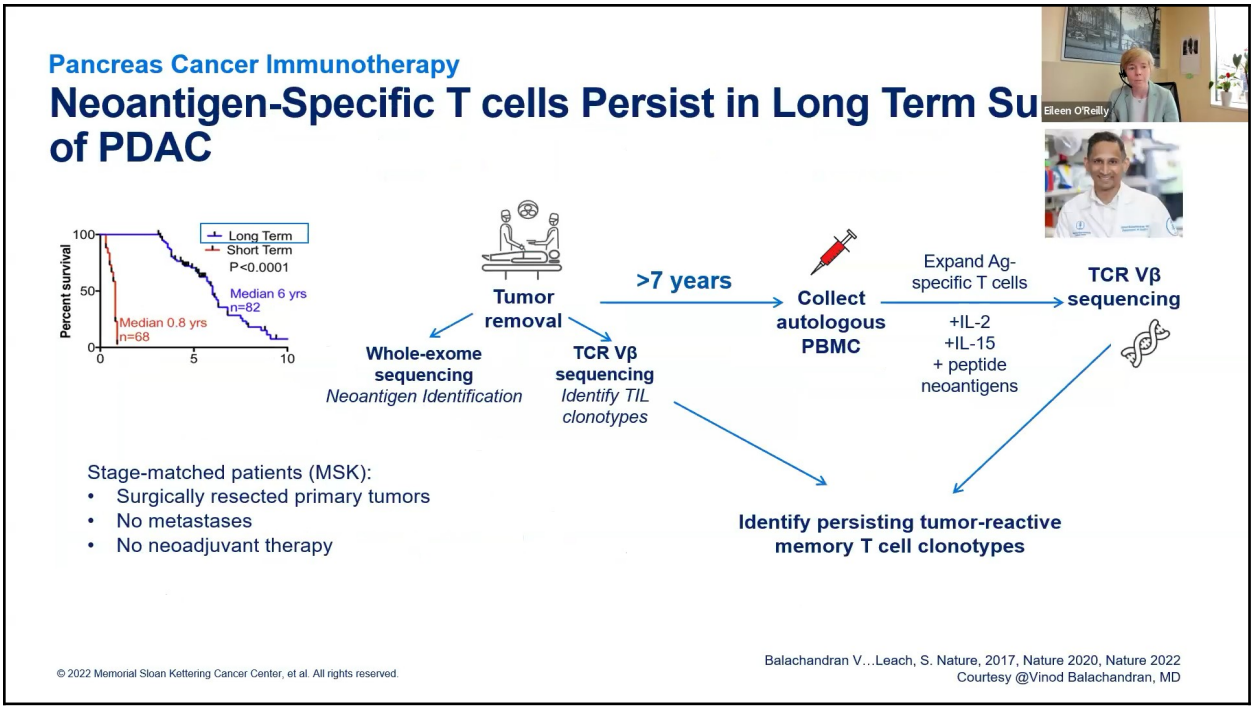


Pancreas cancer is characterized by an intrinsic degree of immunosuppression. There are lots of reasons for that: the whole complex microenvironment lack of oxygen, and immune cells may be excluded. There's lots of immunosuppressive substances in the milieu of the malignant cells, one of them being CD73. This has been correlated with an adverse outcome.



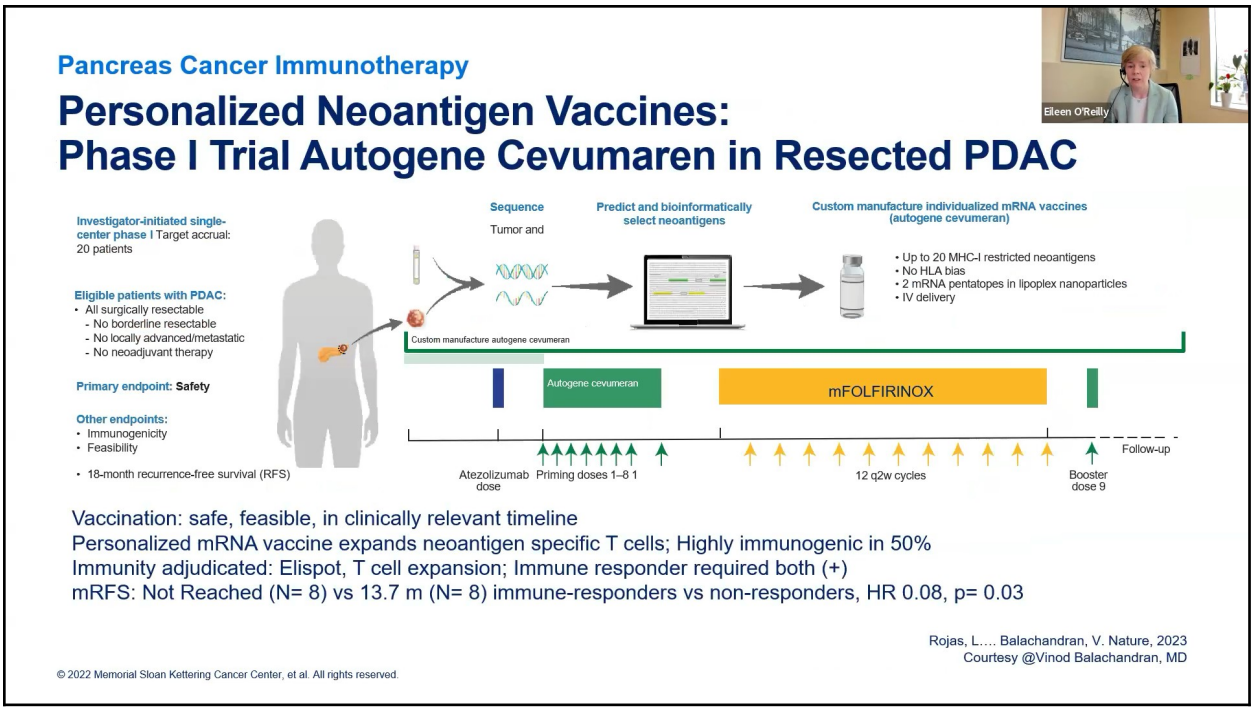
“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

One treatment strategy is trying to remove that immune barrier. Can you impact outcomes in pancreas cancer by using an anti-CD73 small molecule inhibitor that's given intravenously with chemotherapy and an early signal in an early phase study suggests that there once more is something that has potential. This is also moving to phase 3, as we speak, and a lot of potential for this class of drugs, a well tolerated class of agents.



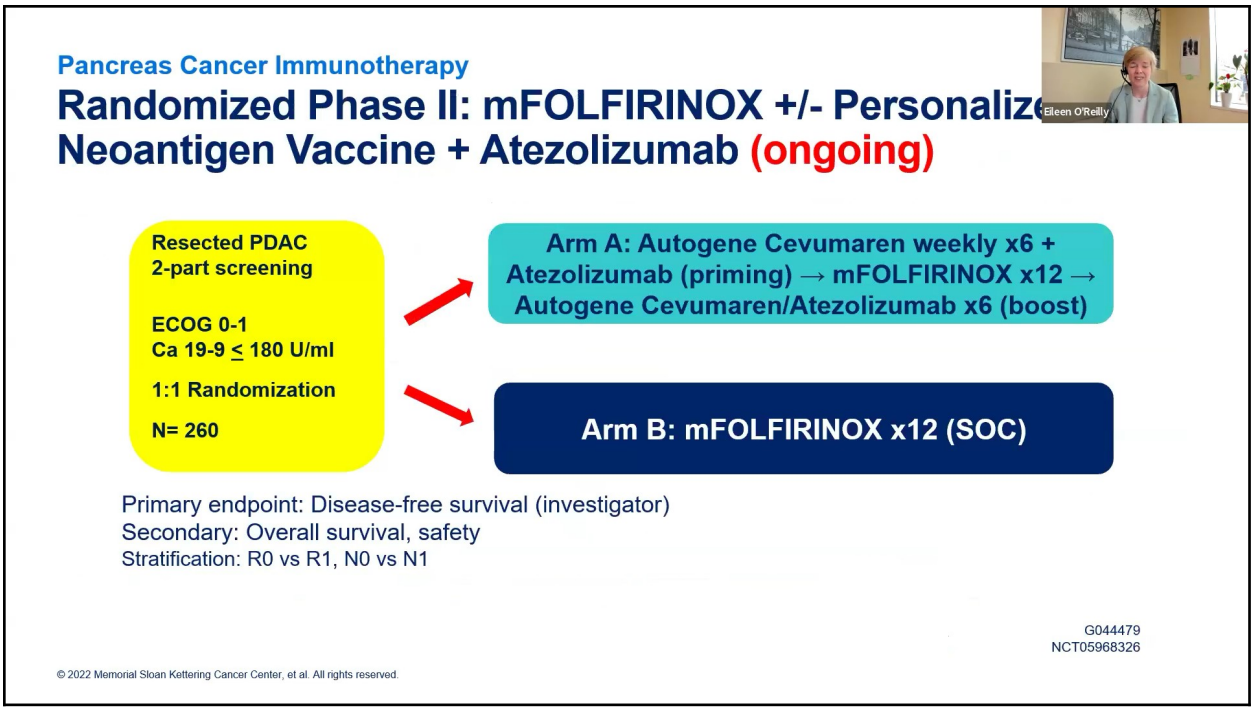
I also want to highlight some work from one of my colleagues here, Vinod Bhallachandran. He is in our group. He made a seminal observation also observed by others, that a subset of people with pancreas cancer who fare well have an enrichment of certain T cells in their immune system and an expansion of that.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]



The idea is that if we could vaccinate and expand this pool of T cells, might this lead to an improvement in outcome? Indeed, that was done with an early phase study, where once more the goal was to show that this was safe and feasible, and this was using a personalized neoantigen vaccine approach. Using an mRNA platform technique with individual customization, so not an off-the-shelf vaccine. It's a lot of logistics to make this happen in the background. This was conducted during the early part of the pandemic. This was feasible, safe, and again showed an oncologic signal with high immunity in about half of patients that was not explained by being innately more immune responsive, but a suggestion that, in fact, it was the vaccine that was contributing.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]



This once more is being evaluated in an ongoing, randomized study for people with resected, pancreas cancer.

The message is that there are two different approaches. This is not doing justice to all the work and strategies that are being developed in the field. But they've independently shown the same thing: that if you generate a potent and specific immune response, that may be translatable into anti-cancer benefits. Both of these are moving forward. It adds increased credence to both that several different approaches have shown this. Again, there are many, many others.

Brad Power 21:10
Thank you. That was a rapid fire runthrough of a lot of options.

It's not just because we have friends from BostonGene here, but there were a lot of questions in the chat around diagnostics, whether that's pre- or post-, or at diagnosis or immediately after.

What's been going on that you see in the diagnostics field?

Obviously, there are a lot of opportunities. If you have this mutation, then we have something for you, if you have BRCA, if you have KRAS, etc.

How do you see that evolving?

Eileen O'Reilly 22:05
This is a very key message for people that this is something we want to do as soon as a person is diagnosed, ideally. Our guidelines have a little catching up to do right now. It's standard of

care to look at the germline, looking for any inherited predisposition, with a panel of genes, and doing either tumor-based or liquid biopsies at presentation.

It's important, though, to acknowledge that there are some unique challenges to pancreas cancer: it can be hard to get tissue. From a technical perspective, we sometimes need a first pass, we need a second pass, we need a third attempt. Partly, it's because of this stromal microenvironment that we talked about, where there is not just the malignant cells, but there's fibrosis or scarring, there's immune cells, and other stuff that we biopsy. Sometimes we don't get an answer.

It's also important to note that liquid biopsies are dependent on tumor shedding, so detectable DNA and other things in the bloodstream. Pancreas cancer, more so than other diseases, can shed less. So the level in the blood and the ability to profile that can be hard. It’s not uncommon that we'll think we have a good biopsy, and then three weeks later, when we do quality control, DNA extraction, etc., we find that we don't have a usable source. These are some of the challenges of pancreas cancer.

But getting this information early, getting the highest quality and the largest amount of tissue and profiling comprehensively, both germline and somatic, ideally, is an integrated approach, and gives the best information. This is a rapidly evolving area. Our ability to detect targets is changing even from a couple of years ago.

Brad Power 24:26
That liquid biopsy then would presumably apply to MRD (minimum residual disease). Monitoring the disease progression would be difficult because of the lack of enough circulating tumor DNA in the blood.

Eileen O'Reilly 24:45
It can be used in that context. That's still an early use in pancreas cancer.

Its greatest use right now is being able to understand KRAS mutational status, whether a person has a KRAS mutation or not and which specific alteration is present. That's a more proximate answer, for the most part, relative to tumor-based sequencing, in that the timelines are quicker. We're not quite there yet, but increasingly, in pancreas cancer we want and need this information at the time of starting treatment. Right now, for the most part, we don't necessarily have that, even with all the setup that one might think could make that feasible to have it in real time for most people with this disease, meaning it takes weeks to sometimes even a month or two.

Brad Power 25:39
On the other side of the equation, a blood test could identify much earlier because typically, when pancreatic cancer is diagnosed, it's very advanced.

Roger Royce: Would you be willing to share your experience with the Guardant or Galleri blood test that you got?

Roger Royse 26:04
Galleri, by Grail. They picked it up early: stage 2, borderline resectable. Then it was six months of chemo and surgery. That was two years ago. I currently monitor it with the Signatera ctDNA test and circulating tumor cell tests on my blood. I keep a strong eye on it, because the doctor is telling me it is extremely likely to recur, but it hasn't yet.

Eileen O'Reilly 26:39
This whole theme of blood-based biomarkers and early detection is a highly relevant and highly interesting one in pancreas cancer, going beyond DNA methylation signatures and protein signatures in the blood. Some of these have shown some early potential. We're going to need a level of even deeper sensitivity for pancreas cancer relative to other diseases. It's likely that their greatest potential will be in an enriched group of people rather than the wider population at large. For example, if we know that a family has a germline mutation that predisposes to this disease, that's a group where perhaps some of these blood-based biomarkers, along with monitoring and other tools may be important.

Or another group that's not as well known, but in the pancreas cancer world, we have our eyes all over, is people who develop diabetes over the age of 50, without personal body habitus or lifestyle or family history that might suggest that they might be at risk of this disease. That to a pancreas cancer oncologist is a red flag. There's a real percentage of people that will go on to have pancreas cancer, and this may be a biomarker, as it were, that's a proximate one, that by a number of years, that could lead to the utilization of some of these screening approaches. There's a big national study and many smaller efforts focused on this space in pancreas cancer.

Brad Power 28:36
Coincidentally, I was at an ASCO Conference this past weekend, and randomly sat next to a doctor who was mentioning that diabetes connection, and that that would be an audience where you might want to do more screening early, or early testing.

Roger: Did you have anything else you wanted to say? I know you've also had apheresis (removal, expansion, and reinsertion of white blood cells) and enhanced some of your immune system.

Roger Royse 29:04
I didn't realize that the idea of expansion was something that was even accepted in the US. I did NK- and T-cell expansion, and I also did a couple of different neoantigen peptide vaccines and for Allen Morris it was nine peptides, or nine amino acids. I don't know what worked.

I want to make one comment about biomarkers. Before this happened, because I was getting tested. A few things should have tipped me off. One: my blood sugar went up for no reason

while my weight went down. Secondly, my CRP (C-reactive protein, a protein made by the liver) went way up. I thought it must be cardiovascular, but it wasn't at all. There were some other things that were just a little off. I had some itching. Just stuff you wouldn't think that would be injurious. It was a bunch of little things. My primary care physician did not associate that with pancreatic cancer at all. But I know now looking back on it, that those were pretty significant clues.

Eileen O'Reilly 30:21
This is an important message. And it's an educational one, for the field at large, that a change in HPLC (High-performance liquid chromatography - mass spectrometry, a broad analytical chemistry technique used to separate compounds in a chemical mixture), worsening of pre-existing diabetes, new onset diabetes, without those traditional characteristics. There's probably something amiss with the pancreas. One may not know it for a few years.

But that's part of the reason your story highlights why there's this now renewed focus on understanding what that means for a given person, whether that can be capitalized on in terms of screening. Not to minimize the challenges of screening. It's this disease, while it's increasing in incidence, it's still a very low frequency event in the wider population. It's always the challenge of: how sensitive can your test be? How many people do you have to screen to avail of an advantage that makes it on a population basis a worthwhile thing?

We think the current guidelines don't suggest that screening for people without any enhanced risk is going to be a value with the current tools we have today. But we hope that will change as we get a greater ability to detect subtleties that predate the emergence of this disease, not just by weeks or months, but by a much longer period of time. I'm sure one will make major inroads into this diagnosis.

Jill Rosen 32:09
You mentioned that the RMC-6236, might be moving to phase 3 soon. (RMC-6236 is designed to prevent the KRAS protein from sending signals that cause cancer cells to grow, slowing or stopping the growth of your cancer cells.) Do you have an idea of when? Or is this something you should still be looking at phase 1 applications if you're a patient, hoping to get into a trial at this point?

Eileen O'Reilly 32:37
There's a lot of RAS therapeutics in the clinic. RMC-6236 is the furthest along in pancreas cancer. In terms of where it is: it's not very imminently going to phase 3. It's in a very specific setting: it's for people with pancreas cancer who have metastatic disease whose disease has grown, despite one initial line of treatment, so it's in a second line specific setting, and, again, comparing the drug to chemotherapy. However, in parallel with all of that, there are multiple ongoing phase 1 and phase 1b combinations that are just starting. They're going to be scaling up over the next three to six months, and maybe even sooner, which we hope will mean a lot more opportunity for a lot more people to access this class of drugs, and not just this drug, but you know, related therapeutics. Some of them are pan-RAS as well. Some of them are more

what we call mutant- or allele-specific, targeting a narrower version of the KRAS spectrum that we see in pancreas cancer.

Jill Rosen 33:56
Are any specific to the specific mutations? Like my aunt has the Q61. So a bit more rare, which is why we had noticed this particular trial. But as you mentioned, I've heard there's many more coming.

How do you get assessed or figure out what the next step is, in terms of what's appropriate, given her profile?
Is that just through meeting with investigators?
How do you go about that process?

Eileen O'Reilly 34:27
It's an important question and a practical one, for the cutting edge in terms of what's happening in the field. Big academic centers are good places to see and consult. It is not always practical for everybody. Usually, they will have a good sense of what's happening and where the field is headed and what trials are most relevant, if not immediately available, what might be an approximate horizon for a given person for Q61 alteration. That's about 5% of people with pancreas cancer. We anticipate that RMC-6236 is going to cover that spectrum. And other agents too. More to come as we see this data mature out and get presented at a major meeting in the hopefully not too distant future.

Kathi Peterson 35:38
I am a KRAS Q61. I have not heard of anyone with this. I don't understand how that fits into the picture. Would I be someone who could potentially be enrolled in a 6236 study at some point? I've been on chemo all this time. Four years. Fairly contained. Stage 4.

Where would I be able to locate these types of clinical trials?
I live in Louisville, Kentucky.

Eileen O'Reilly 36:32
I'll broaden your question. To address the first point first, what is G12? In pancreas cancer, for KRAS, we see three common versions of the gene altered, G12D, G12V, and G12R. And that's about 35%, 30%, and 15%, respectively. Q61H is the next most common, and then there's much rarer versions. But most of them fall at the G12 position in F, G, L, A, etc. All the letters of the alphabet. We think that the current drug that we've talked about, and not to focus exclusively on this, but just because it's the one furthest along, and because there's public data available. We know that it has activity across all of these mutations. We'll need to learn whether some versions of the mutation are more susceptible, whether the degree of response is greater and perhaps more durable. We also need to know whether narrowly targeting that version of the mutation for the more common ones is going to be a better choice versus a pan-RAS inhibitor. It's never going to be scalable for the very rare versions to have a specific drug for that. But for

the common ones, we will, and that's something that will have to be teased out over the next period of time. But we anticipate we'll have insights in the next year on this.

The second part of your question circles back to the other lady who has the question about academic centers. You might want to link in with some of the advocacy organizations that can do a clinical trial search for you that will tailor it to specifics and help guide you geographically. as to what might be practical. If you don't have that I can pass on a few resources to Brad to circulate to those that might be interested.

Brad Power 38:54
That's where we've used Massive Bio, which provides a free pointer to clinical trials, and we just had a session a couple of weeks ago with myTomorrows, which provides a similar service. I'm sure there are others as well. But those are a couple we know.

Gitte Pedersen 39:21
We were contemplating filing a grant application in pancreatic cancer, partly motivated by our personal experience with a friend that we lost last year very quickly, in two months. The very top level understanding is that pancreatic cancer is probably the most deadly cancer out there, and it seems to be very hard to treat.

There are a couple of things that I want to ask you about, because I went to a number of conferences. One of the ideas was that the reason for the lack of response to chemo was due to the pancreatic microbiome. I don't know where that story went, if it's still something that is circulating or needs further validation. So that was question number one.

Number two is there any test, understanding the problem with getting biopsies, that can guide the first line beyond the germline test available?

The understanding that I have gathered from going to these conferences is that the pancreas is so dense. So one of the key problems is getting the drugs into the pancreas. Maybe there are specific treatments to augment that is a separate issue beyond the effectiveness of the drug.

Eileen O'Reilly 41:27
Starting with your first question on the microbiome: Yes, this is a fascinating area, as we learn how this might predict who may respond to treatment, who may respond to immunotherapy, and who may even be more susceptible to get this disease in the first place. We’re in our infancy in terms of understanding what this means in pancreas cancer, and still a ways away from how we might utilize that in terms of direct clinical practice. But clearly a fascinating area of research. I'm definitely not an expert in this area, but watch along and learn and see how this may impact in the future.

I'll circle to the second question. I think it was the theme of maybe what models can we use to predict maybe in the body or outside of the body treatment sensitivity and/or resistance, and apply that in the clinic? There are a number of ways of trying to do that. One of the big

challenges always is: how representative is the model system of the very complex disease that we see in people? What we see there, can we apply that?

There are a number of ways of trying to do that. One of them is we take a sample of a tumor growing in a mouse, and do drug profiling in the lab, and see if we can apply that or using a 3D culture, 2D culture, models, organoids, etc. It is still not clear whether they will truly inform how we approach it in the clinic. Part of the challenge is the timelines for getting the information for most people. Part of the challenge is that we were missing, for example, that whole stroma. That was your third question, and how that may or may not impact response to therapeutics. We are often for some of these models missing the critical component of the immune system, and how that may impact or not impact. They give us some insights.

There are a number of trials that are trying to see if we could use this information in real time to tailor clinical decision-making. But we still have a lot of work to do in this. There are a number of profiling approaches using formalin fixed tissue and looking at expression and seeing if the expression of certain molecules might enrich treatment opportunities. That is a lot of what we're doing in terms of clinical trials. A lot is happening in this space, but still, we don't have a perfect model of this disease, even though we have some very good ones.

Gitte Pedersen 44:40
I just want to add information about a paper.

> From the chat: Placido, D., Yuan, B., Hjaltelin, J.X. et al. A deep learning algorithm to predict risk of pancreatic cancer from disease trajectories. Nat Med 29, 1113–1122 (2023). https://doi.org/10.1038/s41591-023-02332-5

We talked about early detection before. It was a collaboration between researchers in Denmark, somebody I know, and Stanford, where they used EMR data, blood numbers. We talked about some of the early signals of diabetes and how the pancreas is connected. They were able to identify patients 12 months prior to diagnosis, using AI on existing EMR data. Some of these methods, as you talked about, are so low frequency that screening everybody is challenging. But I think with these new technologies, we might be able to narrow the field a little bit. Hopefully, they find some stuff that can be more effective.

Eileen O'Reilly 45:42
I'll give you an example. It's one small example of how this might impact. Our colleagues at Northwell have looked at an AI tool. They are a general health system, looking for people with imaging who came to the emergency room with abdominal pain and had a pancreas finding. Not pancreas cancer, but just a pancreas finding. Using that marker to flag that individual, and to short circuit the system. One: make the awareness known and get that individual into the system to get worked up. Even getting the diagnosis quicker and sooner and people linked in. You can see that if you add up all of these incremental changes, in terms of access, etc., that that can make a difference.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

There are lots of examples of using imaging and AI tools to impact early detection.

I think we're on the cusp of something really, really interesting for this disease, in terms of getting some lead time before the clinical presentation, when, sadly, a lot of people are quite sick.

Rick Davis 47:17
You haven't said a lot about the difference between neuroendocrine and exocrine.

Can you voice a few thoughts on that?

We’re supporting a person who has significant HER-2 expression. He's treated at a community clinic. After three years, they finally figured out they should be focusing on this HER-2 expression, which just astonishes me. I'd like to come back just for your thoughts on the choice of treatment, because I question it.

It seems this is a real problem for pancreatic cancer that so many people are still treated in a community setting, and the people in the community setting don't think the way you think. I'm not sure how we address that. What do we do for all these people who can't get to the types of treatment you're talking about?

Eileen O'Reilly 48:48
I probably should have set the scene a little better, in that the discussion today was focused on adenocarcinoma, but not in any way to take away from the neuroendocrine field. To recap of the spectrum of pancreas malignancies that we see: adenocarcinoma is probably nine-and-a-half out of 10 people. A smaller percentage will have neuroendocrine, which is from what we call the endocrine component of the pancreas, and then we'll rarely see things like acinar (a rare and aggressive type of pancreatic cancer that occurs in the pancreas' secretion glands). Occasionally we'll see metastases in the pancreas from another malignancy. Occasionally lymphoma in the pancreas, and smaller numbers of very rare, rare events.

Neuroendocrine cancer is a distinct and different malignancy and treated very differently. It is prognostically different, and fewer targeted-based approaches than perhaps adenocarcinoma is increasingly seen to have.

Your second point is a very important one for the field. Having been in this field for a while it, there's understandably right over the years been a lot of therapeutic nihilism about the approach to pancreas cancer and goes to even the basic things of somebody with a diagnosis of metastatic disease not necessarily having the opportunity to have a referral to an oncologist to discuss whether or not treatment is indicated, not to mind what type of treatment, and that point was being decided in advance of that. That happens more than we think even today. It requires education. It requires outreach.

It's understanding that the world is changing, and hopefully changing very meaningfully for adenocarcinoma of the pancreas, and that there is access to a comprehensive cancer center. It's not just about the therapeutics. It's an integrated approach for the challenges with bile duct obstruction or blockage of the duodenum, being able to manage that successfully. Treating blood clots, managing pain, optimizing nutrition, getting in pancreatic enzymes, all of the important things that we know can impact quality of life, length of life, and ability to give treatments.

I hope we'll see more of this, in terms of the bigger community-based expertise: it's not for want of interest. It needs dedicated resources and time and people.

Rick Davis 51:49
When we have the opportunity to work with the drug companies in other areas, we talk a lot to them about better education for the community practices for all different types of new drugs and cancers. The specific issue that concerned us for this particular patient was that the community practice happened to be running a TAPUR (The Targeted Agent and Profiling Utilization Registry, a non-randomized clinical trial that aims to describe the performance – both safety and efficacy – of Food and Drug Administration-approved, targeted anticancer drugs prescribed for treatment of patients with advanced cancer that has a potentially actionable genomic alteration.) arm of atezo (atezolizumab/Tecentriq, an immunotherapy drug) plus PHESGO® (pertuzumab, trastuzumab/Herceptin), and hyaluronidase-zzfx), a combination treatment option for HER2-positive breast cancer.

We felt, speaking to our own advisory board experts, that Enhertu (Trastuzumab deruxtecan, an antibody-drug conjugate), which has just been approved, would be a much better option. But they just railroaded this poor guy into their arm, which gives me a lot of concern about academic conflict of interest as well, which I am sorry to have to say, but we do see it. I don't know how he's going to do. He immediately responded badly to atezo with rashes and goodness knows what.

You've got a new drug like Enhertu, which has just been approved. Why don't you use it? Why do you put them into something that's ages old, and we don't even know if that combination is going to work? If a person came to you with high HER-2 expression, what would you do?

Eileen O'Reilly 53:25
Speaking generally, firstly, HER-2 is uncommon in pancreas cancer, just to make the point, in RAS-driven malignancies. It's usually the inverse.

Rick Davis 53:40
He had a KRAS mutation too.

Eileen O'Reilly 53:43
Not knowing anything about the specific profile here, but it always makes me wonder when somebody has a RAS mutation, how meaningful the HER-2 part of the activation is. There are

different ways of looking at that via immunohistochemistry, or looking at the copy number, and looking at it from the next generation sequencing perspective. One would want to be convinced that that truly was the actionable part of the genomic alterations that this individual has to say that going down that route is a good one.

Not to take away from trastuzumab deruxtecan (Enhertu), but data were presented at ASCO this year. Even in the small subset of people with pancreas cancer that did have high expression, the signal was more modest than anyone would wish. “It's not straightforward,” is what I would say. Maybe there's more to the story here that's guiding in the background.

Jill Rosen 55:15
For either the phase 3 or the phase 1 that's ongoing for the RMC-6236: for the exclusion criteria, can they be on more than one type of chemotherapy already? Or does it have to be a first attempt? Can they have had any adjunctive therapy within that?

Eileen O'Reilly 55:45
For the phase 3 that's happening in the second line setting, comparing RMC-6236 to chemotherapy: right now, the way it's planned is just one line of prior chemotherapy, and no prior RAS-targeting approach.

Jill Rosen 56:02
For the phase 1s that are still open, if they are, is it again, just one line?

Eileen O'Reilly 56:10
No. It all depends on how the study is written. But typically, for phase 1s, they're, in general, a lot less restrictive in terms of the extent of prior treatments. Having said that, there are some phase 1s, which are looking at chemotherapy-based combinations, and there may be more limited restrictions in terms of the amount of treatment in that setting.

Jill Rosen 56:34
If you were a patient, considering your second line options, what would you think of to try to decide between a RAS-based treatment versus an immunotherapy route? What would be your top things that you'd consider for that patient?

Eileen O'Reilly 56:54
Understanding the genetic profile of the particular individual's tumor would be important. Also understanding what immune therapy-based approaches. It is a wide field. Some things are relatively far along in development, and others are very early. We really don't know yet. For immune checkpoint blockade, for pembrolizumab (Keytruda), nivolumab (Opdivo), etc., those drugs on their own have value, and about 1% of people with pancreas cancer, where there's mismatch repair deficiency or a lot of mutation. It's not a frequent combination. Not to say that there isn't merit for combinations with immune checkpoint blockade. That would be what you would have to look at. I might suggest, not knowing the specific person, but for most people with

this disease, the high priority is going to be a RAS therapeutic approach, when there's no RAS mutation present.

Allen Morris 58:24
Does a germline BRCA mutation or other homologous repair mutations have greater clinical impact than somatic? In other words, is there a difference between a germline mutation and somatic mutation as far as clinical response?

Eileen O'Reilly 59:17
That's a great question. It's one that we've been looking at, and others in the field, for a while. What we think matters is whether there's loss of the second version of the gene either in the blood or in the tumor. This “LOH”, or loss of heterozygosity, is probably what predicts for benefits. It's biallelic (relating to, affecting, or of both alleles of a gene). For example, in about eight out of ten people with pancreas cancer who have a BRCA mutation, we know that the tumor is driven by the BRCA, but it means that for about two out of ten, it's not driven by the BRCA, and BRCA targeting approaches probably don't have the same value for that person. There are still a lot of ways as to how best to understand that because it's not as straightforward as it might seem in terms of knowing it. But biallelic mutations, whether somatic or germline, or somatic and germline, is probably the key thing that predicts the value of the therapy.

Francesca Paradiso 1:00:30
My question is more about another part of the diagnostic tool. Since I was a postdoc in the lab, and now at BostonGene, as you've said, it's so difficult to get tissue sometimes, and also liquid biopsy. Maybe there is not enough material. Something that is in our efforts at BostonGene, but also I was working on actively in the lab, is to look at PBMCs (peripheral blood mononuclear cells, white blood cells with round nuclei that are found in peripheral blood, including lymphocytes, monocytes, natural killer cells, and dendritic cells). We'll do immunoprofiling from the blood for patients to inform and predict outcomes in immunotherapy, which I totally understand is not the elective if there is a KRAS mutation, but maybe in the future, when those KRAS therapies will also be firstline, maybe we'll think about the combo with immunotherapy. Those kinds of diagnostics might also be helpful. I just wanted to have your opinion on that. What is your feeling about this kind of diagnostic?

Eileen O'Reilly 1:01:27
There is a subset of people with pancreas cancer, where their genomic profile doesn't suggest that they're likely to benefit from immunotherapy, but do. We need the tools to identify who these individuals are. We have some hints in the retrospective setting when we, for example, collect samples as part of clinical trials and profile them, and try to match that with response to resistance. There are some hints of signatures that may suggest that this is a group of people that are more likely to benefit from an immune therapeutic approach. Maybe I'm naive here, but we're going to see more focus on immunotherapies. We know from RAS therapeutics that the immune environment is really important and how those agents work. That's true for chemotherapy. I'm sure that it is. It's just that we haven't focused on that and learned. I definitely

think this is going to be important. Not there today, or tomorrow, but part of the future, I hope, for this disease.

Brad Power 1:02:48
Thank you very much.

“Novel Therapies and New Directions in Pancreas Cancer, 2024” (Eileen O’Reilly, MD) [#106]

CHAT DISCUSSION

00:12:27 Rick Davis, AnCan Foundation: AnCan Peer Pancreatic Support Group (formally sponsored by Canopy Cancer) https://ancan.org/pancreatic-cancer/ Next meeting tomorrow Thu, 7/25 8.00 pm Eastern free & drop-in
00:13:04 Robyn Caldwell: Have you ever seen a cure in a PDA polymetastatic to liver patient?
00:14:04 Robyn Caldwell: Do you ever use "off-label" PD-L1 expression to treat a patient with Keytruda?
00:22:05 Allen Morris: Does germline BRCA mutation have greater clinical impact than somatic mutation?
00:24:13 Allen Morris: What ctDNA company do you recommend for treatment monitoring?
00:27:05 Rick Davis, AnCan Foundation: Dr. Morris, per Dr. Pamela Muenster Co-director of the UCSF Center for BRCA Research, the answer is no.
00:30:50 Allen Morris: How common is autoimmune exocrine pancreatitis?
00:32:42 Allen Morris: What are the amino acid lengths in the peptides used in PCan vaccines?
00:33:08 Ellen Miller: I had to join late. Will the full recording be sent to attendees?
00:33:22 Allen Morris: Do you routinely test for Her2 in pancreatic cancer? I ask because ant-Her2 therapy as of 2024 is FDA tissue agnostic.
00:34:20 Ellen Miller: Do you recommend pancreatic enzyme supplements for anyone with PC, or only if there seems to be a digestion issue?
00:37:41 Allen Morris: I presume you are guided by CA19-9 and radiologic monitoring over ctDNA?
00:38:40 Ellen Miller: G12v KRAS has been identified as an actionable mutation for me. Unless you already shared on this, are you seeing promising trials/work for this mutation?
00:41:06 Allen Morris: Given a group who is high risk, would you recommend MRI for screening, for example, as promoted by a company Ezra?
00:44:27 Allen Morris: Have you heard of the science flyer called "Bioworld", if so have you heard of a company Syncromune?
00:47:33 Allen Morris: If pancreatic cancer vaccines have up to for example 20 peptides, is any researcher concerned with the concept of "antigen competition"?
00:53:16 Saed Sayad: Amazingly, using an AI medical differential diagnosis for Robert's early symptoms showed Pancreatic Cancer as the first diagnosis.
00:53:22 Saed Sayad: Findings .....
1, Y, Sex Male
2, Y, Age 26 To 55
3, Y, CRP Increased
4, Y, Weight Loss Gtr Than 10 Percent
5, Y, Glucose Plasma Fasting Gtr Than 126 mg/dL on Two Occasions

Diseases .....
125, Carcinoma Of Body Or Tail Of Pancreas

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125, Hyperthyroidism (Graves Disease)
63, Hemochromatosis
42, Cryptococcal Meningitis
42, Leptospiral Meningitis
00:53:57 Roger Royse: Reacted to "Findings ....." with 👍
00:54:08 David Plunkett: Reacted to "Findings ....." with 🤔
00:55:25 Allen Morris: There is a belief that combinatory therapy might be the holy grail. And KRAS is the most promising molecular target. And KRAS has many downstream targets. Barring expense and access, what is barring patients from the right to try, an out of the box, N of 1 experiment when they are at the end of the line? Would you be willing to be a copilot in a combinatory approach of which would include the KRAS cascade? And if not, why not?
00:55:58 Roger Royse: Replying to "Do you recommend pan..."

I take them and they help me a lot, now that I only have half a pancreas
00:57:21 Robert Weker: Replying to "Do you recommend pan..."

I'm with Roger. I have been using them for 10 years and very helpful for me
00:57:36 Roger Royse: Replying to "What ctDNA company d..."

I use the signatera by Natera. Also getting the Protean tests - Cell Search, One Cell, and Genomic Testing Cooperative. I have used datar genetics but got 2 indeterminate results
01:08:40 Gitte Pedersen: Replying to "What ctDNA company d..."

Can we link up - one of the things we are trying to do is to enrich for tumor cells in blood and analyze them - so if you do have circulating tumor cells - this is me https://www.linkedin.com/in/proximity/ and you can schedule a call here https://calendly.com/genomicexpression
01:11:06 Gitte Pedersen: Here is the reference to the AI paper I mentioned: Placido, D., Yuan, B., Hjaltelin, J.X. et al. A deep learning algorithm to predict risk of pancreatic cancer from disease trajectories. Nat Med 29, 1113–1122 (2023). https://doi.org/10.1038/s41591-023-02332-5