“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Brad Power
April 3, 2024

“Precision cancer medicine for pancreas cancer is finally becoming real for the clinic.” – John Strickler

“I'm particularly optimistic about our new approaches to target KRAS, which could open up a whole range of new therapies for patients with pancreas cancer outside of traditional cytotoxic chemotherapy, which nobody likes.” – John Strickler

“We can learn a lot from people who are willing to stray from outside of the norm or convention because with pancreas cancer, that convention is just not acceptable. As I'm sure Roger [Royse] will tell you, the long term outcomes with the standard of care for pancreas cancer are unacceptably poor. We need paradigm shifts in order to move the needle with this very difficult-to-treat disease.” – John Strickler

Meeting Summary

Patients who are diagnosed with pancreatic cancer and do an online search for their prospects are confronted with a poor prognosis and dire statistics:

- The overall five-year survival rate is 7.2%.
- Looking only at pancreatic cancers that have not spread beyond the pancreas (“localized” cancers), the survival rate is 27.1%.
- For cancers that have spread, but only to nearby areas (“regional” cancers), the survival rate is 10.7%.
- Metastatic (Stage IV) pancreatic cancer has a five-year survival rate of 1 percent.

If they then search for standard treatment options, they find:

- Pancreatic cancer treatment may involve surgery, chemotherapy, radiation therapy, vaccination, pain management, immunotherapy and dietary changes.
- Surgery remains the gold standard of treatment, but can be achieved only in a small number of patients whose cancer is caught early and is localized. The main surgical approach (the "Whipple" procedure) involves removing the head (wide part) of the pancreas, which is connected to the top part of the small intestine. Those who undergo a successful Whipple procedure may boost their 5-year survival rate up to 25%.
- Pancreatic cancer which has spread more is treated with chemotherapy and possibly radiation.

Despite the grim survival statistics and poor prognosis associated with this disease, improvements in supportive care, chemotherapy, and molecular diagnostics are enabling some patients to live longer and better. Key among these developments are drugs which target a mutation (e.g., KRAS). If you have this mutation, you have a new treatment option to consider.

John Strickler, MD, Associate Professor of Medicine in the Division of Medical Oncology at Duke University and co-leader of the Molecular Tumor Board and Precision Cancer Medicine

and Investigational Therapeutics Research Program, is uniquely qualified to discuss advances in pancreatic cancer care. Dr. Strickler specializes in the treatment of esophageal, gastric, pancreatic, and colorectal cancers. with a focus on clinical trials. Clinical trial patients usually come to him looking for an alternative therapy once standard treatments have not been effective. He recently published results on a study of pancreatic cancer patients with a specific mutation (*KRAS G12C*).

What are the improvements in treatments for pancreatic cancer coming online today?

- **Personalized medicine** is emerging as a key approach for pancreatic cancer, with targeted therapies based on your tumor profile showing promising results. For example, drugs targeting KRAS and BRCA mutations are showing promise in clinical trials and entering the standard treatment guidelines.
- **Genetic testing and molecular profiling** are becoming increasingly important to identify if you can benefit from targeted therapies.
- **Early detection** remains crucial for improving patient outcomes. “Germline” (hereditary) testing, a type of genetic (DNA) testing that looks for inherited mutations or inherited predispositions to certain types of cancers via cheek swab, spit sample or a blood draw, can help identify individuals at higher risk.

What are future improvements to keep an eye on?

- **Testing advances**: New tests, such as RNA sequencing and proteomics, will provide a richer profile of your tumor and tumor microenvironment.
- **Liquid biopsies** (blood draws) hold promise for easier cancer diagnosis and treatment monitoring, although challenges remain in their accuracy for pancreatic cancer. If you can pick up pancreatic cancer earlier, say five years before it becomes a full blown cancer, you might be protected from an aggressive malignancy.
- **Cancer vaccines**: Early data from studies indicate that cancer vaccines may generate an anti-tumor immune response, with hints of beneficial impacts in early pilot studies.
- **Cryotherapy:** Cryotherapy (sometimes known as cold therapy, the local or general use of low temperatures for treatment) is being explored as a potential treatment, with some case studies showing positive results.
- **Radioligands:** Radioligands (a kind of radiation therapy made of a radioisotope and a molecule that binds to specific markers on cancer cells) have potential for pancreatic cancer treatment, particularly for neuroendocrine tumors (cancer in the nerves or glands that produce hormones).
- **Drug repurposing**: We will develop better ways to fund research on therapies that don't have much of a financial incentive – that don't cost $50,000 per dose, but cost $5 a dose.

What are the challenges in finding additional future treatments for pancreatic cancer?

Challenges remain in developing effective treatments for pancreatic cancer due to factors like resistance and tumor complexity. New strategies are needed to overcome these hurdles. For example:

- **Heterogeneity of resistance**: Pancreatic cancer cells will typically develop multiple resistance mutations simultaneously. For example, if you have cancer in five spots in

your body, each spot may develop an independent and unrelated resistance mutation. Even if you could target one of them, it would leave the other four spots untreated.

- **Finding a treatment for a target**: 90% of pancreas cancers have a KRAS mutation. If you were to choose one mutation to target in pancreas cancer, this would be it. The problem is that it has taken us literally decades to figure out how to target this mutation.
- **Adverse selection for trials**: The field for cancer vaccine trials has been held back because these trials tend to be conducted in patients who have more advanced disease. It may be that vaccine trials are at their best when the patient has minimal disease. And because patients may have just had surgery, it would take sometimes years to even show that you've altered outcomes for them, compared to a control.
- **Merging diagnostics with bioinformatics**: We will need bioinformatics and machine learning and AI to take the information from advanced tests (like RNA sequencing and proteomics) and apply it to understand the disease and guide therapies. We're going to need a whole next generation of therapies that are designed to target those proteomic signals.
- **Finding signal in the blood**: Pancreatic tumors have very little active tumor content, so they don't produce a lot of circulating tumor DNA into the bloodstream that can be captured on a blood test.
- **Test accuracy**: When you are trying to get an early warning for a cancer that is aggressive and doesn’t happen very often, you need a test with very high specificity (low false positives) and sensitivity (low false negatives) to avoid the expense and upset of incorrectly telling someone whether they have the disease or not.
- **Treatment proliferation**: It is difficult for an oncologist who is treating many kinds of cancers to keep up with the evolving treatment landscape. Patients should be empowered to know their own disease.

What can you do?

- **Get genetic testing:** You should ask your doctor, “Have you done the molecular profiling on my cancer? Can I see the report?” You should have the report printed out and bring it with you when you get a consultation because that's something that typically exists outside the medical chart.
- **Learn**: Keep up with the evolving pancreatic cancer testing and treatment landscape.
- **Engage**: Get involved in patient advocacy groups and funding pancreatic cancer research.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Meeting Notes

KEYWORDS

pancreas cancer, KRAS, therapies, mutation, patients, cancer, tumor, pancreatic cancer, target, prostate cancer, drugs, vaccine, test, BRCA, work, call, people, germline, disease, chemotherapy

SPEAKERS

John Strickler (66%), Roger Royse (8%), Allen Morris (8%), Rick Davis (8%), Richard Anders (4%), Debbie Denison (2%), Brad Power (2%), Brian McCloskey (1%), Jeff Krolick (1%)

OUTLINE

1. Recent advances in pancreatic cancer treatment. (0:06)
2. Personalized cancer medicine for pancreas cancer. (1:31)
3. Targeting KRAS mutations in pancreatic cancer. (6:47)
4. Pancreatic cancer treatment and new approaches. (12:36)
5. Using cryotherapy for cancer treatment. (17:50)
6. Liquid biopsies for pancreatic cancer diagnosis and treatment. (27:01)
7. Pancreatic cancer treatment and genetic mutations. (33:49)
8. Early detection of pancreatic cancer through blood tests. (38:25)
9. Radioligands for pancreatic cancer treatment. (43:29)
10. Cancer treatment resistance and empowering patients. (50:12)
11. KRAS mutations and resistance in cancer treatment. (53:56)

SUMMARY

Recent advances in pancreatic cancer treatment.

- Dr. John Strickler discusses recent advances in pancreatic cancer treatment at Duke University.

Personalized cancer medicine for pancreas cancer.

- John Strickler discusses the future of pancreas cancer treatment, highlighting the importance of personalized cancer medicine.
- He believes that personalized medicine has the potential to improve outcomes for pancreas cancer patients, minimizing toxicity and maximizing effectiveness.
- In 2013, there were no targeted therapies for pancreas cancer, but now there are FDA-approved therapies for germline BRCA mutations.
- Profiling tumors for driver mutations can improve survival, with survival doubling when treated with targeted therapy.

Targeting KRAS mutations in pancreatic cancer.

- KRAS mutations are a main driver of pancreas cancer, responsible for 87% of cases.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

- John Strickler highlights promising breakthroughs in targeting KRAS mutations in pancreatic cancer, with minimal side effects.
- New drugs targeting KRAS mutations show promise in clinical trials, including high potency targeting, degraders, molecular glues, and covalent bonds.

Pancreatic cancer treatment and new approaches.

- John Strickler emphasizes the importance of genetic testing and molecular profiling for pancreas cancer patients, as it can help identify potential eligibility for targeted therapies and improve treatment outcomes.
- He notes that cancer vaccines are a promising area of research.
- He mentions early data indicating that cancer vaccines may generate an anti-tumor immune response, with hints of beneficial impacts for patients in early pilot studies.
- Roger Royse, a pancreatic cancer patient, is participating in a cancer vaccine trial with no side effects after 6 doses, but with no visible changes on scans yet.

Using cryotherapy for cancer treatment.

- Allen Morris questions the conventional wisdom that cold tumors are the least likely to respond to therapeutic vaccines, citing promising signals in other tumor types, including pancreatic cancer.
- Dr. Gary Onik uses cryotherapy to produce an auto vaccination for prostate cancer, with a cure rate of no evidence of disease times five years, despite being a stage four metastatic cancer.
- Allen Morris shares a case of a patient with liver metastases who had a complete response to cryotherapy, which is rare in the field of oncology.
- Roger Royse agrees that case reports like this can inspire research and funding, but emphasizes the need for hypothesis-driven studies to make progress in the field.
- John Strickler discusses the need for new therapies to treat pancreas cancer, citing poor long-term outcomes with standard of care.
- John Strickler and Roger Royse discuss the potential of proteomics to guide therapy, with John Strickler suggesting it may become part of standard of care in the future, but this is years away..

Liquid biopsies for pancreatic cancer diagnosis and treatment.

- Brad Power discusses the potential of liquid biopsies for cancer diagnosis and monitoring, including the advantages of using RNA over DNA.
- John Strickler highlights the limitations of blood-based profiling for pancreas cancer, including the difficulty in detecting active tumor content in desmoplastic lesions.
- He highlights the limitations of blood tests for pancreas cancer detection, but sees potential in their use for early detection and preventive medicine.
- Jeff Krolick discusses challenges in funding research on off-label drug uses for pancreatic and prostate cancer, citing high costs and lack of financial incentives.

Pancreatic cancer treatment and genetic mutations.

- Rick Davis asks about BRCA mutations in prostate cancer and their monitoring for pancreatic cancer.
- Olaparib FDA-approved for germline BRCA-mutated pancreas cancer, but controversial due to lack of survival benefit.

Early detection of pancreatic cancer through blood tests.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

- John Strickler discusses the potential benefits of germline testing for pancreatic cancer patients.
- Roger Royse shares his story of early detection and successful treatment of pancreatic cancer, highlighting the importance of early detection for improving outcomes.
- John Strickler expresses concerns about the specificity of early detection assays, acknowledging the need for high sensitivity and specificity to avoid false positives and unnecessary follow-up tests.

Radioligands for pancreatic cancer treatment.

- Radioligands have potential for pancreatic cancer treatment, despite limited development in this area.
- Brian McCloskey discusses use of radioligands for pancreatic neuroendocrine cancer treatment, with a focus on leutetium and new developments in DLL3.
- John Strickler suggests targeted therapies may be more effective for CML than solid tumors due to fewer mutations.

Cancer treatment resistance and empowering patients.

- John Strickler discusses challenges in treating solid tumors with targeted therapies, including lung cancer, and the need to develop new strategies to prevent resistance.
- Oncologists face challenges keeping up with the rapidly evolving treatment landscape for rare cancers.

KRAS mutations and resistance in cancer treatment.

- John Strickler discusses challenges in developing drugs for KRAS mutations, including the need to attack a "light switch" when it's in the "on" position.
- He highlights Revolution Medicine's pipeline of drugs designed to target KRAS variants, showing promising data in pancreatic cancer.
- John Strickler explains that pancreatic cancer cells typically develop multiple simultaneous mutations to resist treatment, making it challenging to target a single mutation.
- Dr. Strickler explains the complexity of targeting KRAS mutations in cancer, which can be in an "on" or "off" state, and how new drugs are being developed to target it in both states.

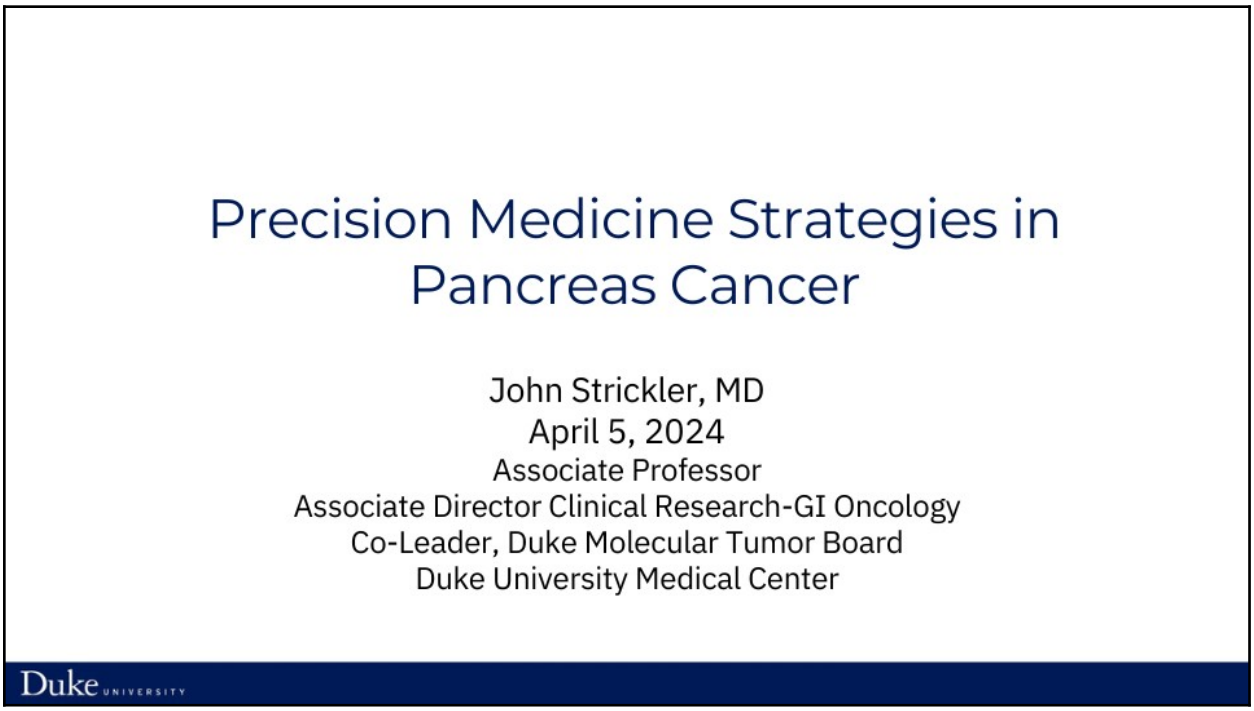
“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Meeting Transcript

Roger Royse
This is the Cancer Patient Lab. Today we have a guest to talk about navigating pancreatic cancer. This is all just informational. It's not medical advice.

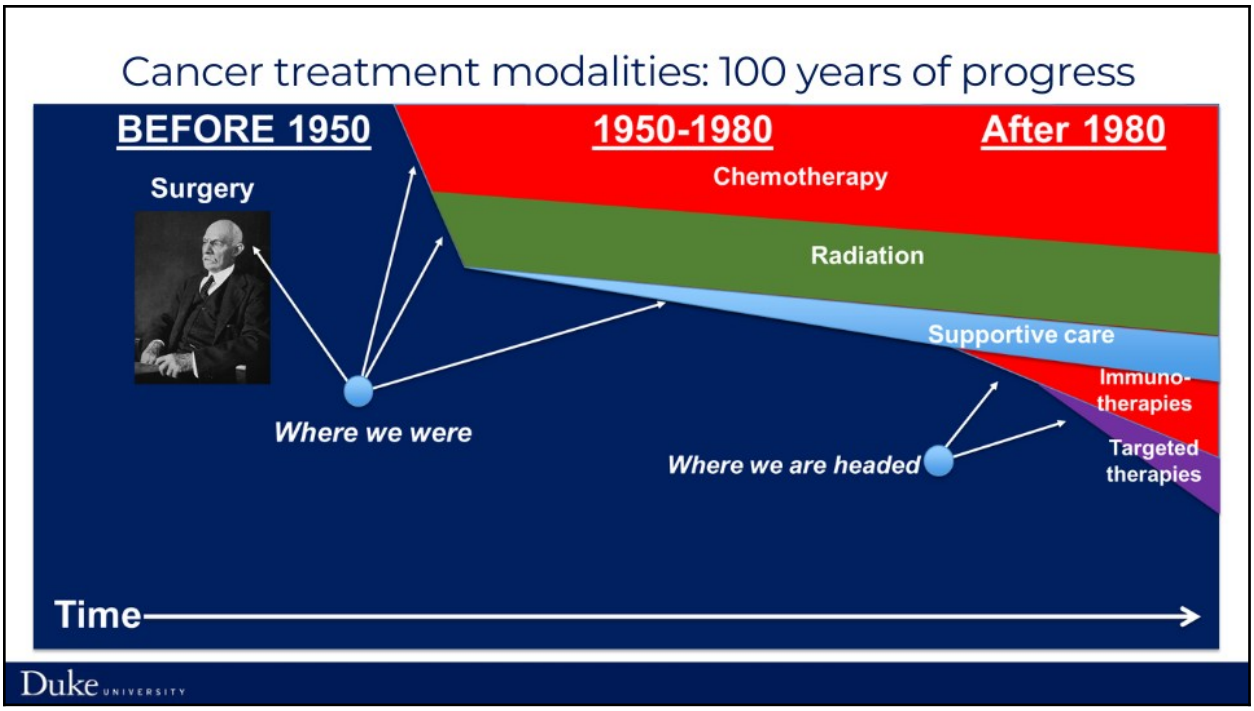
Cancer Patient Lab is a nonprofit organization. We would encourage you all to donate so that we can keep doing programs like this.

Our guest today is Dr. John Strickler. He is an Associate Professor of Medicine in the Division of Medical Oncology at Duke University, and the co-leader of the molecular tumor board and precision cancer medicine and investigational therapeutics research program. So he is very qualified to discuss the recent advances in pancreatic cancer.



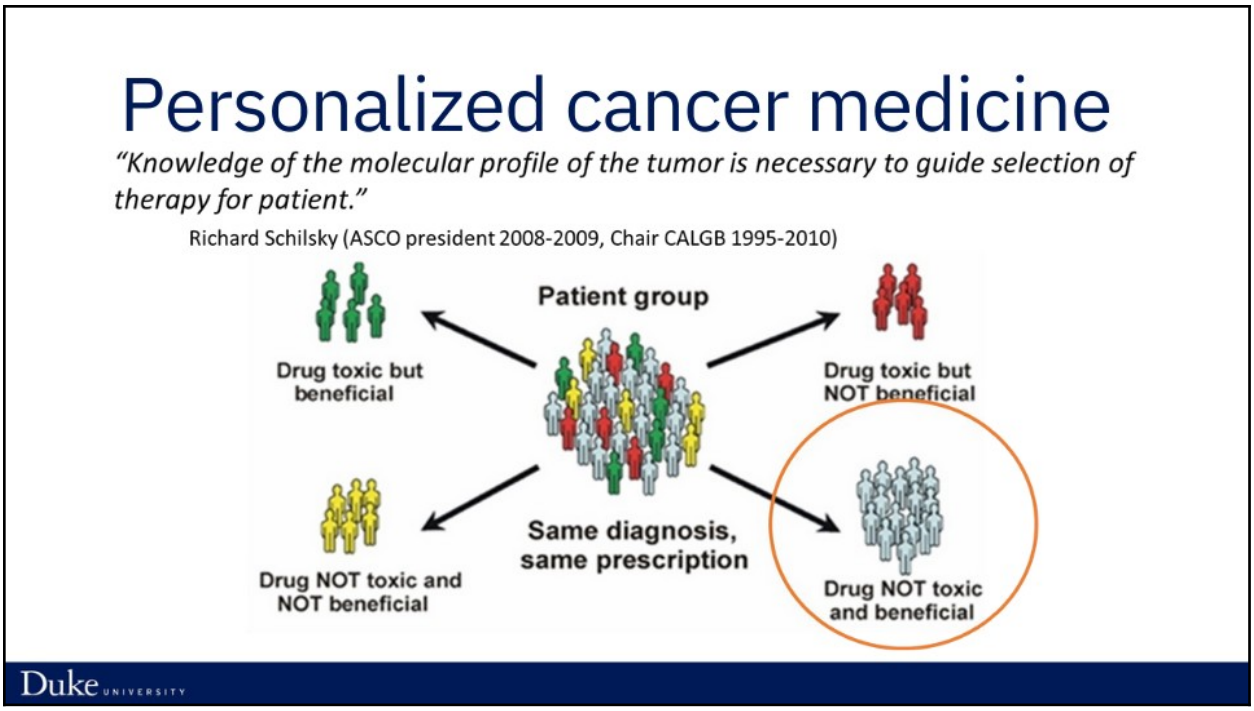
John Strickler 1:30
There are a lot of resources for more basic topics around pancreas cancer and epidemiology, prevention, treatment, those kinds of things. I wanted to bring my own personal spin on pancreas cancer, which is around what I consider to be the future of pancreas cancer. And that is our era of precision cancer medicine, now coming to pancreas cancer, and what that means for patients and families and physicians.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]



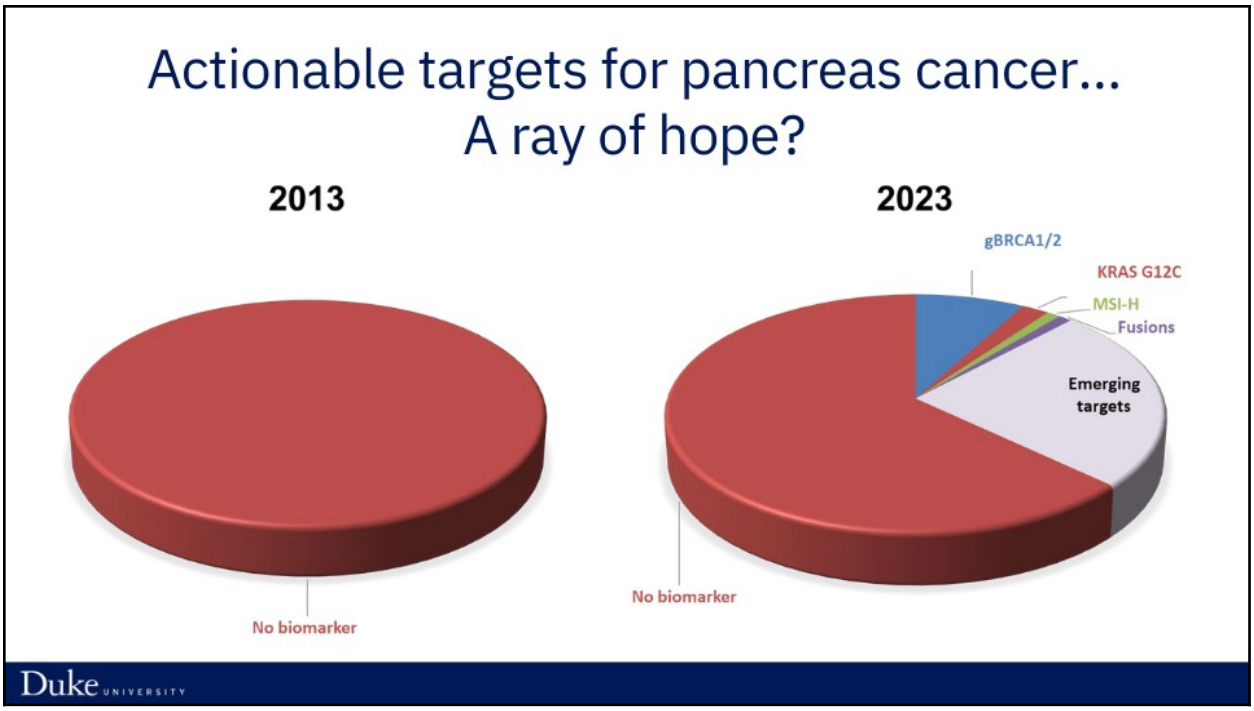
Before diving too deeply into this precision medicine future for pancreas cancer, it's important to look backwards. When you look backwards at how we treated cancer, certainly before 1950, the treatment for pancreas cancer was primarily surgical. Turn-of-the-20th-century surgeons masterminded these very aggressive surgical techniques to try to remove or cure cancers. But we can all see, particularly with pancreas cancer, that that's rarely a curative modality. Around 1950 some new treatments came into play. In the 1950s and 1960s, chemotherapy, radiation, and supportive care got better. Now we're in an era where we're bringing in immunotherapies and targeted therapies. For a disease like pancreas cancer, which is so rarely cured with surgery alone, or with chemotherapy and surgery alone, it's important to know that this future that we're looking at is probably going to be the way that we can really move the needle on a disease that's largely been considered to be incurable for most people up until this point.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]



What do we mean when we say “personalized cancer medicine”, and to boil it down? This is the idea that you can bring the right treatment to the right patient at the right time, potentially sparing people toxic therapies that are ineffective and giving them hopefully therapies that are geared to an individual tumor mutational burden profile, so that you minimize toxicity and improve activity. Now, pancreas cancer has been very slow to the party with personalized cancer medicine. So in 2013, I was a couple years on faculty at this point, we this was our pie of actual target for pancreas cancer, basically nothing. There was no reason to do profiling because there was really nothing to target. Fast forward 10 years later to last year, I stopped in 2023. Because 2024 is going to be a very different experience. But now we've got some FDA-approved therapies really to target what we call a germline BRCA. And so that's been a big breakthrough in the last few years KRAS G12C therapies, it's very rare, but they are now available to us in the clinic. It's just that it's 1- 2% of patients. But then we have some other alterations where we have pan tumor approvals like MSI high disease for immune therapy. And then in rare cases, we have fusions, and I'll go into those in a little bit more detail.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]



As of last year, there was this emerging target category as well, which I might speak about a little bit as well. So why do we need to start checking these tumors for driver mutations? Well, increasingly, it's becoming clear that when you sequence a tumor, look for mutations in a cancer, even a tough to treat cancer like pancreas cancer, when you do the profiling, and you find something actionable, you can improve survival. So this was a multi-year analysis by a friend of mine, Dr. Mike Pishvaian at Johns Hopkins, he profiled several 100 patients. And when there was no driver mutation identified, the survival was not great at 1.3 years, when there was a driver that was present but not treated, survival was about the same. So no impact on survival. But when you profiled a cancer, and treated that with target therapy, survival doubled, and that's with a better quality of life as well, because oftentimes, these targeted therapies are much better tolerated than chemotherapy, which is the current standard of care for pancreas cancer.

Pancreatic cancer: Targeting driver mutations improves survival

	Patients (N)	Median survival	95% C.I. (years)
No driver mutations identified	488	1.3 years	1.2-1.5
Oncogenic driver not treatedwith targeted therapy	143	1.5 years	1.3-1.9
Oncogenicdriver treatedwith targeted therapy	46	2.6 years	2.4-NR (*P* <0.001)

Where we were

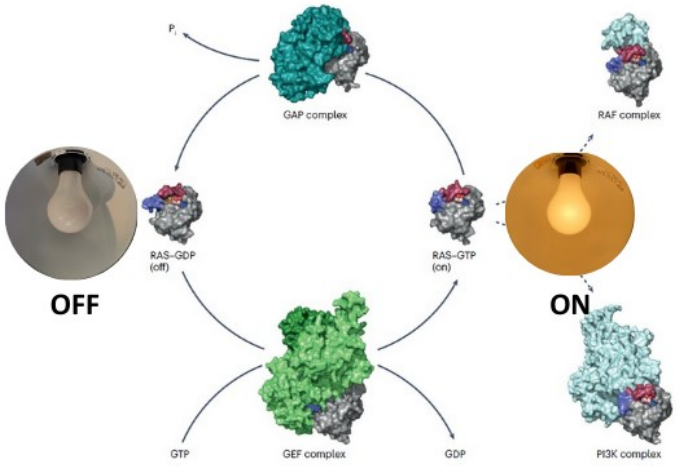
Where we are headed

Duke UNIVERSITY

Pishvaian et al., Lancet Oncol2020; 21:508-18.

So this is where we were. And this is where we're headed, we are trying to improve survival with sequencing these cancers, finding drivers and then targeting those drivers with breakthrough drugs. So I had mentioned the germline alterations. But I think what we're seeing now in 2024, potentially a paradigm shift in precision medicine for pancreas cancer, and that's around targeting something called KRAS. And I'll explain what KRAS is all about. Okay, so, KRAS is a protein that's present in cancer cells and also throughout normal cells in the body.

KRAS as a Target: Background

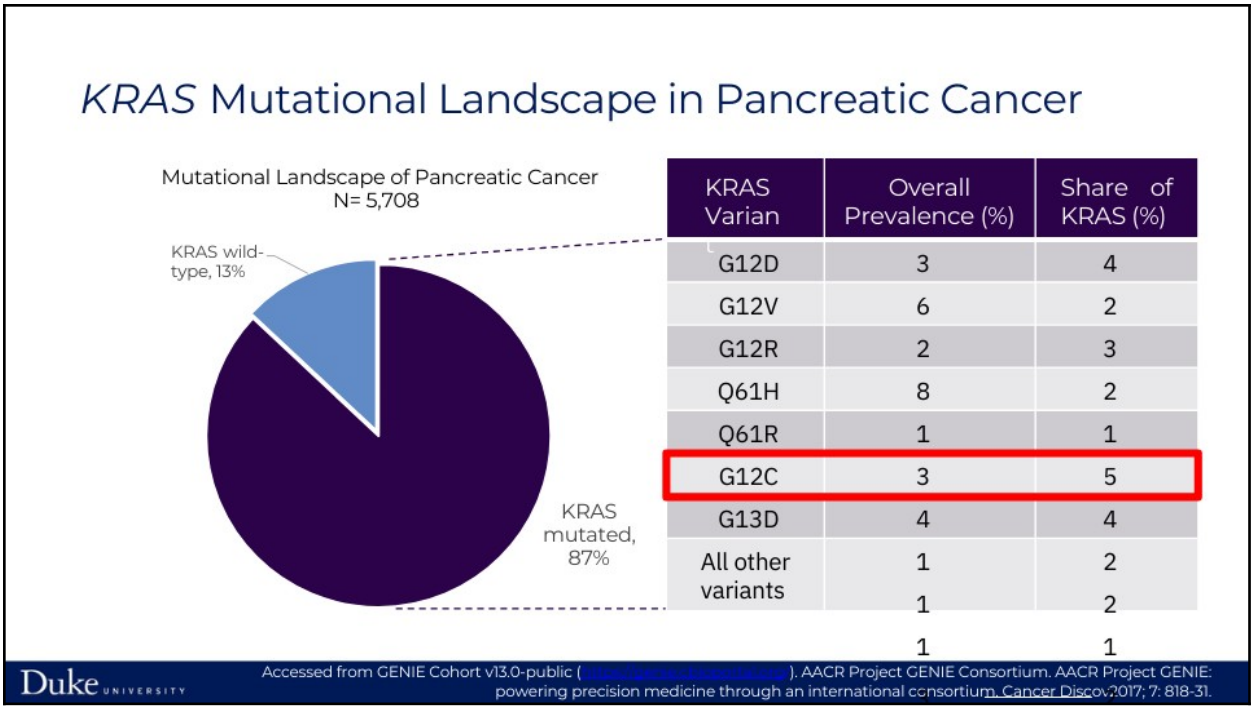


Duke UNIVERSITY

Ostremet al., Nature Reviews Drug Discovery2016 vol15, p 771–785. Permission granted for reuse of figure.

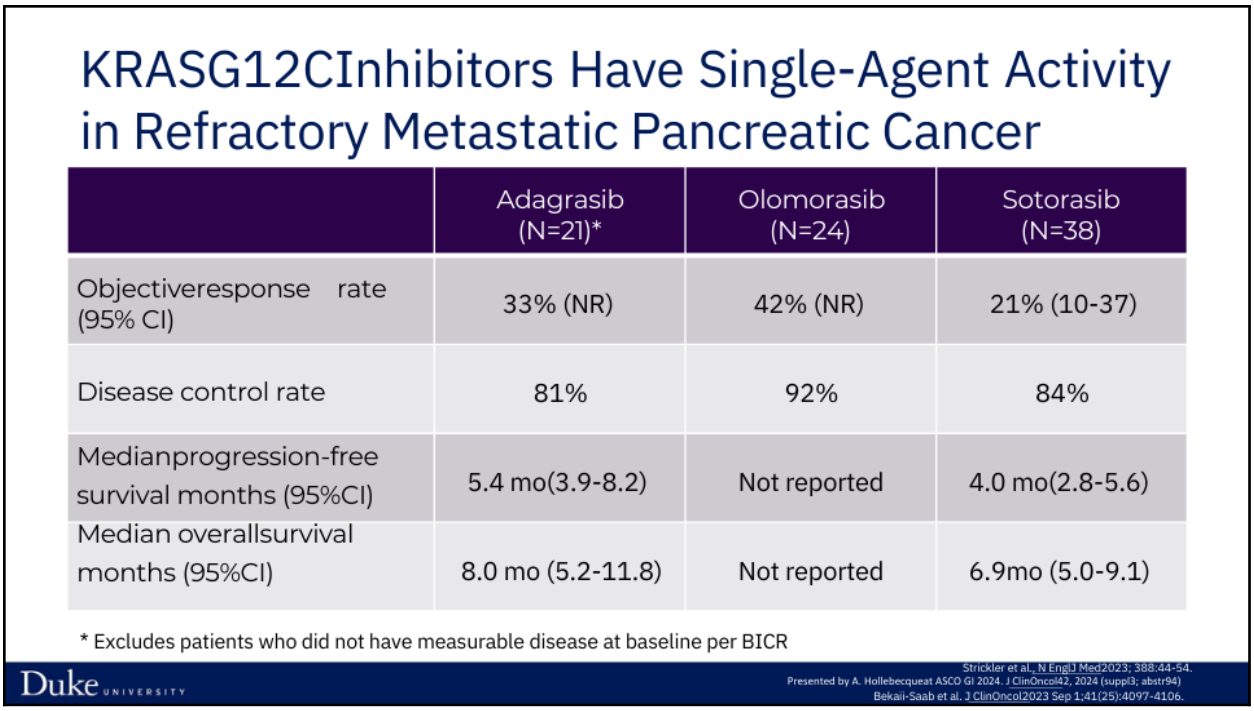
“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

I like to think of KRAS, which is shown right here, as a light switch. So a light switch is designed to turn off or turn on depending on if you need that light bulb on or off. But when the light switch is broken, and RAS has a mutation, the light switches perpetually on. And no matter how hard you flip that switch, it is stuck in the on position. And this has plagued us for decades now, 90% of pancreas cancers have a KRAS mutation. So if you were to find one mutation to target in pancreas cancer, this would be it. The problem is that it's taken us literally decades to figure out how to turn off this light switch. Because there are so many backup mechanisms, even if you know, unscrew that switch from the wall and try to shut it off. There's like backup ways to keep that light turned on even if you tear the switch out of the wall. So that's really what KRAS is all about. KRAS is a switch that is stuck in the on position and this is the main driver for pancreas cancer.



When I say that this is the mutational landscape of pancreas cancer, 87% of pancreas cancers have a KRAS mutation. 13% are wild type, I'll talk about these. “Wild type” means not mutated. And then when you look at the specific types of mutations, I listed these top to bottom KRAS G12D, V, and R. These are the main driver mutations in pancreas cancer which accounts for about three quarters of all pancreas cancers. Now down the list, we have KRAS G12C, and here we do have FDA-approved therapies. But look at how often you see them in pancreas cancer, just 1% of patients. So if we're going to make a breakthrough for personalized therapies for pancreas cancer, it's got to come from targeting these particular variants. And already, when you look at KRAS G12C, there are some very promising signs that we can start to figure out a way to turn off the light switch.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]



KRASG12CInhibitors Have Single-Agent Activity in Refractory Metastatic Pancreatic Cancer

	Adagrasib (N=21)*	Olomorasib (N=24)	Sotorasib (N=38)
Objectiveresponse rate (95% CI)	33% (NR)	42% (NR)	21% (10-37)
Disease control rate	81%	92%	84%
Medianprogression-free survival months (95%CI)	5.4 mo(3.9-8.2)	Not reported	4.0 mo(2.8-5.6)
Median overallsurvival months (95%CI)	8.0 mo (5.2-11.8)	Not reported	6.9mo (5.0-9.1)

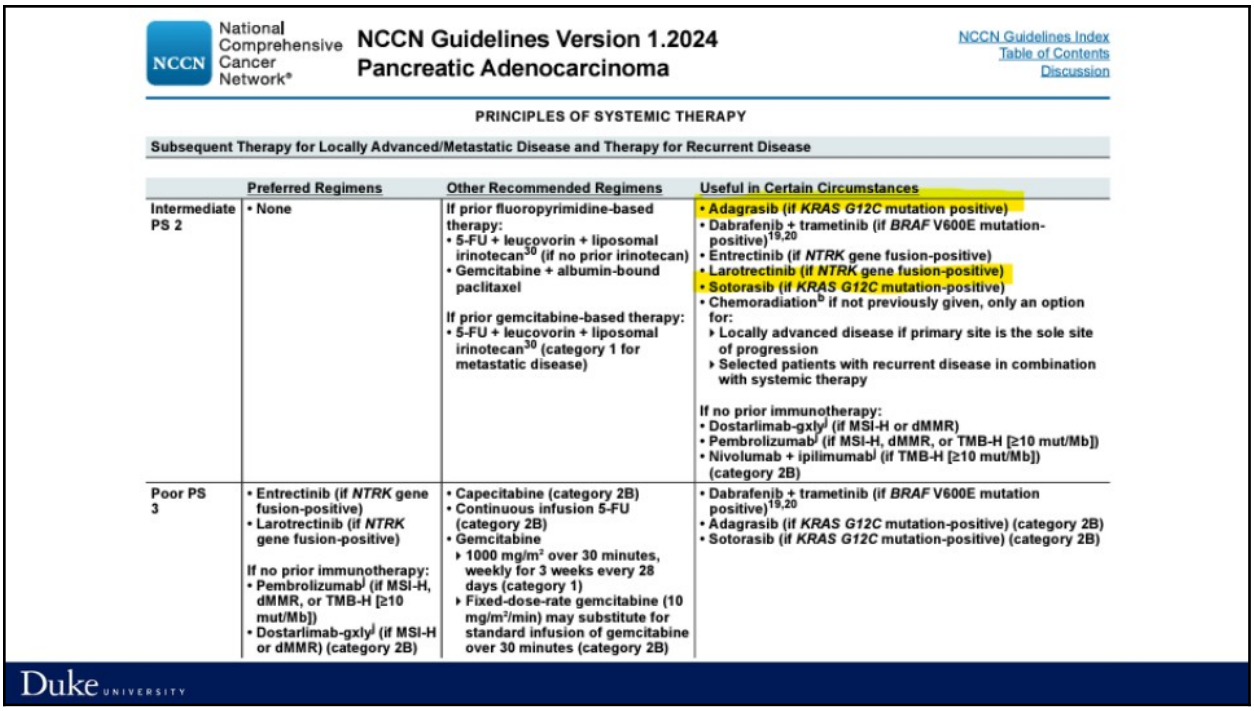
* Excludes patients who did not have measurable disease at baseline per BICR

Duke UNIVERSITY

Strickler et al., N Engl J Med 2023; 388:44-54.
Presented by A. Hollebecqueat ASCO GI 2024. J ClinOncol 42, 2024 (suppl 3; abstr 94)
Bekaii-Saab et al. J ClinOncol 2023 Sep 1;41(25):4097-4106.

These are three different trials, three different drugs, and to target KRAS G12C, and Adagrasib (brand name Krazati, an anticancer medication used to treat KRAS in non-small cell lung cancer) about a third of patients had shrinkage 42% for this one, 21% for this one. Now, the responses are not durable. But remember, these are patients who have totally run out of options that have limited life expectancy. So not only are we able to shrink these cancers and improve survival, but we're doing so with almost no side effects in most cases. So this is a major breakthrough because remember these patients in this setting have been heavily treated with very aggressive chemotherapy. So to be able to control their cancer, even for a short period of time, with minimal side effects is a big breakthrough. And I copied this out of our national guidelines.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

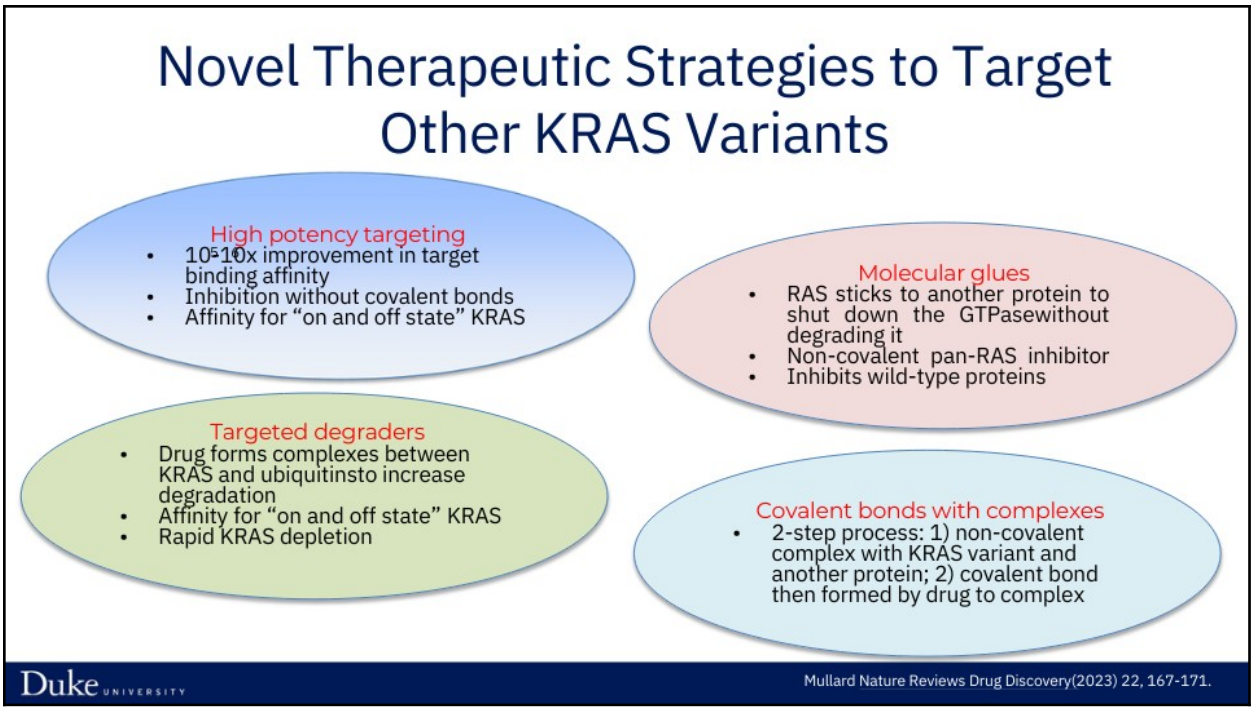
Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Intermediate PS 2	• None	If prior fluoropyrimidine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[30] (if no prior irinotecan) • Gemcitabine + albumin-bound paclitaxel If prior gemcitabine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[30] (category 1 for metastatic disease)	• Adagrasib (if *KRAS G12C* mutation positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Sotorasib (if *KRAS G12C* mutation-positive) • Chemoradiation[b] if not previously given, only an option for: ▸ Locally advanced disease if primary site is the sole site of progression ▸ Selected patients with recurrent disease in combination with systemic therapy If no prior immunotherapy: • Dostarlimab-gxly[j] (if MSI-H or dMMR) • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Nivolumab + ipilimumab[j] (if TMB-H [≥10 mut/Mb]) (category 2B)
Poor PS 3	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) If no prior immunotherapy: • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Dostarlimab-gxly[j] (if MSI-H or dMMR) (category 2B)	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ▸ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)	• Dabrafenib + trametinib (if *BRAF* V600E mutation positive)[19,20] • Adagrasib (if *KRAS G12C* mutation-positive) (category 2B) • Sotorasib (if *KRAS G12C* mutation-positive) (category 2B)

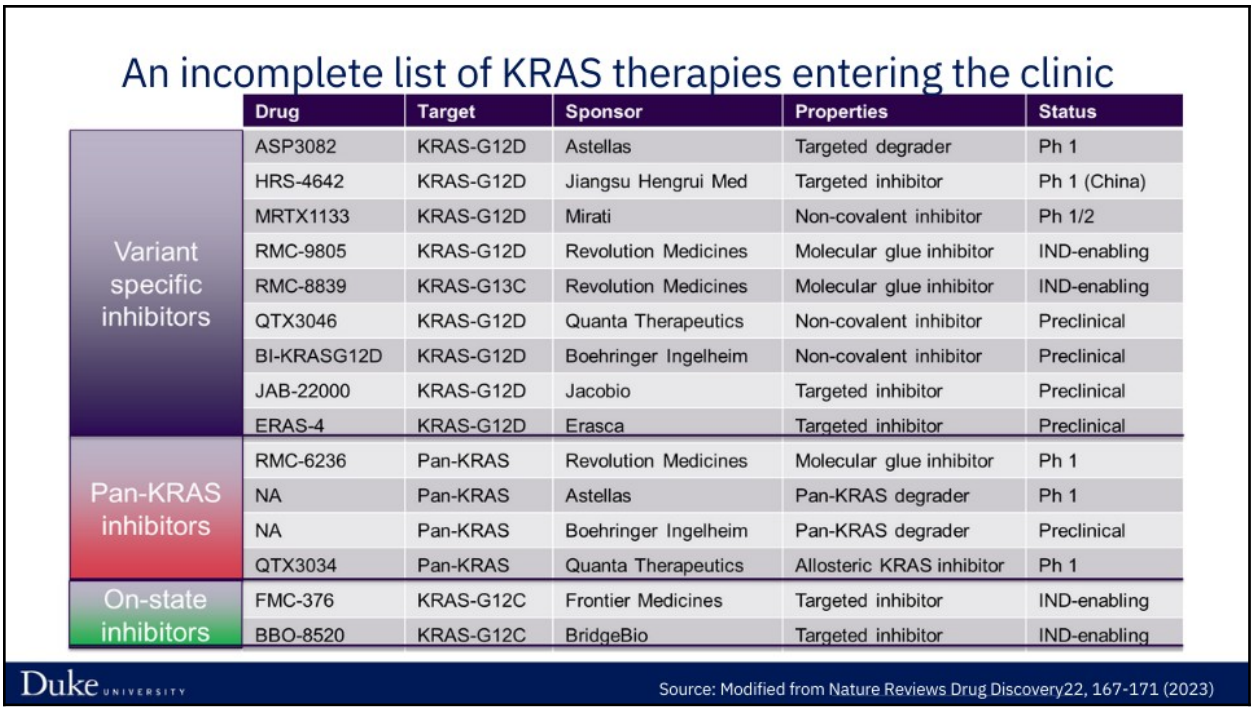
Duke UNIVERSITY

This is our national NCCN guidelines that we as doctors follow. When you look at what is useful in certain circumstances, already these KRAS inhibitors are making it into our national guidelines. This is telling us that, at least for that rare variant, we now have therapies available to us. Can we do better? Yes, we could. We'd love to see people having more durable responses, but that's a great place to start. Now, if we're going to make breakthroughs, though, we've got to get to the big three G12D, V, and R. And here's what's happening in 2024. There are drugs coming into the clinic right now that are designed to attack these types of mutations. And they do so with lots of different strategies.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]



One is what we call high potency targeting, where the drug can just flip that switch in the off position and override it, there's degraders, where you can basically degrade that light switch, so it no longer exists and shuts the light off. And then we have these things called molecular glues and covalent bonds with complexes. All this is a lot of drug chemistry lingo to say basically, they're coming up with more and more creative ways to figure out ways to turn off the light switch. That's exciting. I just made this list of all the KRAS inhibitors coming into the clinic this year. Many of them are already in the clinic. Some I have not listed here.



	Drug	Target	Sponsor	Properties	Status
Variant specific inhibitors	ASP3082	KRAS-G12D	Astellas	Targeted degrader	Ph 1
	HRS-4642	KRAS-G12D	Jiangsu Hengrui Med	Targeted inhibitor	Ph 1 (China)
	MRTX1133	KRAS-G12D	Mirati	Non-covalent inhibitor	Ph 1/2
	RMC-9805	KRAS-G12D	Revolution Medicines	Molecular glue inhibitor	IND-enabling
	RMC-8839	KRAS-G13C	Revolution Medicines	Molecular glue inhibitor	IND-enabling
	QTX3046	KRAS-G12D	Quanta Therapeutics	Non-covalent inhibitor	Preclinical
	BI-KRASG12D	KRAS-G12D	Boehringer Ingelheim	Non-covalent inhibitor	Preclinical
	JAB-22000	KRAS-G12D	Jacobio	Targeted inhibitor	Preclinical
	ERAS-4	KRAS-G12D	Erasca	Targeted inhibitor	Preclinical
Pan-KRAS inhibitors	RMC-6236	Pan-KRAS	Revolution Medicines	Molecular glue inhibitor	Ph 1
	NA	Pan-KRAS	Astellas	Pan-KRAS degrader	Ph 1
	NA	Pan-KRAS	Boehringer Ingelheim	Pan-KRAS degrader	Preclinical
	QTX3034	Pan-KRAS	Quanta Therapeutics	Allosteric KRAS inhibitor	Ph 1
On-state inhibitors	FMC-376	KRAS-G12C	Frontier Medicines	Targeted inhibitor	IND-enabling
	BBO-8520	KRAS-G12C	BridgeBio	Targeted inhibitor	IND-enabling

But this is all to tell you that these studies are ongoing and patients are now getting on trials of these KRAS inhibitors. And we hope to learn a lot more over the next year about how well they work. But I'm cautiously optimistic that this will be a major paradigm shift.

I did promise I would talk about those rare patients who do not have a KRAS mutation, we call it KRAS wild type. What do we do for them? Well, there's good news for these patients as well. And that is these patients tend to have other mutations that are actionable with other drugs.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

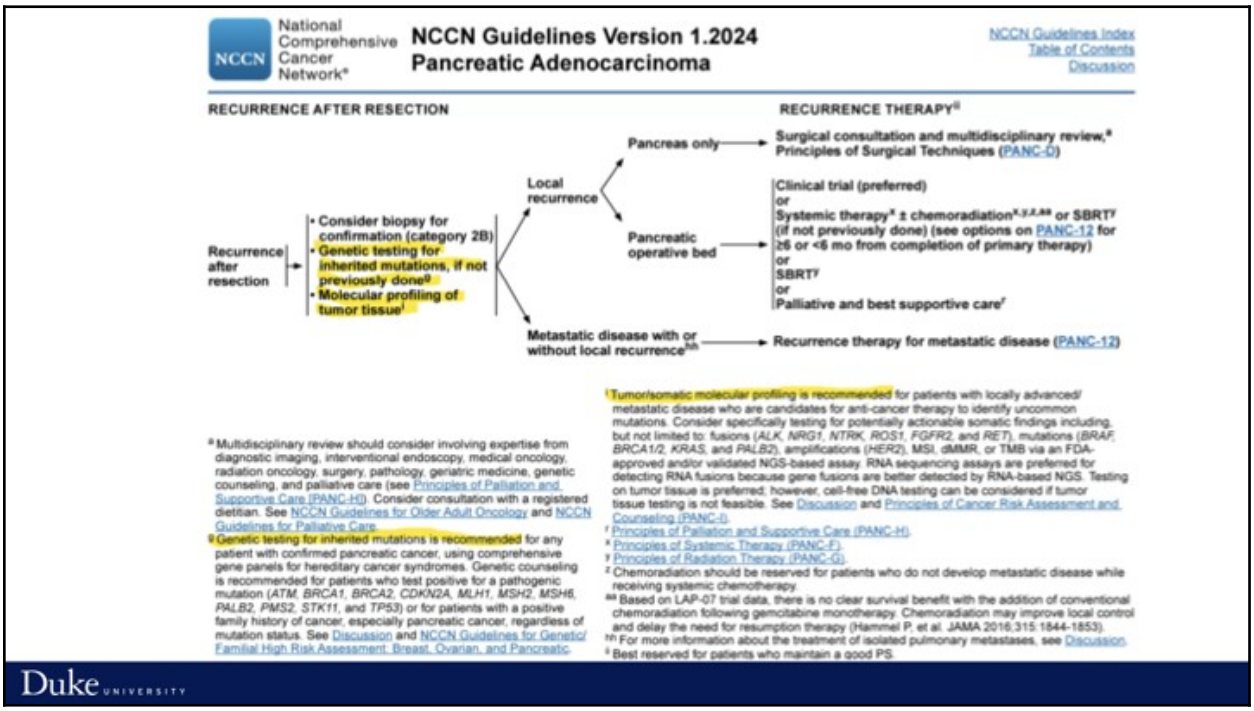
KRAS “Wild-Type”? Look for fusions

Fusion Prevalence Drug ClinicalOutcomes			
ALK1	0.16% of all PDAC 1.3% in age<50	Crizotinib Ceritinib Alectinib	Disease control in 3of 4 patients
NRG15	0.5%	Zenocutuzumab	8/19 patients with objective responses
NTRK1/2/3	0.18%	Larotrectinib	Objective response in 1 of 6 patients
2 RET3	0.02%	Pralsetinib	Objectiveresponse in 3 of 3 patients
ROS14	0.07%	Entrectinib	Diseasecontrol in 1 of 1 patients

1. Singhiet al., JNCCN. 2017 May;15(5):555-562.
2. GarraldaE, et al. Poster presentation at WCGI 2022: Abstract SO-31
3. Subbiahet al., J ClinOncol39, 2021 (suppl3; abstr467).
4. Pishvaian et al., JCO Precis Oncol2018 2, 1-7.
5. Schram et al., Presented at ASCO AM 2022

Duke UNIVERSITY

So across this column, you can see different types of mutations or alterations that are present in these wild type tumors. And then all of these drugs that are now entering the clinic are already in the clinic where we see responses. We won't focus on the details of these drugs. The key thing to know is if the tumors are wild type, look for some of these other rare alterations.

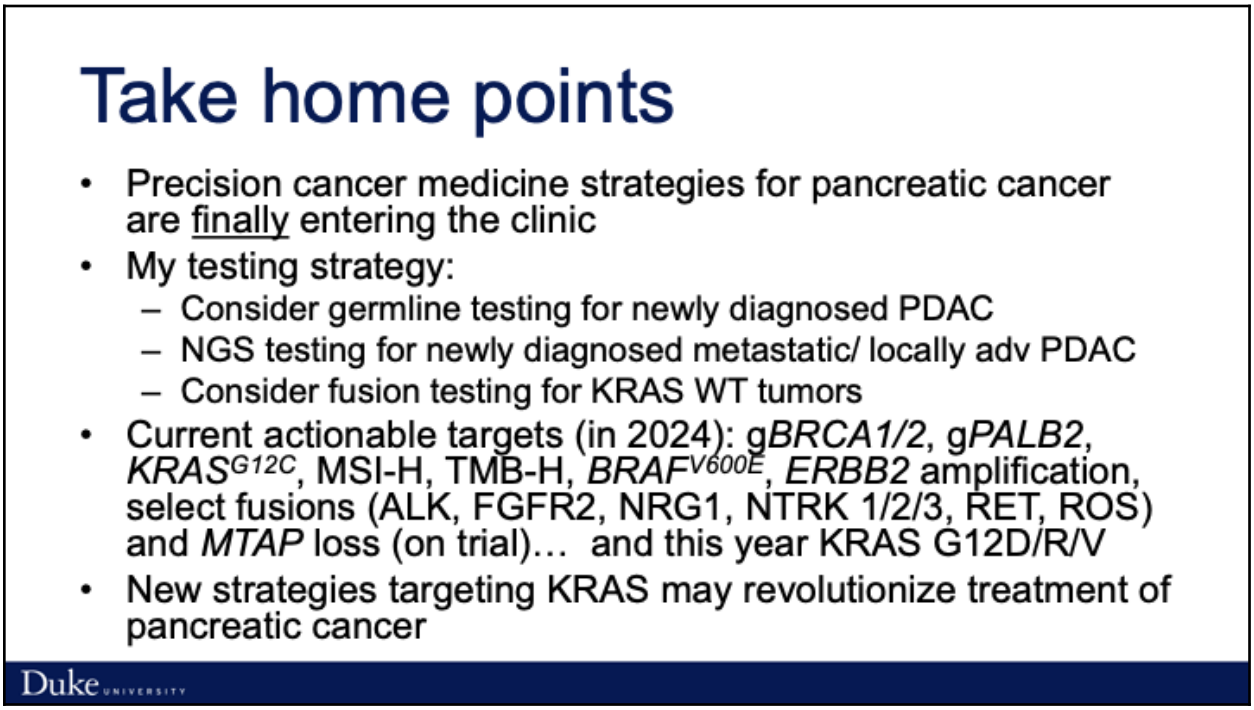


Duke UNIVERSITY

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

In fact, when you go back to our national guidelines, they even say now: “genetic testing for inherited mutations is recommended.” But do you know your molecular profiling? This is in our national guidelines now.

Every pancreatic cancer patient should ask their doctor, “Have you done the molecular profiling on my cancer? Can I see the report?” And carry that with you because that's something that typically lives outside the medical chart. So it's important for a patient to have that printed out and keep that on them. Because oftentimes, when patients go to get second opinions, that's one piece of paperwork, that doesn't make it because it doesn't come out of the chart.



To wrap up, I think precision cancer medicine for pancreas cancer is finally becoming a real thing entering the clinic.

I strongly recommend, and consistent with our national guidelines, genetic testing of the patient. We call it “germline testing”, to look for inherited predisposition for pancreas cancer. This is an important new addition to our guidelines. It also can make the patient potentially eligible for certain types of therapies. I recommend molecular testing as well, just like I talked about.

I'm not going to focus on our actual targets. But this is a list of all the things we have in 2024, where we have therapies available for these patients. I'm particularly optimistic about our new approaches to target KRAS, which could open up a whole range of new therapies for patients with pancreas cancer outside of our traditional cytotoxic chemotherapy, which nobody likes, not even the guy who gives the chemotherapy, who's me.

Roger Royse 14:31

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

I noticed you didn't talk too much about cancer vaccines, which seems to be the latest biggest thing right now. Do you have a view on that?

John Strickler 14:44
There is some early data in the realm of cancer vaccines indicating that you may be able to use cancer vaccines to generate an antitumor immune response. And there are some hints from some early pilot studies that that could potentially lead to beneficial impacts for patients. But these vaccine trials are in early days. I'd say we're probably a year or two away from making them widely available.

I also think that when you talk about vaccine trials, I think the field has been held back because these trials tend to be conducted in patients who have more advanced disease. And it may be the case that vaccine trials are at their best where the patient has minimal disease. And so I think those types of trials are a lot more difficult to run. And because patients may have just had surgery, it would take sometimes years to even show that you've altered outcomes for them, compared to say, a control. So it's early days, I'm cautiously optimistic, but there are some signs that maybe we're making progress in this.

Roger Royse 16:15
Okay. By way of background, I'm a pancreatic cancer patient, and I am in a clinical research program for a cancer vaccine and neoantigen peptide. I just had my sixth dose yesterday, I had five doses with no side effects. And I had the sixth one yesterday, and it just wiped me out. So I don't know what that means. I hope – it's a good hope – it means that my body's reacting to it, but there's no nothing on my scans at this point. I'm kind of early in the process, so hopefully I get a better result.

John Strickler 17:00
Roger, I wish you well with that vaccine trial. I don't know which one you're on. But we did see some publications late last year, particularly coming out of that multi-institutional team, and then Sloan Kettering has one as well. The data is intriguing. But it's tough to run those trials. There's a reason why it's been super slow to the clinic.

Roger Royse 17:30
Mine is here at the Jamie Leandro Foundation in San Francisco. It was difficult to get into that process. But they seem to have had pretty good results. But like you say it's so early.

Allen Morris 17:50
You're part of the molecular tumor board at Duke. I have questions about that. But I don't want to start with that. I'm going to make some statements, and if they're wrong, tell me. Pancreatic cancer is viewed as a cold tumor. Is that correct?

John Strickler
Yes.

Allen Morris
And is it also correct that the conventional wisdom is that the cold tumor, in the cold versus hot dichotomy, is the worst tumor to try to evoke a vaccine response?

John Strickler 18:32
Yes, that's true.

Allen Morris 18:36
Thank you for allowing those two axioms. The only therapeutic vaccine that has been successful to date has been in prostate cancer. Needless to say, you know, this site started as a prostate cancer site. Prostate cancer is considered a cold tumor. You're aware that the only therapeutic cancer vaccine to date is in prostate cancer?

John Strickler 19:16
Yes, but there have been promising signals in other tumor types, particularly melanoma.

Allen Morris 19:21
Okay. But that's with ICIs (immune checkpoint inhibitors, like Keytruda). That is, when it's combined with an ICI, so it's not a pure vaccine kind of situation.
Would you admit that that's a paradox: that everybody thinks that a cold tumor is the one that is least likely to result in a successful therapeutic vaccine for and therefore, in the cancer vaccine race, everybody is chasing hot tumors such as melanoma? In fact, Moderna and BioNtech have been chasing melanoma for >10 years unsuccessfully.

Now that I started with that, I'm going into a punch line. It turns out you weren't present, but there is – I believe he's an interventional radiologist –a vaccine pioneer named Dr. Gary Onik, who presented to Cancer Patient Lab, his novel cryotherapy approach for auto vaccination. In other words, for example with prostate cancer, he stuck a needle into a bone metastasis, just a one millimeter focus of bone prostate cancer, and he – believe it or not – evoked a cure in himself. What do I mean by a cure? He has no evidence of disease times five years, yet he had stage four metastatic cancer and is on no treatment.

The reason I'm bringing this up is I'm segueing it with pancreatic cancer, which is also a cold tumor; of course, a cancer with a much worse prognosis. Another aside, and I'm sorry for this tangent, one of the hallmarks of pancreatic cancer is desmoplasia, the fibrotic thing. It turns out unbelievably prostate cancer has a uniqueness as far as fibrosis goes.

Are you a general medical oncologist?

John Strickler
No. I’m a GI medical oncologist.

Allen Morris

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Prostate cancer is the only solid cancer that advances from stage 1 to stage 2 by virtue of a positive digital rectal exam. That's my tangent. It's one of my soapboxes. [And what underpins this stage 1 to 2 progression is desmoplasia/fibrosis. So, desmoplasia/fibrosis further likens Prostate Cancer to Pancreatic Cancer in addition to both being prototypes of cold tumors].

But let's go back to Gary Onik. Believe it or not, he induced a miraculous response in a pancreatic cancer patient. [Per the above cold and fibrotic similarities, I believe, not a coincidence.]
Miraculously, a pancreatic cancer patient who had multiple liver mets, after Onik’s cryotherapy, had a complete response: complete resolution of all his liver mets with Onik’s cryotherapy.

Have you ever seen any vaccine tested to date with a complete response of metastases?

John Strickler 22:00
No. I'm not seeing that certainly in the GI (gastrointestinal) world.

Allen Morris 22:03
Well then: You need to see Dr. Gary Onik’s stuff because it happened. On another note: Roger is doing some personalized neo epitope vaccine which I'd love to drill down on. Roger on another date, if we can have a conversation, I want to know what your neoepitope formula is. But not knowing any kind of epitope formula for a vaccine, just using the lysate of a person's own pancreatic cancer, Onik was able to induce a complete response.
Since you're a researcher trying to get a cure for pancreatic cancer, you need to talk to Gary Onik, at least in my opinion, because he was able to do that. The Onik success with Prostate and Pancreatic cancer, both cold tumors, but not so much with hot tumors, supports my belief that a cold tumor is the best tumor to chase in the race for a cancer vaccine.
And I know why the cold tumor is the best candidate for a vaccine; but I presume, you won't ask me why, just as no one else has.
[Onik claims dozens of patients have undergone his treatment and his prostate cancer subset has the best response rate at 50%. So, his case series is not an N of 1 anecdote.]

John Strickler 23:14
In order to make progress in the field, we need to learn from these N-of-one cases. N-of-one cases inspire research. They inspire funding for these kinds of studies. But that can't move the needle. We can't change the world with case reports. We have to hypothesize that this intervention will lead to a certain outcome. Then we need to get funding, ideally, from a foundation source. Because this is obviously a type of intervention that doesn't have a reliable funding source. So you'd have to go through PanCAN or whatever it may be. We need to bring larger pilots. Some of the exciting tumor vaccine results that we saw last fall were published off of a 20 patients series. Because once you show that positive effect, then you can take it a step further and make it standard of care, so you don't have to know somebody to get it, you can get it as part of our national guidelines. This is all part of the process. We can learn a lot from people who are willing to stray from outside of the norm or convention because with pancreas cancer, that convention is just not acceptable. As I'm sure Roger will tell you, the long term

outcomes with the standard of care for pancreas cancer are unacceptably poor. We need paradigm shifts in order to really move the needle with this very difficult-to-treat disease.

Roger Royse 24:57
You mentioned the mutation testing of the tumor. I know PanCAN has a “Know your tumor” program, and I was in it. We went through Tempus, and I went through BostonGene. But since I joined the Cancer Patient Lab, I learned about proteomics, which I didn't know anything about. No one had ever told me. I got a proteomics test, and it found a whole bunch of new therapies and targets that were useful for me.

Do you think that's something that might become part of the standard of care anytime soon? Because I think it was immensely valuable to me.

John Strickler 25:32
When you run DNA-based tests, you're talking 300 to 500 targets. Some of them are actionable, some of them are relevant, some of them are not, but we're going to run out of targets and therapies eventually, and then you get to RNA-based tests, through Tempus and some other assays. And there, you can get into expression profiling, and whether those could be used to predict sensitivity or resistance to certain types of therapies.

You're right: proteomics gets to another whole level. Bioinformatics and machine learning and AI, you need to truly be able to take that information and apply it to therapy, like we've only now just developed the computing capabilities to understand even how to use that very complicated data to guide therapies. To really capture the value of it, we're going to need a whole next generation of therapies that are designed to target those proteomic signals. So yeah, I agree. I think if you're looking at where we're going to be 10 years from now, I would not be surprised if you're starting to see these proteomic readouts driving therapeutic decision making particularly for difficult diseases like pancreas cancer.

Brad Power 27:01
Staying on this topic of more diagnostics: more data gives you more treatment options and more personalization. What about liquid biopsies? I know, your colleague at Duke (Andy Armstrong) talked to us about some AI he used to come up with a multidimensional biomarker that was based off of a blood biopsy. We also recently had a discussion with Tony Magliocco, who mentioned that there are now RNA liquid biopsies that provide visibility into a whole range of things where you might not have enough enough circulating tumor DNA to look at, but with RNA, all of a sudden, a liquid biopsy becomes much more viable, because there's a lot more that you can read. And that gets you closer to real time monitoring. We can take liquid biopsies quite frequently, whereas tissue may be hard to access.

What are the advances that you're seeing that might be available now or in the next six months, or the next year, in the domain of liquid biopsies that would allow a closer monitoring so you can observe what's happening and then maybe nudge things, approaching on a real time basis?

John Strickler 28:19
I love this question, because circulating tumor DNA has also been a major new diagnostic technology that's entered the clinic in the last 10 years. It's got its strengths and limitations. So the major strength is it's convenient, you just draw two tubes of blood. Unlike a biopsy, which many of you know what that feels like to get a biopsy. It's not particularly pleasant. You can sometimes get the readouts much quicker. It's easier to put people on a trial when you're using that liquid biopsy because the speed is so much quicker as well. And in general, the results are for the most part trustworthy. If you see a KRAS mutation in blood, you know it's real; it's not some bogus lab. So I think for that reason, it's got major advantages.

However, when it comes to pancreas cancer itself, there are some major limitations for blood-based profiling. As Allen pointed out, it's a desmoplastic (adhesions or fibrous connective tissue) tumor. When you look at a lesion, say a liver lesion on a scan, it's 90% stroma (liquid filler). There's very little of it that's actually active tumor content. As a result, you think about that cancer, it's almost surrounded by a rubber ball. So it doesn't produce a lot of DNA into the bloodstream that can be captured on one of these tests. The yield of circulating tumor DNA for pancreas cancer specifically is much lower than say colorectal cancer, which is another disease that I treat, which means that the test is just less reliable for identifying the target that's of interest. That's been a frustration we've had about bringing these tests in for pancreas cancer, and why I've tended not to use some of the commercial assays just because I will order the test, and it'll show nothing in the blood. But I will order the same test on tissue, and it'll show me all these targets in tissue.

That said, we are now entering an era where these blood tests are doing more and more. One intriguing application of the blood test is a hypersensitive early detection tool for pancreas cancer. If we're going to move the needle for pancreas cancer, we've got to detect this earlier because it is very difficult to cure the disease once it becomes a bulky tumor. Once it has spread to the lymph nodes, it becomes a very concerning development for the patient. So if you can pick this up earlier, say five years before it became a full blown cancer, you could potentially move the needle and protect people from a pretty aggressive malignancy. Where I see the greatest opportunity in the future with these blood tests is not so much the molecular profiling, but more on the preventive medicine, the early detection. Those kinds of tools could be a really interesting application for that type of test.

Jeff Krolick 31:25
What do you see in exploring the off-label use of existing medications that research has never looked at for pancreatic or prostate cancer, but sometimes by accident, and sometimes, maybe just beginning right now through some artificial intelligence review or finding possible applications.

John Strickler 31:57
One of the frustrating things that we've got is that it costs a lot of money to develop a drug, sometimes billions of dollars. And if the drug is off patent, then the company can't recoup the cost of their investment. There are probably some therapies out there, discarded therapies,

natural therapies, where we just can't get that type of research going because there's just not enough funding for it. That can be frustrating because not every new therapy has to cost $3 billion to develop. It could be something that's widely available. But it's a challenge because patients are obviously seeking out these kinds of therapies. They're smart. They understand that there's never going to be a randomized trial. Sometimes there's what I call “internet lore” around certain things that aren't proven yet. It can be very confusing to navigate that as a patient because you don't know whether that product that you're researching wouldn't be FDA-approved if it had the financial backing, or if it's just as effective as sugar water. And that's a challenge that I've got as an oncologist as well, because I don't have access to that data either. I do hope that in the future, we will have better ways to fund research on therapies that don't have so much of a financial incentive, that don't have to cost $50,000 per dose. Like we should be able to do research on things that cost $5 a dose.

Rick Davis 33:49
We run a peer support group for patients with pancreatic cancer, which is a partnership with Canopy Cancer (a learning health collaborative), and Hirshberg (a foundation for pancreatic cancer research), and a couple of others. It's peer-led. If you have any patients, don't hesitate to send them over. We're running once a month right now, but we're about to move it to twice a month. I've learned a little bit about pancreatic cancer.

I have two questions. One is about BRCA (a biomarker), and one is about TMB (tumor mutational burden). BRCA really should be interesting to the prostate cancer folks because it's relatively common in prostate cancer, probably more common than in pancreatic cancer, although that's one of my questions because you sort of skipped over the BRCA stuff in your presentation, so I'm really interested to know how often you see it. You also talked about germline BRCA in your slide, but in somatic BRCA. My understanding has always been that it doesn't really matter whether it's germline or somatic, it's still going to be sensitive to treatment for PARP inhibitors.

My first question about BRCA is: can you talk a little more about it? One big question for our prostate cancer folks is: what monitoring do they do if they're BRCA-positive? Germline BRCA positive not in the tumor, but if they're germline BRCA positive? How do you monitor pancreatic cancer? You can squeeze your breasts and see if you have breast cancer, and you can check for melanoma. You can do other things. What do you do for pancreatic cancer?

John Strickler 35:55
I love this question. We have an FDA-approved therapy for germline BRCA in pancreas cancer. It's olaparib. I'm sure the prostate cancer folks know that drug well. That came to us out of a trial that took patients with metastatic pancreas cancer and randomized them to olaparib by itself or just standard maintenance treatment. It was interesting, because all the patients had to have **germline** alterations. I will go back to the somatic later. But what they found is that the patients who got the olaparib were put into a longer remission after completing chemotherapy than those people who didn't. One of the challenges with that trial though is it did not show a survival difference long term for giving olaparib, so the drug was FDA-approved, but it was because it

delayed relapse of the cancer, but it didn't improve survival. So it's somewhat controversial: if it doesn't improve survival should we give it? Our feeling is that patients still benefit because they're spending more time off of chemotherapy. But that's why it's a little bit of a thorny topic for us around that.

Just for the sake of the audience, germline means it's something you're born with; germline BRCA mutations are basically a genetic predisposition to different types of cancer, including prostate cancer. Somatic means that you're not born with it. The cancer acquired it in some way, and it's part of the cancer but not part of the person. So it appears that those PARP inhibitors are truly only active in pancreas cancer patients who were born with that BRCA mutation or the other one is probably not somatic. Now, I understand that there's some literature around this and prostate cancer as well. I'm way out of my lane with prostate cancer, but my recollection is that those therapies, those PARP inhibitors, are most active in patients with germline alterations, particularly BRCA1, 2, and PALB2, but you all can correct me if I'm wrong, since I don't know.
[Olaparib - PSA50 response rate in Prostate Cancer, BRCA patients:
germline mutation 43% vs. somatic monoallelic 17% -
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9414325/]

Rick Davis 38:30
BRCA1, BRCA2, maybe ATM may be part of the conversation that we've had has been largely with Pamela Munster, who's really a BRCA expert. She says, “Well, if it worked for BRCA, it's got to work for PALB2.” But we don't really have the evidence. But we know for prostate cancer, that it doesn't matter if you're germline or somatic.

John Strickler
Yeah.

Rick Davis
It's really interesting for me to hear that it may matter in pancreatic cancer. If you found a somatic BRCA mutation in an assay from Tempus, Foundation Medicine, you'd have to go check if it was germline before you use a PARP inhibitor, whereas in prostate cancer, you wouldn't need to do it.

John Strickler 39:37
Although I would say that in prostate cancer, you would probably still want to test.

Rick Davis 39:45
Yes. For relatives and what have you, I absolutely agree. But not from the standpoint of whether it would work or not.

John Strickler 39:54

That's why we're recommending that patients with pancreas cancer get germline testing. Hopefully Roger had his done, and I don't know which vendor you used for your tests. But it's something that's increasingly standard, and about up to maybe at most 5% of patients have a germline BRCA1, 2, or PALB2 mutation in pancreas cancer.

Roger Royse 40:21
In my case, I caught my cancer at stage 2. It was resectable. I had six months of chemo. I'm NED right now. I found it through a Galleri blood test. I had to fight to get it. I'll just tell you that two years ago at least, doctors were not recommending it. Some of them are just hostile to it. But that's what found it. It was pretty significant.

I like to tell people the story about this radiologist that I contacted. He called me up one day and assumed he called me to schedule some sort of radiation. He said, “Oh, no. So you're not a candidate for radiation. I just had to talk to you because you're the luckiest person I've ever met. Because it was distal tail. (“Distal” means distant, or the farthest part from the center.) You'd never know about this otherwise.”

I guess that leads me up to early detection, because that seems to me to be one of the best ways to fight this disease. What do you think?

John Strickler 41:31
Well, that was my point with the blood-based testing before if we're going to move the needle. Pancreas cancer is extraordinarily difficult to cure. I'm thankful that they found yours early and that it was a distal tail, because that's a lot easier surgery than some of the other surgeries we offer patients in your cohort. But that's going to be the way we can do better with this disease. We have to catch it earlier and earlier. You're right. When you talk about these early detection assays, from my perspective, as a practicing medical oncologist, I've only seen patients who've shown up in my clinic who found their cancers through these tests. I've never seen a false positive, because you can't get to me unless you have a true positive.

I was talking to a primary care colleague, and I think the challenge they've got is that when you're dealing with a low prevalence tumor, you need a very high sensitivity and specificity test to avoid a lot of false positives. The primary care doctors are worried that if the test is not specific enough, we're going to be terrifying a lot of people, and they don't actually have cancer, or they may end up getting a lot of extra biopsies and other things that they wouldn't otherwise need. That's where the pushback is coming. It's understandable. When you think about the fact that the numbers have to be really tight on one of these tests to avoid a lot of unhelpful follow-up studies and biopsies. But from my perspective, your story is the story I've seen, which is that these tests have been used to find things earlier than people would have otherwise found them.

Brian McCloskey 43:38
I was recently at a symposium, and a doctor was talking about radioligands in pancreatic cancer. Of course, this is a field that's been pursued for quite a while in prostate cancer.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Curious to get your thoughts on the use of radioligands in pancreatic cancer.

John Strickler 44:13
Radioligands have really gotten a big boost from the prostate cancer work, where we do see the radioligands have been successful for that tumor type. In order for a radioligand to work, you need a target that's universally expressed that's not a normal tissue, or low expression on normal tissue, and then an effective therapy tag to it. There's no reason why you could not develop a radioligand for pancreas cancer, whether it's CA99 or some other protein. You just have to find the protein and the target and engineer that molecule. I'm not aware of anything being developed though, strangely enough, for pancreas cancer, at least in this radioligands category. So maybe there are some technical issues that make that drug development a little trickier. But to me it is fair game as a potential avenue for novel therapies.

Rick Davis 45:23
Telix is working on something for PanCAN (the Pancreatic Cancer Action Network advocacy group), but it's tied into what they're doing for neuroendocrine with DOTA-TATE (a protein that can be used as part of a radioligand), so it wouldn't be applicable obviously to the exocrine PanCAN folk, but it might be applicable to the to the neuroendocrine PanCAN folk. I know this because I have an old school friend who's a professor and a pediatrician and in Australia with PanCAN. I just reached out to Telix on his behalf and connected them. So it's not here yet, but if you want to know more then I'm happy to connect you to Telix.

John Strickler 46:14
You're absolutely right. We do have radioligands. We've got lutetium dotatate, Lutathera is the trade name for it. That is available to us. I believe it is FDA-approved. We use it routinely, but there are new radioligands that are coming in the clinic, specifically for the neuroendocrine type. But what I was referring to was specific to the exocrine pancreatic adenocarcinomas.

Rick Davis 46:45
The work that Himisha Beltran has been doing and Rahul Agarwal on DLL3 (inhibitory notch ligand delta-like ligand 3, plays a role in tumor growth). They've also used that in some pancreatic neuroendocrine patients.

What percentage is neuroendocrine? And what percentage is exocrine?

John Strickler 47:04
I think most – 90% would be my guess – is exocrine pancreas, and in this adenocarcinoma category, the neuroendocrine subtype is pretty rare, and they have a much different natural history, in general do much better with therapies, tends to be fairly chemotherapy sensitive. And then we, of course, have these radioligands available. You would never wish a pancreatic malignancy on your worst enemy. But if you were to choose between the two, as a patient, you would rather have a neuroendocrine type, I would think, than an adenocarcinoma. The adenocarcinomas also tend to be far more symptomatic. I'm personally convinced that there is a cytokine pattern that makes people feel awful with adenocarcinomas. It affects people not just

physically, but mentally and emotionally, and I'm sure in your AnCan work you've seen how it can affect you not just physically, but emotionally, mentally as well. I think cancer is much bigger than just a physical phenomenon. The body knows something's wrong, and it feels that inflammation, and the mind absorbs that in its own way.

Roger Royse 48:30
I'm really glad to hear you say that. Because I went for probably a year of having that feeling. And everybody was like, “You're such a hypochondriac. There's nothing wrong with you.” I just knew something was off.

Debbie Denison 48:47
I am a huge fan of targeted therapies. I have been on Imatinib (a type of cancer growth blocker called a tyrosine kinase inhibitor; tyrosine kinases are proteins that cells use to signal to each other to grow. There are a number of different tyrosine kinases and blocking them stops the cancer cells growing.) for coming up to 19 years, and I'm still on firstline therapy.

Realistically, what is the outlook in terms of the KRAS inhibitors that are in the pipeline that are coming to market? I see there's one that's sort of pan-KRAS. I think that Moringa is bringing that out. Is this going to be kind of a game-changer? A lot of these targeted therapies are already out in lung cancer, and I've worked on quite a few of them over the years.

John Strickler 49:29
The Imatinib story is the poster child story for how amazing and life changing target therapy can be. And that's of course for CML (Chronic myelogenous leukemia), which is a type of leukemia that's very clonal and very dependent on that target. The problem with solid tumors is that they tend to have a lot more mutations in them, and they can morph, they can be chameleons, they can change under that selective pressure of therapy much more quickly than, say, CML can under the treatment of Imatinib. So as a result, we see the outgrowth, we see the evolution of resistance much quicker in most solid tumors, than we do over in, say, CML treated with Imatinib. And that creates a challenge for us because we are always chasing that evolution.

Now, in the case of lung cancer, we have therapies that will hold the disease back for years. And then every cancer has its own kind of what I've called, for lack of a better term, its own natural history, its ability to evade that targeted attack. Interestingly, when you look at that KRAS-G12C story which I showed you a little bit, lung cancer was most sensitive to it. And the least sensitive to it was colon cancer, meaning colon cancer could rapidly morph into a resistant type of cell. And pancreas cancer was somewhere in between. And I think in order for us to make long term, like to truly turn pancreas cancer into a chronic disease that you just take a pill every day for, would require us getting smarter about what that pattern of resistance looks like, and being able to short circuit it and prevent it in a way because we're a long way from the Imatinib story with these targeted therapies and solid tumors.

But what I really find promising is that we are making progress here, as I showed you. In 2013 we had nothing. We didn't even have PARP inhibitors at that point. For the BRCA germline

tumors, we are now bringing in therapies that are beginning that attack. But now the next level two years from that once those therapies establish their worth, then we're going to say, “Okay, do we pair this thing up with something else to make it work better? Do we give something else to prevent that outgrowth of resistance? What does resistance look like?” But this is where we're headed. Right now even having any treatment at all is a breakthrough for pancreas cancer, which is kind of sad, but also encouraging at the same time.

Debbie Denison 52:21
That's how lung cancer was when I first started working in this space. I work with life sciences. In the development and commercialization of these molecules, I saw that the high unmet need in lung cancer initially, which has now become a space where there are many, many treatment options, even for the very, super rare once in a career people like NTRK fusion cancers (Neurotrophic tyrosine receptor kinase gene fusions are an actionable biomarker for cancer therapy and can be found in over 25 different types of cancer.) What I see now is almost a situation where the oncologist can't keep up with that treatment landscape. And the patients actually have to become empowered to know their own disease, which is important as well.

John Strickler 53:00
Patients need to be empowered, and it's okay to get a second opinion, and make sure that the things that they're hearing and seeing and understanding are calibrated, because you're right, I don't know how a doctor that treats every single cancer under the sun. CML, breast cancer, multiple myeloma, pancreas cancer, all the different subtypes of lung cancer, to know what's coming out two years from now is practically impossible for somebody who has to treat literally hundreds, if not 1000s, of different diseases in their clinic. I personally get referrals, and I work with those doctors to say, “Hey. Look out. In six months there's going to be an FDA approval for drug X.” And they're very appreciative to know how we're changing. This is what's on the horizon.

Richard Anders 54:05
Are there any of the mid-stage to late-stage KRAS trials that you're excited about?

Is there any history or knowledge about if somebody escapes one of the KRAS inhibitors of which there aren't many yet, do they hop into a different KRAS mutation? Or do they hop into unknown territory, with some other kind of mutation that's not in any of the target lists?

John Strickler 54:51
One of the challenges of developing drugs for KRAS is that, as I said, most of the time when there's a mutation it locks the switch in the on state. But the drugs we have currently in development, the ones that I showed you for KRAS-G12C, lock the protein in the off state. Well, the protein has to be in the off state to be locked in the off state. And so that's probably why it has struggled to be active in certain contexts. In order for us to build, I think, a next generation of therapies, we need to be able to attack a light switch when it's in its on position. And there are drugs now entering the clinic that do this. I point out the Revolution Medicines pipeline, which is designed to attack these so-called “RAS(ON)” variants. Already they've shown some interesting

data in pancreas cancer. So I'm really excited about that particular technology from Revolution Medicines. But this is an era where there are going to be countless different approaches taken for that.

Now, the second part of your question is what does resistance look like? There are two types of resistance. One is acquisition of new mutations, outgrowth of new mutations that rescue the tumor to keep the light switch on. So if the mutation is KRAS-G12D, one way to escape would be to make a different KRAS mutation that is not impacted by that drug, like maybe KRAS-G12R will outgrow. It'll be present in one in a million cells, and it will by process of selection grow out of that attack.

The other interesting biology that we've learned is that there are receptors on tumor cells that can also rescue the disease by activating what we call wild type or non-mutated processes. So like when you inhibit KRAS, you can activate normal proteins in the cell to keep the cell turned on. That's another tricky piece of biology that we'll have to figure out for certain types of tumors. That's particularly a problem for colon cancer, a little less of a problem in pancreas cancer, but it can rescue tumor cells, even when you think you've got your light switch in the off position.

Richard Anders 57:31
For Gleevec there are a whole host of downstream mutational drugs that deal with whatever the first set of mutations are. It sort of hopscotches along with it. But I guess if you get a constituent of the active cell, you're in trouble. And if you get an alternate pathway, you're in trouble. But if it's a KRAS mutation, is there any sort of insight about whether it goes to a different potentially druggable KRAS mutation? Or is there no history or not enough knowledge yet?

John Strickler 58:05
It will typically grow out as multiple simultaneous mutations. For example, you think about cancer being in maybe five spots in the body. Each spot will have different clones that grow out that are resistant. That's why it's so challenging. With some of these GI cancers, like pancreas cancer, you can have multiple simultaneous resistance alterations. So even if you could target one of them, you'd have to target all five different ones simultaneously. It becomes very tricky.

Richard Anders 58:39
You might have a C and a D at the same time, for example.

John Strickler 58:45
Yes. A C and a D, and a D and an R, plus a KRAS wild type amplification, plus a BRAF mutation. And you notice all those mutations are designed to rescue the same pathway that was activated by the original KRAS mutation. They won't go through a different pathway, they'll activate the exact same pathway in that cancer.

Richard Anders 59:08

One clarification about the first part of your answer, you said that some of these KRAS drugs typically target KRAS off? Is that like, it's an off confirmation? And from time to time, it gets into the off confirmation? That's the moment you target it?

John Strickler
Yes.

Richard Anders
And then if it's on confirmation, it's just it's not targeting some part of the path that some part of the receptor that is always available, it's targeting the part that's only available when it's false.

John Strickler 59:42
The concept here is called cycling like a KRAS switch turns off, and a switch turns on, and certain types of mutations are always in the on state, and certain will flip back and forth between on and off. So if you have an off inhibitor, a protein that is flipping over to off, that's when the drug will bind, but not when it's in the on, but there are now drugs being developed that can target it in the on state as well, which is hugely interesting.

Richard Anders 1:00:07
That's really interesting. Because KRAS is so flat. It's a hard drug to hard molecule.

John Strickler 1:00:14
You're absolutely right. That's why it has taken 40 years to figure out how to build drugs for it.

Richard Anders 1:00:20
Wow. Thank you.

Roger Royse 1:00:23
Thank you, Dr. Strickler, for being here.

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Here are some additional slides on immunotherapies in pancreatic cancer that Dr. Strickler didn’t have time to get to:

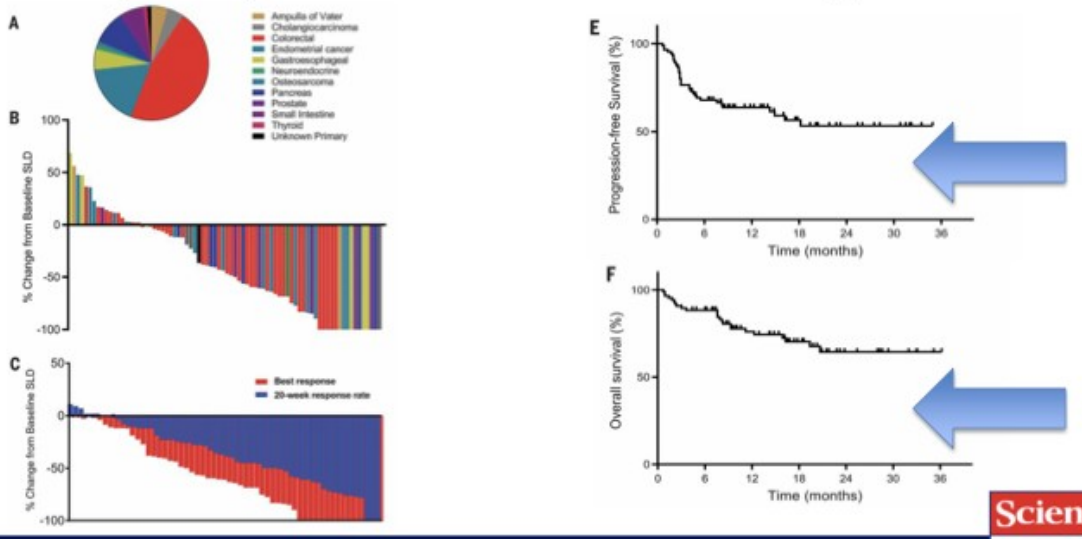
Precision Medicine Strategies in Pancreas Cancer

IMMUNOTHERAPY

Duke UNIVERSITY

Long-term response to immunotherapy (MSI-H)

Clinical response to pembrolizumab across 12 different tumor types with dMMR



Duke UNIVERSITY

Dung T. Le et al. Science 2017;357:409-413

Science AAAS

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Efficacy of Pembrolizumab in Patients with Non-colorectal MSI-H Cancer: Results from KEYNOTE-158

Tumor type	N	ORR, %	Median PFS, mo	Median OS, mo	Median DOR, mo
Endometrial	49	57.1	25.7	NR	NR
Gastric	24	45.8	11.0	NR	NR
Cholangioca	22	40.9	4.2	24.3	NR
Pancreatic	22	18.8	2.1	4.0	13.4
Small bowel	19	42.1	9.2	NR	NR
Ovarian	15	33.3	2.3	NR	NR
Brain	13	0.0	1.1	5.6	--

Duke UNIVERSITY

Marabelle et al., J Clin Oncol 2020 Jan 1; 38(1): 1–10.

Immunotherapy for *KRAS*^{G12D}-mutated Colon Cancer: Adoptive T-cell Transfer Therapy

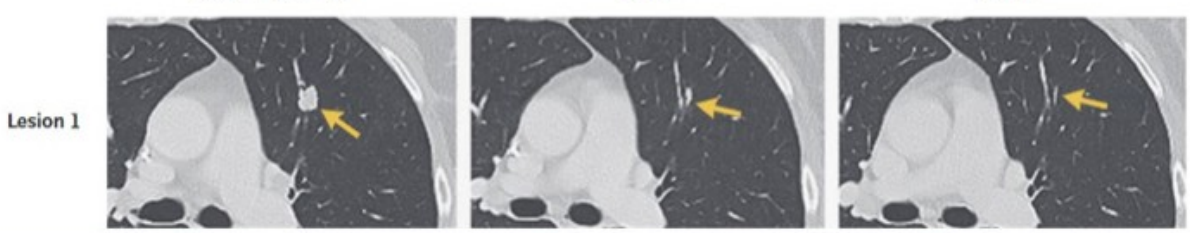

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

- A polyclonal CD8+ T-cell response against mutant *KRAS*^{G12D} in TILs was obtained from a patient with metastatic CRC
- After the infusion of HLA-C*08:02–restricted TILs all lung metastases regressed
- One of these lesions progressed after 9 months- the lesion lost the HLA-C*08:02 class I MHC molecule



Duke UNIVERSITY

Tran et al., N Engl J Med 2016; 375:2255-2262

“Navigating Pancreatic Cancer” (John Strickler, MD) [#91]

Immunotherapy for *KRAS*^{G12D}-mutated Colon Cancer: Adoptive T-cell Transfer Therapy

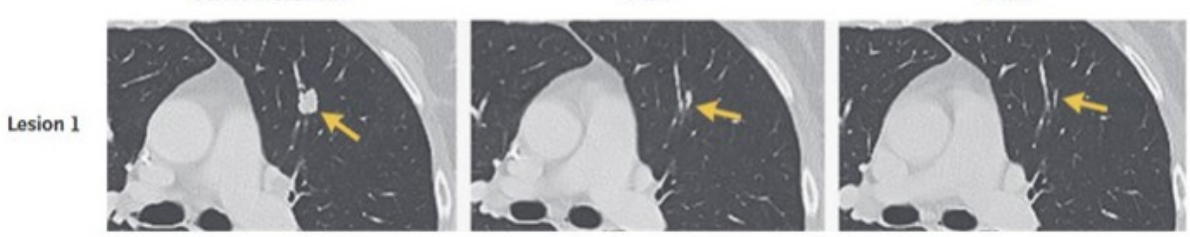

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

- A polyclonal CD8+ T-cell response against mutant *KRAS*^{G12D} in TILs was obtained from a patient with metastatic CRC
- After the infusion of HLA-C*08:02–restricted TILs all lung metastases regressed
- One of these lesions progressed after 9 months- the lesion lost the HLA-C*08:02 class I MHC molecule



Tran et al., N Engl J Med 2016; 375:2255-2262

Immunotherapy for *KRAS*^{G12D}-mutated Colon Cancer: Adoptive T-cell Transfer Therapy

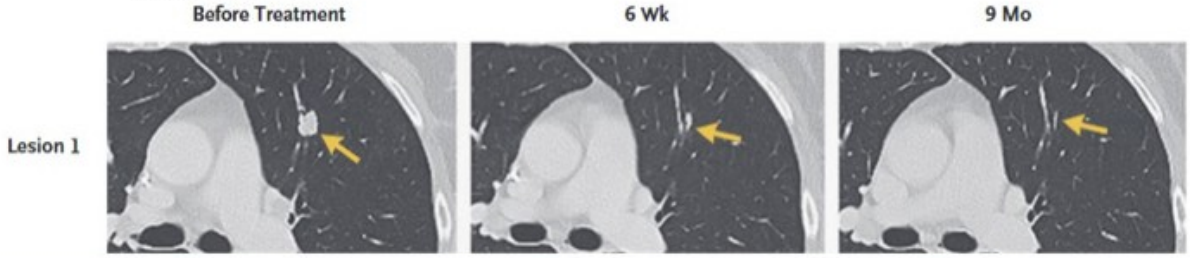

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

- A polyclonal CD8+ T-cell response against mutant *KRAS*^{G12D} in TILs was obtained from a patient with metastatic CRC
- After the infusion of HLA-C*08:02–restricted TILs all lung metastases regressed
- One of these lesions progressed after 9 months- the lesion lost the HLA-C*08:02 class I MHC molecule


Before Treatment
6 Wk
9 Mo
Lesion 1

Duke UNIVERSITY

Tran et al., N Engl J Med 2016; 375:2255-2262