

Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on myelodysplastic syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join in, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about clinical trials and GI cancer with Dr. Stacey Stein. Dr. Stein is Assistant Professor of Medicine and Medical Oncology at Yale School of Medicine and here is Dr. Anees Chagpar. Chagpar Stacey, maybe you can start off by telling me a little bit about GI cancer as that seems to be a really broad group. How do you wrap your arms around GI cancers, how do you categorize it? Stein It is a broad group, even though we are a specialty, and basically we cover all of the GI tract from the esophagus which includes stomach cancer, liver cancer, pancreatic cancer, gallbladder biliary cancers and then colon and rectal cancers and anal cancers, so we really cover the whole tract, a lot different diseases and different treatment. Chagpar I know that a lot of people have heard about colon cancer and I guess that is in that whole spectrum and is the most common, but can you give us a sense of how common all of the different GI cancers are and maybe a little bit about their prognosis? Stein So colon cancer is the most common one. There are about 150,000 people a year diagnosed with colon and rectal cancer in the United State and fortunately, a lot of these patients are diagnosed at an early stage where they can have surgery and hopefully a cure. Some of the other diseases are less common like pancreatic cancer which is probably about 45,000 people diagnosed in this country a year and often their diagnosis is at a later stage, and we are really focused on diseases like that for developing new treatment options and some of the other cancers are less common but certainly we see many patients with them and feel that the need for more treatment options, more clinical trial involvements, more basic research, is so important. Chagpar I know that a lot of people know that pancreatic cancer does not tend to do very well a lot of the time because of exactly what you said, which is unlike colon cancer where everybody knows that they should be getting a colonoscopy to see if they have any polyps which can often find cancers at the earlier stage, there really is not a screening test for pancreatic cancer, is that right? Stein That is right, for most of the cancers besides colon cancer and the GI tract, we do not have a good screening test and certainly there is a lot of research looking at potentially different blood tests that 3:43 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3 maybe could help us with that in the future, so you are right, it is important for people to get colonoscopies for colon cancer screening but sometimes for the other diseases including pancreatic cancer, the early symptoms are so nonspecific that it makes it really hard I think for the

patient and their primary care doctor to recognize what is happening. Chagpar Can you give us a little bit of a clue about what some of those nonspecific symptoms are, because I think that many people have heard about pancreatic cancer, certainly there have been some celebrities diagnosed with pancreatic cancer who have not done well and a lot of people might want to avoid it, what symptoms should they be looking for? Stein They are pretty nonspecific, sometimes it is just a feeling of bloating, a feeling of maybe feeling full a little bit earlier when they used to be able to eat a larger meal, sometimes people notice that they are having loose stools, but unfortunately, these are really symptoms when you think about it that everybody has had at some time or another. Certainly, weight loss is always a concern, when someone is losing weight, maybe I am a little bit of a pessimist but I feel like even when people are trying to lose weight and when it is kind of easy to do that, it is a little bit of concern to me and obviously abdominal pain and certainly jaundice, when someone's skin turns yellow it is a very concerning sign that we have to take a look at, even though that is coming from the liver, that is often a first sign of pancreatic cancer that the tumor in the pancreas is actually blocking the flow of the liver. Chagpar So certainly with those symptoms, as you were rattling them off, I was thinking, I can think of a day in the last week or two that I have had many of those symptoms, albeit not jaundice and abdominal pain, but many of those symptoms and so are there any real kind of warning signs aside from the jaundice and abdominal pain that does not go away that would trigger people to go to their doctor or is this something where you have to wait until you get those symptoms before you present and is it too late when you have those symptoms? Stein That is a good question, sometimes people may have symptoms of malabsorption meaning that they have loose stools that may smell funny or float which is not normal and what is interesting is that we know that because the pancreas is starting to not function well, many people develop diabetes in the six-month window before their diagnosis. Unfortunately though, the rate of diabetes is so high that the vast majority of people being diagnosed with diabetes do not necessarily have pancreatic cancer, so I think that it is still not enough of a target group to screen but that is certainly a known fact. Chagpar So people who are just diagnosed with diabetes should not all go and get their pancreas evaluated with the CT scan or something. Stein Right, absolutely, but I do think there is research in developing blood tests or stool tests, that may help us diagnose cancer in the GI tract at an earlier stage and the reason why that is so important is for 7:06 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3 most of these cancers, surgery is a very important treatment modality and when the tumor is found early enough where it is possible to remove everything with surgery even if we may be giving other treatments like chemotherapy and radiation in conjunction with the surgery, that is usually our best chance at potentially offering a cure. Chagpar So then that really gets to, with all of the research that is going on in early detection, maybe there is a blood test, maybe there is a stool test, are these things that you would envision everybody would be eligible for or are these

things that you say, well if you have had particular predisposing symptoms or if you have had a family history, that this would be a more tailored group that would be screened with these blood tests and stool tests?Stein That is a good question. I think that if the tests developed were good enough, sensitive and specific enough, and hopefully inexpensive enough, they could become more universal screening tools. In general, most of these diseases occur with aging, so they are more common in older people but certainly, we do see patients that are younger than expected and we would like to avoid all of our patients having these cancers.Chagpar It sounds like one of the big hurdles that we need to overcome is finding these cancers early, but let us suppose, somebody does present with symptoms, they have got jaundice, they have got malabsorptive symptoms, they have got these loose stools, they have been losing a bit of weight, they go to their doctor, how are these actually diagnosed because I can imagine that even if you had all of these symptoms, perhaps with the exception of jaundice, they are so nonspecific. How does your doctor actually get from these vague symptoms to guess what you have got is pancreatic cancer. Can you walk us through that diagnostic paradigm?Stein Sometimes people might have had a CAT scan as their initial test and that may be because of abdominal pain, especially if they are in the Emergency Room, they will often have a scan. Many people develop jaundice as their initial symptom and that would prompt any physician to get imaging and blood work and sometimes that starts with an ultrasound and then moves to a CAT scan and certainly, the blood work is important too to see the liver function and then what is important also is that regardless of which cancer we are discussing, patients need a biopsy and depending on where the tumor is located, the biopsies are done in different ways. If we are trying to get a biopsy from the pancreas, that usually means that the patient needs an endoscopy where a gastroenterologist will put a scope down their throat, down into their stomach and then they actually can put a needle through the wall of the GI tract into the pancreas to get a sample of tissue, so it is really important before we think about treatment options that 10:37 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3we have a biopsy so we make sure that it is the type of cancer that we think it is and then complete imaging so that we can get the sense of the stage, meaning where it is located, if it has spread and if it is surrounding blood vessels that would make it not possible to do a surgery.Chagpar When we talk about pancreatic cancers, like so many cancers that we talk about, there are often so many different kinds of cancers, so are there different kinds of pancreatic cancer that are maybe managed differently or have different prognosis?Stein I think when most people say pancreatic cancer, what they really mean is pancreatic adenocarcinoma, and that is the vast majority of tumors that arise in the pancreas, probably about at least 85% of them. Less commonly, there are neuroendocrine tumors and those overall usually have a better prognosis, they are slower growing, occasionally we are surprised that the pathology comes back as a lymphoma and that is pretty uncommon and then obviously the treatment is very different, so it is really important that we have that tissue.Chagpar Yeah, and even in pancreatic adenocarcinoma, if we

narrow our focus even more, in many cancers these days we are talking about tumor profiling and genomics and different targets, does the same thing play out in pancreatic cancer? Stein Not really, in pancreatic cancer, actually there are just a handful of mutations that are present in the vast majority of tumors and unfortunately we do not have any drugs as of yet that target those common mutations, the most common one being KRAS. There is one exception to that though. We now know that there are patients with mutations in the BRCA genes that occur in pancreatic cancer and so people may be familiar with those genes because they are much more commonly discussed in breast cancer and ovarian cancer and people often think of them as being familial and often people from Jewish Ashkenazi background, but we now know that about 8 to 10% of pancreatic cancers also have these mutations and so we are actively now screening patients to find those people that carry a BRCA mutation and we do have clinical trials open looking at drugs like olaparib which we know are active in ovarian cancer with BRCA mutation looking to see if there is activity in pancreatic cancer. Chagpar One of the things in BRCA patients in breast is that we found that at least their breast cancers are potentially more sensitive platinum-based agents and so some of the clinical trials that we have open in the breast cancer arena are treating patients with randomizing patients either to receive standard of care, chemotherapy before surgery or chemotherapy with a platinum agent before surgery to see whether the platinum agents are better in these patients, has that been looked at in pancreatic cancer? Stein There are 2 main active regimens in pancreatic cancer and one of them is FOLFIRINOX, and one of the drugs in that regimen is oxaliplatin which is a platinum drug so most patients are treated with a platinum drug in their treatment. 14:10 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3 Chagpar Regardless. Stein Yeah. Chagpar That is so interesting and we are going to learn much more about clinical trials and pancreatic cancer after we take a short break for a medical minute. Please stay tuned to learn more with my guest Dr. Stacey Stein. Medical Minute The American Cancer Society estimates that over 1500 people will be diagnosed with colorectal cancer in Connecticut alone this year. When detected early, colorectal cancer is easily treated and highly curable and as a result, it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the one at Yale and at Smilow Cancer Hospital to test new innovative treatments for colorectal cancer. Tumor gene analysis has helped improve the management of the disease by identifying the patient's most likely to benefit from chemotherapy and newer targeted agents resulting in a more patient specific treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas. Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Stacey Stein. We are talking about GI cancers and pancreatic

cancer in particular and clinical trials and right before the break, Stacey, we were talking about some of the chemotherapeutic regimens that you use for pancreatic cancer and you were mentioning that many patients, or at least some patients with BRCA mutation, actually can get pancreatic cancer and very similar to breast, they are treated with a platinum containing agent. Tell us a little bit more about different chemotherapeutic regimens in pancreatic cancer. Are they effective and what things are novel in that space that are going on now?

Stein For a very long time there was one drug that was known to be active in pancreatic cancer, gemcitabine and there were many clinical trials done that unfortunately showed no benefit over gemcitabine and then a few years ago, there were 2 trials that showed regimens that had more benefit that we regularly use now. One of them is called FOLFIRINOX and the other is gemcitabine plus a second drug named Abraxane, and so those are two active regimens that definitely do prolong the length of people's lives and certainly most patients wind up getting both regimens, so we are always looking for novel drugs, new drugs that can add other treatment options for out-patients, but one thing, to take a step back, that I think 16:55 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3 is of interest is that even for the patients that have surgery, so patients with early stage disease that we do not see any spread of disease on imaging, it is not involving the blood vessels near the tumor, for a lot of different cancers, if you are able to do surgery at an early stage like that, patients often do very well, like in breast cancer and colon cancer, but what we see in pancreatic cancer is that even with surgery, there is a high recurrence rate and we think that that is probably because the cells spread even before the surgery even though we cannot see them on imaging, so one focus in pancreatic cancer is to increase that cure rate in patients who can go for surgery and different people are developing different clinical trials to look at this problem but many of them focus on similar practices which include giving chemotherapy even before the surgery, we call that neoadjuvant treatment, and I think that that potentially is going to be an important part of these patients treatment in the future. For instance, we have a clinical trial now that is being led by one of my colleagues, Dr. Jill Lacy, of giving FOLFIRINOX chemotherapy for patients who are going to have surgery before and after their surgery and none of these trials are complete yet, so we do not have data to share yet but we are hopeful that these types of trials are going to improve the cure rate for our patients.

Chagpar Stacey, in that trial, is standard of care to do surgery followed by FOLFIRINOX in these early stage of cancers and now the experimental one is adding a new adjuvant piece to that?

Stein No, actually the standard of care is surgery followed by six months of gemcitabine alone but I want to say I find the term standard of care a little bit misleading because I think it implies something that is of a lot of benefit that should be what we do for everyone and in this situation, the standard of care is really lacking, so there is an improvement to doing gemcitabine versus no treatment after surgery but it is a small benefit and we want the benefits to be much greater for our patients, so I do feel that given

the information we have for what is standard of care now, we really should be encouraging patients to go on clinical trials. We actually just had another trial open where patients get either gemcitabine or the combination of gemcitabine and Abraxane after surgery if they have not received chemotherapy before surgery and that study recently just finished accruing patients, so hopefully we will have some data back from that in a year or so. Chagpar Right and that is also the regimen you said had shown benefit in other studies. Stein Right. Chagpar I think your point is an absolute spot-on one which is, standard of care, we talk about standard of care but really the emphasis is on the standard part and not on the care part because so often we find that people really do get the best care and best outcomes on trials because you are getting tomorrow's standard of care today, you are getting what we think is better and we know people who participate in clinical trials tend to do better. 20:33 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3 Stein Right and we do know that the regimens that we are talking about giving patients around their surgery are regimens that we already know are effective in pancreatic cancer for patients with more advance disease. Chagpar Just to go back to the whole neoadjuvant concept, that is something that we looked at in breast cancer many years ago as well and so it is interesting to see the parallels between different tumor types, we know that for example, in breast cancer, giving chemotherapy upfront followed by surgery was exactly the same as surgery upfront followed by chemo except that giving chemotherapy upfront really had some advantages in terms of making the disease more resectable and allowing more breast conservation, so do you think that is another potential advantage in patients who have pancreatic cancer that maybe you can shrink the disease and make the surgery, which can sometimes be, as I understand, a fairly major surgery, a little less morbid? Stein I am not sure about that. It is a big surgery and I think even when the tumor is very small, it is always going to be a big surgery. Depending on location of the tumor, it may involve removing part of the pancreas, part of the stomach, part of the small intestine. If the tumor is at the other end of the pancreas by the spleen, it could involve removing the spleen and part of the pancreas, so they are big surgeries. I think what our goal is in this situation is try to prevent the high recurrence rate and that is really our main focus. Chagpar Wouldn't giving chemotherapy after the surgery also get rid of micro-metastatic disease? Stein It probably does, I think the potential benefit of giving the chemotherapy before the surgery is that that may even improve the rate higher to decrease the micro-metastatic disease and also after surgery, there is a potential risk of people having complications from their surgery, if someone has an infection or is in the hospital a little bit longer than we thought, they may not feel up to getting the chemotherapy and then there is a longer window of time where they have not gotten the treatment and people are recuperating from their surgery. They are getting used to eating again with the changes in the anatomy, so we feel that it might be easier for people to start the chemotherapy prior to the surgery, have the advantage and benefit of that and then get their surgery and then finish the chemotherapy. Chagpar

Has there been any thought to giving all of the chemotherapy upfront instead of having more of a sandwich technique? Stein That is an interesting idea, you are trying to balance having the surgery done in a reasonable timeframe and potentially we know that there is a risk of extending that out if the tumor becomes resistant to that chemotherapy that we might lose our window of opportunity for surgery, so I think that the sandwich 24:09 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3 approach which is one that we often use in other cancers like stomach cancer is kind of a balance between getting the maximal response to the treatment and not losing our window for surgery. Chagpar Yeah, but certainly doing clinical trials like this really helps you to get the right answer. It is the data from those kinds of trials that says, you know doing a sandwich technique is better than doing the back only technique or doing everything upfront is either better or worse than doing the sandwich, so I think that is one of the big reasons why it is so great to have patients participating in these trials is that it really helps us to figure out what is best. Stein Yeah, for me that is my passion. I love taking care of my patients and I want to also advance the field and have better treatment options for the patients I have now and the patients that we are going to have in the future, and I think it is just so important to have new treatment options to offer our patients especially when the standard of care is not as good as we want it to be. Chagpar The prognosis, especially in pancreatic cancer, the prognosis being as dismal as it is, we have got a big window of improvement, so tell us a little bit more about how people figure out what regimens, we talk about clinical trials all the time and we talk about how we are now trying FOLFIRINOX versus gemcitabine or we are trying gemcitabine plus Abraxane, is the next regimen that you are going to “try” in a clinical trial, is it you wake up one morning and say hmm, I think I am going to try this or what is the science behind that? Stein We are always looking to work with our partners in the lab for novel agents that may be coming out and showing the benefit, so for instance, there is another trial that we are participating in as part of the Southwest Oncology Group which is the collaborative group that were part of at Yale and it is combining FOLFIRINOX which is the regimen that I already mentioned that we know is active in pancreatic cancer, but what is interesting is that we know that in the pancreas around the tumor, there are these changes that happen where it is hard for the chemotherapy to get into the tumor. There is this stromal reaction and the pressure is very low in the tumor. These cells kind of get together and almost form a wall around it and there is a drug available that works on these cells and cell bonds and hopefully breaks them down to allow the chemotherapy to get in better, so even though it is not a chemotherapy drug, it is a hyaluronidase which is an enzyme that works on the cell and cell bonds and we are giving that in combination with the FOLFIRINOX to see if we can make the chemotherapy drugs that we already have more effective, so that is a trial that is ongoing that we are excited about participating in. Chagpar How do you figure out whether other modalities are also going to be of benefit, in a lot of cancers we also add radiation, but I have not heard you mention radiation

in pancreatic cancer? Stein There is potentially a role for radiation, so when I think about the treatment options and the way that I 27:37 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200424%20YCC%20Answers%20-%20Dr%20Silber_252093_5.mp3 explain them to my patients is that some treatment is local and some treatment is systemic, so chemotherapy is systemic. It goes into the blood vessels and it goes everywhere. An option like surgery or radiation is more local treatment, so we have to be targeting a certain area, so there actually is a group of patients who may not be candidates for surgery because the tumor is around the blood vessels in the area of the pancreas but they also do not have disease that spread outside of the area and we call that group locally advanced, so locally advanced pancreatic cancer is a group where overall potentially there is a role for radiation in treating those patients. Often the treatment that we give these patients is chemotherapy and then sometimes we move to radiation and I have many patients who have had chemotherapy and then radiation and then actually are able to take a break from all treatments. We know that the tumor has not gone and that it is not a curative treatment but I think for pancreatic patients to be able to have sometimes more than a year off from treatment with the disease kind of controlled and we get scans every few months to keep a close eye on things, it really offers them a very good quality of life and ability to travel and do things and be pretty symptom free for that time. There have been different trials looking at radiation and to be honest, I think the role is not clear. The trials have not shown clear benefit, although some of the trials were with other chemotherapy options and not with better options that we have now, so we are working on opening some new trials for patients with locally advanced disease to really look at the benefit of chemotherapy regimens that we have now with radiation. Dr. Stacey Stein is Assistant Professor of Medicine and Medical Oncology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.