Transcript of Key Opinion Leader Event

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Company Participants

Daniel Schmitt – President & CEO, Actuate Therapeutics, Inc

Deva Mahalingam, MD, PhD - Professor of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University

Tanios "Toni" Bekaii-Saab, MD - Chairman for the Division of Hematology/Medical Oncology at the Mayo Clinic in Phoenix, Arizona

Rachna T. Shroff, MD, MS - Associate Professor of Medicine and Chief of GI Medical Oncology, Leader of the Gastrointestinal Clinical Research Team at the University of Arizona Cancer Center (UACC)

Colin D. Weekes, MD, PhD - Director, Medical Oncology Research for Pancreatic Cancer, Massachusetts General Hospital

Other Participants

Christopher Liu – Managing Director, Lucid Capital Markets
Albert Lowe – Analyst, Craig-Hallum
Kaveri Pohlman – Managing Director, Clear Street
Ramakanth Swayampakula – Managing Director, Senior Healthcare Analyst, H.C. Wainwright
Silvan Türkcan – Analyst, Citizens

MANAGEMENT DISCUSSION SECTION

Daniel Schmitt

My name is Dan Schmitt. I'm the President and CEO of Actuate Therapeutics. I really appreciate you taking the time out of a very busy, hectic, completely filled schedule to make time to meet with us tonight. This is a KOL discussion focused on the Phase 2 topline data that was presented this afternoon by Dr. Deva Mahalingam on the 1801 3b study in first-line treatment of metastatic pancreatic cancer. The trial represents a major milestone in our development of elraglusib, and we're really honored to have four world-renowned clinical leaders in GI oncology here with us to provide their perspectives and insights.

It's now my pleasure to introduce our panel. Dr. Colin Weekes to immediately to my left is Director of pancreatic research at Massachusetts General Hospital and Associate Professor at Harvard Medical School. His research focuses on early drug development and targeting the tumor microbial environment in pancreatic cancer. He is also leading a trial with elraglusib in combination with FOLFIRINOX in metastatic pancreatic cancer.

Dr. Deva Mahalingam is a professor of medicine and GI oncologist at Northwestern's Robert H. Lurie Cancer Center. He directs the Clinical Trials Office and the Developmental Therapeutics Unit where he leads early phase research across GI malignancies. He is also the principal investigator in our Phase 2 Part 3B trial and was the presenter in the main session today.

Dr. Rachna Shroff is a nationally recognized expert in pancreatic and biliary cancer. She co-chairs the SWOG Hepatobiliary Subcommittee. She led GI ASCO 2024 as the Chair and is the national PI for SWOG 1815.

And last but not least, Dr. Tanios Saab is a David F. and Margaret T. Grohne Professor at the Mayo Clinic and Chair of Hematology and Medical Oncology in Phoenix. He leads GI cancer research across the Mayo Clinic cancer centers and co-chairs several national committees, focused on hepatobiliary cancers.

So, please join me in welcoming all four of our panelists. I'm really proud to have them here. So thank you.

What I'd like to do is, this is a fireside chat. I try to make it as conversational as possible. But I'd like to begin with Dr. Weekes and ask him to provide an overview of the pancreatic cancer treatment landscape, existing treatment regimens and his experience with elraglusib. And then after that, we'll have Dr. Mahalingam discuss the Phase 2 1801 3B study, and the results that were presented this afternoon. And then following that data review, we're going to open it up to the panel with Dr. Shroff and Dr. Saab, who will share their perspectives on the data and how elraglusib may ultimately fit into the treatment paradigm. So after those discussions, we'll open it up to the floor for any questions that you may have.
So, Dr. Weekes, the floor is yours.

Colin Weekes

All right. Hello, everyone. So I think I would like to do is just sort of outline in general sort of how we think about pancreas cancer. And that stems from patients who have localized disease all the way to metastatic disease, which is what we're going to talk about ultimately. And so in patients with metastatic – or excuse me, localized disease, we sort of break those down into resectable versus borderline resectable and locally advanced.

And right now, it is somewhat controversial in terms of what chemotherapy we use in that setting. But the two real chemotherapies that we use are either nab-paclitaxel plus gemcitabine or FOLFIRINOX. And then there's most recently now NALIRIFOX which is, I think, just a fancy version of FOLFIRINOX. So I think for most of us, we think about FOLFIRINOX and now they're perhaps more similarly.

I would also say that I think that when we think about treating these patients, it's really sort of two treatment, two therapeutic paradigms, either sort of gemcitabine nab-paclitaxel or a FOLFIRINOX paradigm. And I think what's beginning to come out is that we have these different molecular subtypes of pancreas cancer. And those patients may respond differently to different types of these chemotherapy regimens. And so I think this, like, if I'm talking to my patients about it, I'll say, okay, there's male and female pancreas cancer cells and the cancer tumors are an amalgamation of these male and female cells. And it may be that, let's say, the female cells respond to chemotherapy with FOLFIRINOX better than, say, the male cells. And what we also know is that sometimes these cells can transition from male to female and that process is called epithelial-mesenchymal transition, EMT. And that's one of the ways that elraglusib works by inhibiting the EMT.

In addition to that elraglusib potentially also alters the immune function. So, we saw today in the presentation that we see an augmentation of CD8 positive T cells and then the release of Granzyme B from those T cells. So that demonstrates that, in fact, not only the T cells present, but they're actually active in killing cells. So, that's the importance of that piece of information that was presented today.

And then in addition to that, elraglusib potentially targets the proliferative pathway, which is shown by its ability to inhibit NF-kappa B. And so, it functions in many ways in pancreas cancer. And I think that's

important in terms of pancreatic cancer because pancreas cancer, if I was to cut that tumor open, it would look very different than, say, if I cut a lung cancer tumor open. So, if I cut a lung cancer tumor open and look at it, what I'm going to see is lung cancer cells only versus in the pancreas cancer, what we see is an amalgamation of cells.

The plurality of those cells are actually the tumor cells. We also see what are called cancer associated fibroblasts, and there's also called the desmoplastic reaction, which is the stroma, the concrete of the tumor.

And all of those things are active in pancreas cancer. And it turns out that elraglusib potentially targets all of those different components of the tumor. So, I think that's one of the unique things about elraglusib as a drug for pancreas cancer.

So, as you said, I have experience with FOLFIRINOX. So, I've been doing a clinical trial for FOLFIRINOX over the last couple of years. And I think what I've sort of come to the conclusion from that experience, that study is a small study. So, it's a total of 60 patients, and it's randomized to receive FOLFIRINOX. And then we were also using a drug called Losartan, which is a blood pressure medicine. But we think that Losartan alters the function of the stroma. And so, that's why we're doing that and also alters potentially that whole EMT process. So, we are asking the question if we give elraglusib with FOLFIRINOX we alter the EMT process and we maintain cells in a female state with a response to FOLFIRINOX. And then, I think the interesting thing for us in that study is we do have some incredibly long responders, who have done really well on that. We've done well in that study. These patients had a very high burden of disease to begin with, and they did very well.

All the patients that we took care of on that study, it's a much smaller study of 60 patients total. But all the patients that we treated on the study had eye or vision changes. Those vision changes lasted for just about 24 hours, and then they were fine after that. So, it wasn't anything that was permanent. And that's – these are patients who were on study for some of them for two years and really didn't have any problems. So, I don't see that as a sort of an inhibitory toxicity of this particular drug.

So, I think the question really then becomes, which one of these pathways do we go down in terms of drug development? I think both pathways are valid. I think that the control arm for one study versus another. I think there's a question out there about that. I think from my perspective, you want to do a control – the control arm should be whatever the arm is that you're combining the drug with. And so, you're asking that question, right? Does that drug improve this chemotherapy, FOLFIRINOX because that drug improve this chemotherapy, nab-paclitaxel, and gemcitabine?

I think the real importance of this study at the end of the day and I'll be quiet is, if you think about pancreas cancer, drug development. So now, FOLFIRINOX and – excuse me, FOLFIRINOX was studied in 2011. I think nab-paclitaxel with gemcitabine is around 2013. So, it's been quite some time since we've had anything that says it improves outcomes for patients with these chemotherapy backbones despite a lot of negative trials. Right? So, we could fill this room with negative trials. So, I think that's really the importance of this study, is that for the first time, seeing an overall survival benefit.

The magnitude of that benefit, I think, is actually substantial. So, that's how I think about the study is. And then given what I know in terms of my experience with patients for FOLFIRINOX, I'm really quite excited about what we're seeing with this drug in the context of chemotherapy. So, with that, I'll be quiet and I'll pass it on to the rest of the team.

Daniel Schmitt

Deva. So, Dr. Mahalingam. Some very compelling data was presented today. We have some – we have your slides here if you want to refer to any of them. So from your experience, before we get into the data, what are some of the biggest challenges that you see patients facing as they go into first line treatment? And then what are the current limitations of the alternatives they have right now?

Deva Mahalingam

I think in general, when patients have come events with metastatic pancreatic cancer, it's usually – I would say about a third of them are already symptomatic because of the disease burden that they have. A lot of them have lost weight, poor nutritional levels because the pancreas is really part of your kind of absorption of food.

Yeah. And so, I think the challenge is – the first question we are often asking is, are they a candidate for treatment, versus symptom management, versus nutritional support? So, there's a lot of things that goes into decision when someone initially presents. And if they are usually a candidate for treatments, we are kind of deciding whether we want to treat them with one of the two chemo backbones that Colin just mentioned, you know, the FOLFIRINOX chemotherapy or the gem nab-paclitaxel chemotherapy. And I think there is possibly a selection bias, especially in community practices where patients may want to lean a little bit more to the gem nab-paclitaxel because they feel it's easier to treat with as opposed to FOLFIRINOX where maybe some of the toxicity profile is a bit harder for kind of perhaps older patients and frailer patients. So there's only a selection bias in there. And so, generally when we think about this patients, we're trying to figure out what regimens. And then on top of that, we then trying to see if there's a regimen in a clinical trial that we can add them on to as well?

And in this trial, by way of background, you know, this started as an early phase study and as it developed and we went into pancreatic cancer, as we allow a flexibility of patients to come in. We didn't really restrict who could come in. And I suspect that's part of the reason why you're seeing a little bit of the death early in the study.

But then I think that the drug kicks in and then you start seeing this kind of slowing down of the progression, and which is why the survival benefit is seen later. And when we did the early trials without elraglusib, you know, we saw hints of something, you know, these were patients who were all refractory to multiple lines of treatment. And we started seeing complete response, a response in melanoma.

And so that second – maybe there's an immunomodulatory function going on. And as we developed the drug and came into an earlier line in this case in the first-line setting, then we can appreciate that survival difference is that we may not have appreciated if someone is in the third-line pancreas, for example, where the survival is usually less than six months. So I think that really the journey of the drug and how we kind of think about trials in general.

And so, you know, I'm surprised, I can tell you when I started the study, you know, and we are as physician, we want to see response and shrinkage of see response and shrinkage of tumor. But then when we start seeing patients that are still in the study one year on, we're going like, what's going on here with this treatment. So that's my little spiel on that.

Colin Weekes

So I would also say that in the FOLFIRINOX-treated patients, right, so if you look at most of the trials that are out there with – for pancreas cancer, it's mainly that paclitaxel and gemcitabine because it's very challenging to combine with FOLFIRINOX. And most of the studies that you see with FOLFIRINOX, they actually don't make it because of the toxicity associated with the combination of the drugs.

So in my case, with my study, what I've really actually been really pleasantly pleased with is it's very tolerable in terms of combination with FOLFIRINOX. And what we see as patients go along, they actually feel back to their normal self, at least in my studies. So I think I've been pleasantly surprised along with you, Dan, about that experience as well.

Daniel Schmitt

So Colin, when you say they feel back to their normal self, is that different than what they would have normally been on the FOLFIRINOX?

Colin Weekes

Yeah. Yes. FOLFIRINOX is challenging. I'm not saying patients are not having toxicities associated with FOLFIRINOX because they are. But what I have appreciated many times this patient saying to me, I'm able to do the things that I was able to do before I was diagnosed with cancer. So they really feel like they're getting some of their lifestyle back. And when you look at their partners, which is really, I think, the telltale thing in this conversation, when we look at their partners, their partners are elated because they have their spouse back. I think that's something that I find very encouraging with this.

Daniel Schmitt

Excellent. So, Deva, in terms of your Phase 2 data, we have a few slides, are there any ones that you want me to pull up or you would like to direct and sort of run through? Because not everybody was at the presentation today. But if there's any highlights that you think are important that the audience here has access to it.

2025 ASCO ANNUAL MEETING

Preliminary results from the randomized phase 2 study (1801 Part 3B) of elraglusib in combination with gemcitabine/nab-paclitaxel (GnP) versus GnP alone in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC)

Devalingam Mahalingam[1], Rachna Shroff[2], Benedito A. Carneiro[3], Yan Ji[4], Andrew L. Coveler[5], Andres Cervantes[6], Vaibhav Sahai[7], Anne Ploquin[8], Sandrine Hiret[9], Noelle K. LoConte[10], Ivor J. Percent[11], Charles D. Lopez[12], Simon Pernot[13], Petr Kavan[14], Mary Mulcahy[1], Ryan Carr[15], Francis J. Giles[16], Andrew P. Mazar[17], Gil Fine[18], Tanios S. Bekaii-Saab[19]

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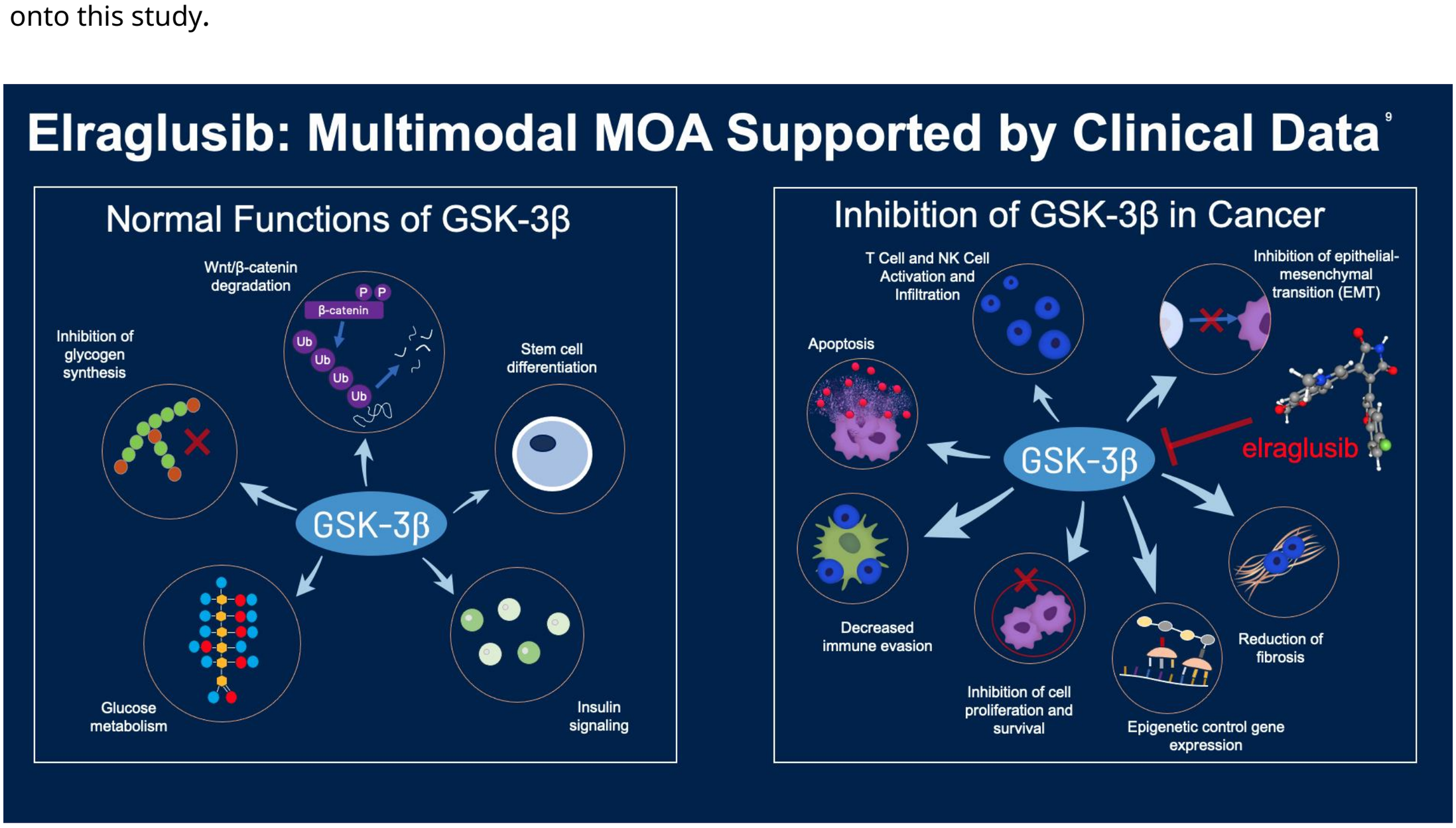
Presented by: Dr. Devalingam Mahalingam, MD, PhD

Deva Mahalingam

So, this is a multicenter effort. So, I want to kind of thank all of the people on stage that enrolled patients onto this study.

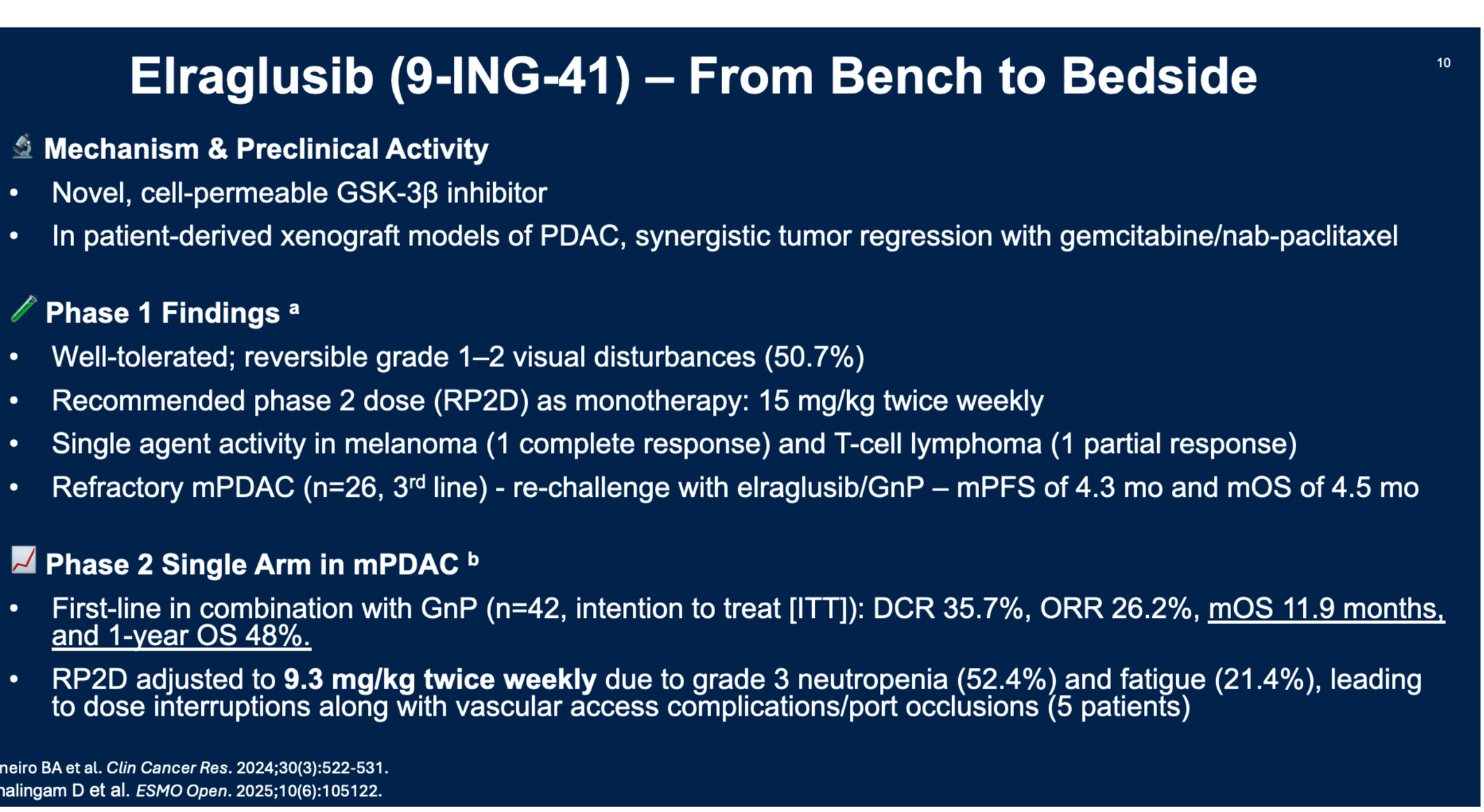


The – let me just start with the mechanism of action. That's the first thing, right. So this is a – it's been a while since we have kind of come up with a new drug with a kind of a different mechanism of action. It's not just in pancreatic cancer. But just to have a drug that can target a protein called GSK-3 beta itself is unique. And it has been attempted before, I think three drugs that came before this. But pharmacokinetically, it was just not as good because of shorter half-lives and poor distribution and rapid clearances.

So, this drug came in and tried to hit a target that we know has kind of proven effects across multiple

pathways. So we talk about like the – we only listed about four or five targets here, but there are multiple kind of regulatory targets in normal cells. And then, in cancer, obviously, when you inhibit it, we kind of see all these things that we – and this has been shown in laboratories and also preclinical data. We see this kind of signals that are increasing, decreasing in cell proliferation.

And Colin referred to the EMT and this is really relevant in pancreatic cancer as well as the fibrosis down there because pancreatic tumors are usually fibrous tumors, and we can't even get drugs penetrated into the tumor. And so, the question is whether it's allowing more chemo to penetrate into the tumor as well. And then ultimately, this is obviously the thing that I think probably helps that survival curve, the survival benefit you're seeing is the T cell and the NK cell activation in tumors. And usually, a hot cancer for immunotherapy to even work in the first place.

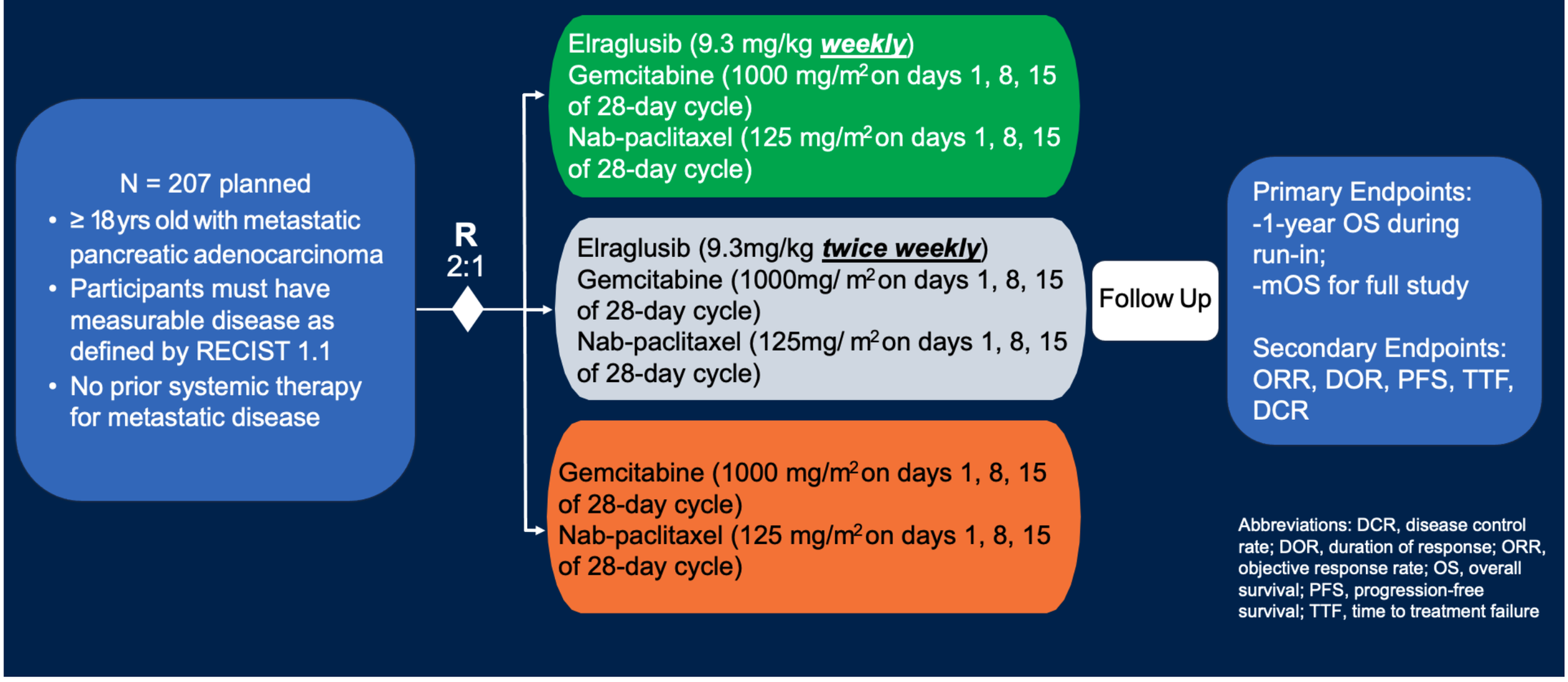


I think the key thing with this study is that – this is the second line, this is the first line study that we saw an improvement in overall survival. We also started seeing things like neutropenia in the patients, and the question is, why were these patients getting neutropenia? And I think Andrew summarized it well, is that the assumption is that elraglusib has a regulatory role in hematopoietic stem cells. So it does actually have proliferation of cells, and some of the older agents we actually see a neutrophilia, and it's the stem cells that are trying to regenerate.

And then when you come in with chemo, it causes more of the neutropenia. But in essence, we did not see any of this kind of toxicities associated with neutropenia such as febrile neutropenia and sepsis. So that was one of the things we noted.

11

1801 Part 3B Study Design



And so the twice-weekly arm, and this was obviously something that has been developed as a drug when we opened it, that should we do a weekly regimen or a twice-weekly regimen because of potentially the half-life of the drug and the pharmacokinetics And we realized that the weekly regimen would be as – would suffice compared to the twice-weekly regimen.

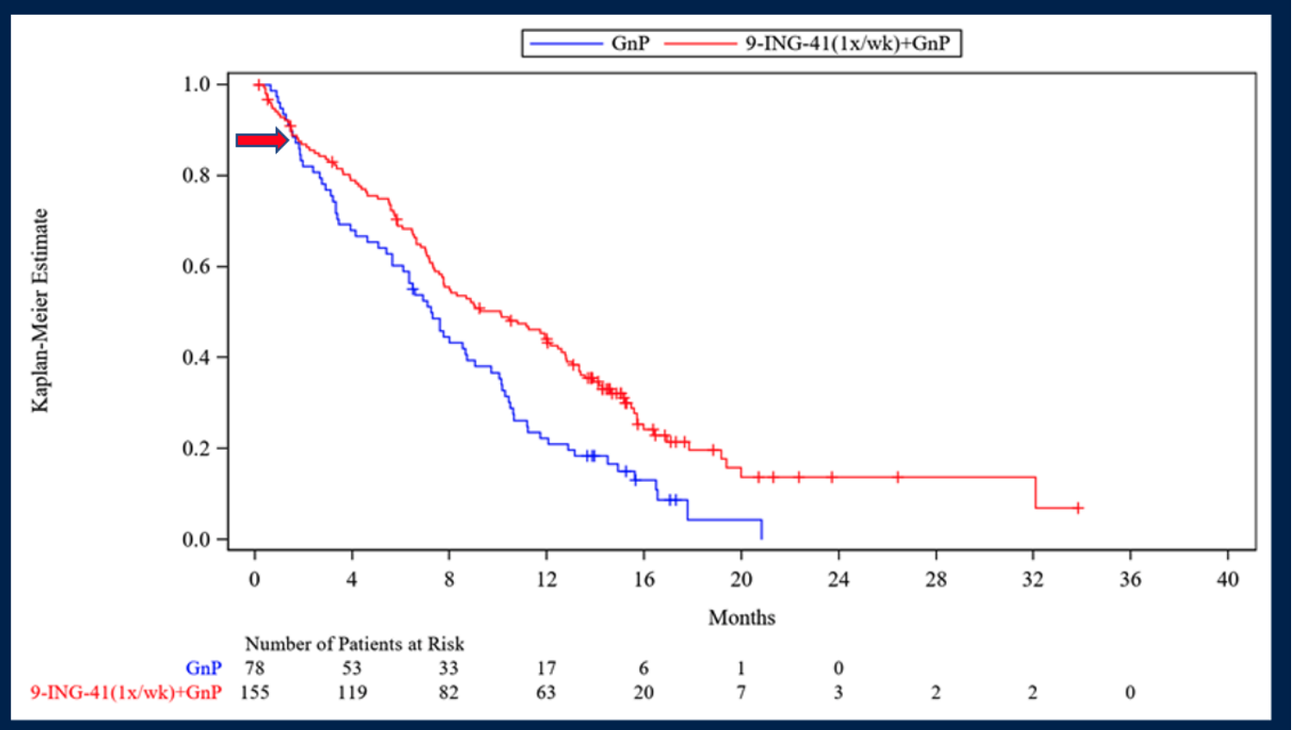
16

Met Primary Efficacy Endpoint of Improved Survival

Safety Population	Elraglusib/GnP (N = 155)	GnP (N = 78)
Primary Endpoint: mOS (months) HR=0.63; log-rank p=0.01*	**10.1**	7.2
12-month OS (%) p=0.0005*	**44.1**	22.3
Events (% event)	**114 (73.5)**	70 (89.7)
18-month OS (%)	**19.7**	4.4
24-month OS (%)	**13.8**	0

*statistically significant
Abbreviations: GnP, gemcitabine plus nab-paclitaxel; HR, hazard ratio; mOS, median overall survival; OS, overall survival

37% reduction in risk of death in safety population/mITT



And then we ran the study. I think the only other thing I would say here is the – let's go to the Kaplan – this is the main slide. And as you can see in the modified intent-to-treat population, we see this improvement in survival. But as I pointed out, and the thing is we see this sharp decline in the first two months in about – I see on average about 15% of patients between the two arms.

And we see this actually. We're starting to see a lot of this in pancreatic cancer trials where we see this early drop-off probably because the patients have a poor biology and we're starting to see a lot of things about basal subtypes, which are a lot more aggressive. They tend to perhaps drop off a little bit earlier, and then you start seeing the Kaplan-Meier curves diverge stay separated, and I think that's when the drug starts hitting you.

Part 3B patients treated for one cycle (4 weeks)

	GnP (N=58)	9-ING-41(1x/wk) +GnP (N=116)
Progression-Free Survival		
Sample Size (% of patients)	58 (100%)	116 (100%)
Censored Obs. (% of sample size)	3 (5.2%)	11 (9.5%)
Mean/Median Duration of Follow-Up	6.3/5.6	7.3/6.6
25th Percentile [95% CI]	3.1 [2.3,3.9]	4.1 [2.9,5.1]
Median [95% CI]	5.6 [4.1,6.4]	6.9 [5.7,7.3]
75th Percentile [95% CI]	9.0 [6.5,10.3]	9.7 [8.1,12.7]
Hazard Ratio [Wald 95% CI]		0.78 [0.56,1.08]
Stratified Log-Rank[a] P-Value		0.459
Time to Treatment Failure		
Sample Size (% of patients)	58 (100%)	116 (100%)
Censored Obs. (% of sample size)	1 (1.7%)	10 (8.6%)
Mean/Median Duration of Follow-Up	5.5/4.9	6.6/5.7
25th Percentile [95% CI]	2.7 [2.1,3.4]	3.4 [2.3,4.5]
Median [95% CI]	4.9 [3.4,5.8]	5.8 [5.3,7.0]
75th Percentile [95% CI]	7.4 [5.8,9.7]	8.6 [7.3,10.1]
Hazard Ratio [Wald 95% CI]		0.74 [0.53,1.02]
Stratified Log-Rank[a] P-Value		0.262

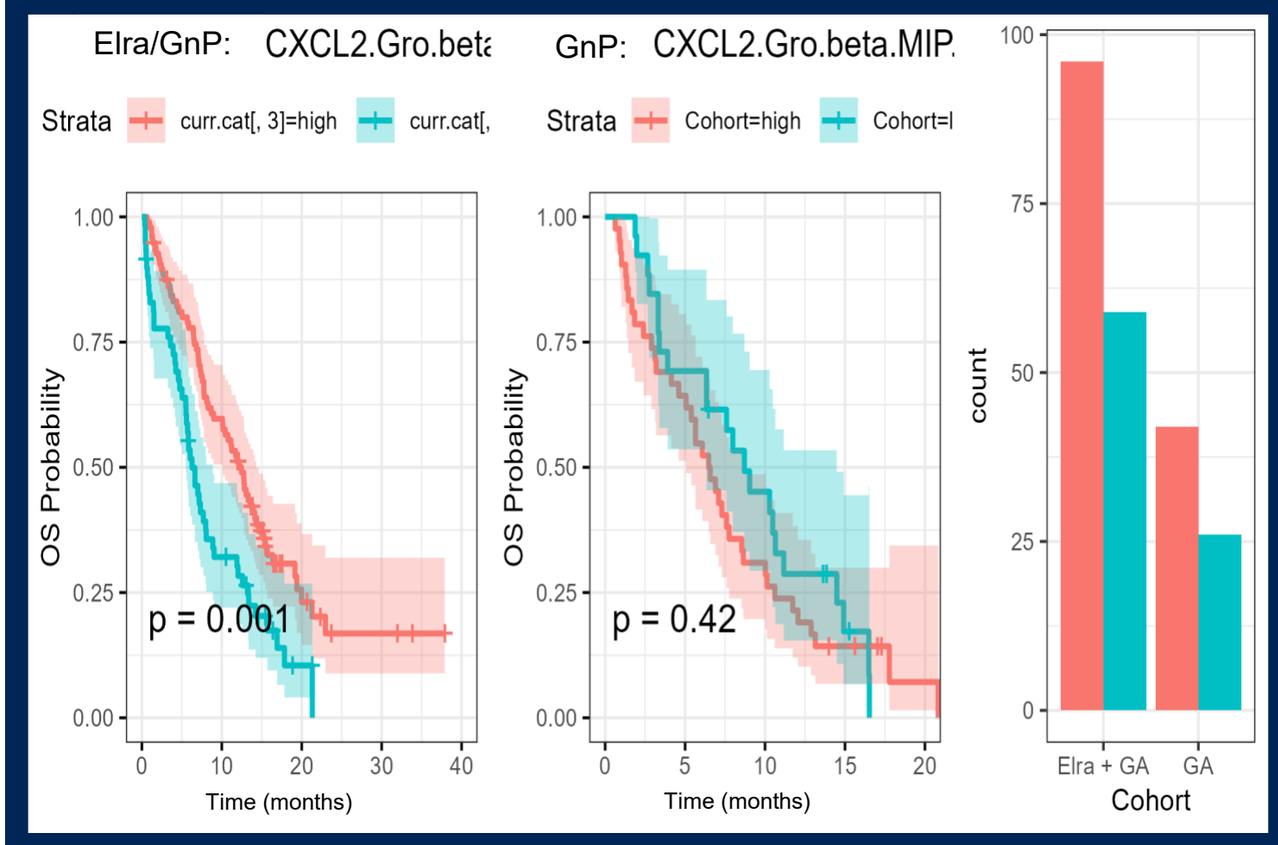
Almost identical to efficacy population defined in SAP

	GnP (N=58)	9-ING-41(1x/wk) +GnP (N=116)
Overall Survival (months)		
Sample Size (% of patients)	58 (100%)	116 (100%)
Censored Obs. (% of sample size)	8 (13.8%)	31 (26.7%)
Mean/Median Duration of Follow-Up	9.0/8.3	11.6/11.9
25th Percentile [95% CI]	5.7 [3.3,6.6]	7.2 [6.4,8.0]
Median [95% CI]	**8.5 [6.6,10.3]**	**12.5 [10.1,13.9]**
75th Percentile [95% CI]	12.9 [10.3,16.5]	16.9 [15.4,19.4]
Hazard Ratio [Wald 95% CI]		**0.57 [0.40,0.81]**
Stratified Log-Rank[a] P-Value		**0.018**
Landmark Survival (%)		
6-Month [95% CI]	72.4 [59.0,82.1]	84.3 [76.3,89.8]
12-Month [95% CI]	28.3 [17.4,40.3]	52.5 [42.9,61.2]
18-Month [95% CI]	0.0 [-,-]	21.5 [13.0,31.3]
24-Month [95% CI]	0.0 [-,-]	12.1 [5.1,22.2]

	GnP (N=58)	9-ING-41(1x/wk) +GnP (N=116)
Response Rate (Regardless of Response Confirmation)		
n (%)	17 (29.3%)	44 (37.9%)
95% Confidence Interval	[18.1%,42.7%]	[29.1%,47.4%]
P-Value[c]		0.263
Disease Control[b] Rate		
n (%)	26 (44.8%)	62 (53.4%)
95% Confidence Interval	[31.7%,58.5%]	[44.0%,62.8%]
P-Value[c]		0.285

And I think we have a slide. I don't know whether it's after this. And so let's just say we assume that a patient can at least complete the first cycle. We selected the patient, and we had – we're maybe a little bit more stringent. Everybody said we were not as stringent in the trials and in our patients that we enrolled. We can be a little bit more stringent, I think, we will – did you put it at the end? Okay. So, this is a slide at the end that he added in. Here. So, this – anyone who has kind of had a – completed one cycle, that's all we wanted, is one cycle. And then we looked at the analysis in a different way. And you can see in the red there that the median overall survival then steps up to about 12.5 months. And the 8.5 is actually what we saw in the mPDAC Study with overall survival as well. Then we are kind of seeing this difference again of approximately three months. So, I think, anytime we see a three-month benefit, I think, the discussion I'd say that – four months, yeah, four months. Sorry, my math's – I'm tired. But four months in this thing. But anything above three months, I think would be kind of significant. Obviously, this is just a sub group analysis that we are doing to see if we can account for that rapid decline in the group of patients. And I think, we are looking at the data because when we look at our data now and I think that's being pulled up right now, right? The – we see a lot of patients with low albumin. And if you look at the NAPOLI Trial – NAPOLI-3 Trial, they had a cutoff of three in terms of the albumin because this is actually albumin has been shown to be a good marker for in terms of survival, as well as tolerance to treatment, as well. Because some of the toxicities can be more pronounced, just the patients are frailer with the lower albumins. And so if we can benchmark that to the NAPOLI Trial, I would say that we would have also another way of preventing this kind of earlier decline that we see with our trial that perhaps we didn't see with the NAPOLI Trial as well.

Cytokine-Based Predictive Survival Algorithms



CXCL2

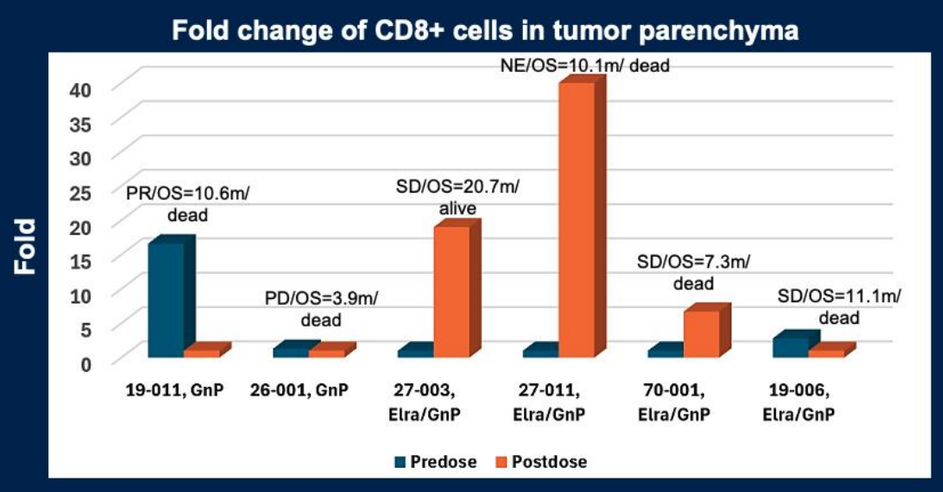
Methods & Correlative Analysis:

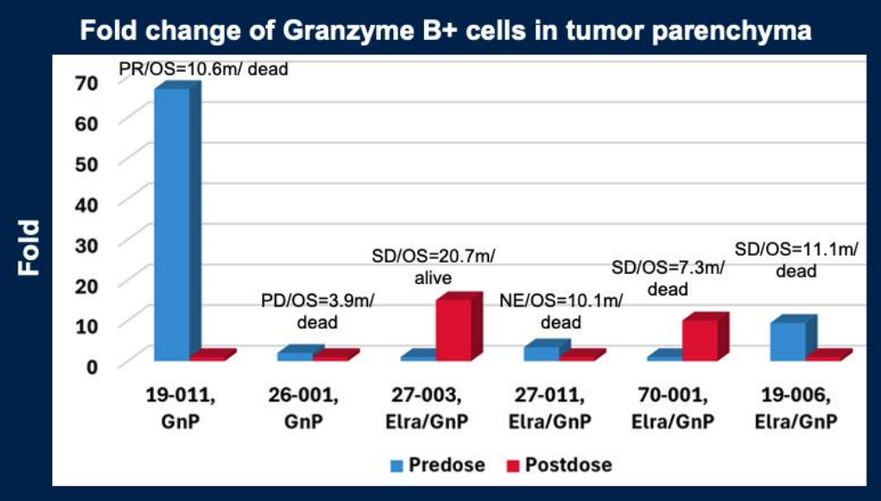
- Pre-dose plasma collected from all patients
- 40 cytokines measured
- 16 exclusively stratify patients on elraglusib/GnP but not patients on GnP only
- Elevated cytokines correlate with increased survival
  - CXCL2, TRAIL
- Decreased cytokines correlates with increased survival
  - CCL3, IL-1α, IL-18, TGF-β, TRAIL R3

*Presented in Weiskittel et al. Abstract: 4185 with Additional Multivariate Machine Learning Models

And then, we – I think, this is a nice slide because it's important to show the mechanism. And we – you know, it hits different targets. So, we know we can get cytokine levels on all patients. And these cytokine levels, which suggest that the drug is doing some sort of an immunomodulatory function to the T cells. And we can see that at least some of the cytokines, the CXCL2, which suggests that in the elra-only cohort, we see this kind of improvement in overall survival with the high CXCL2 at baseline but not in the GnP arm.

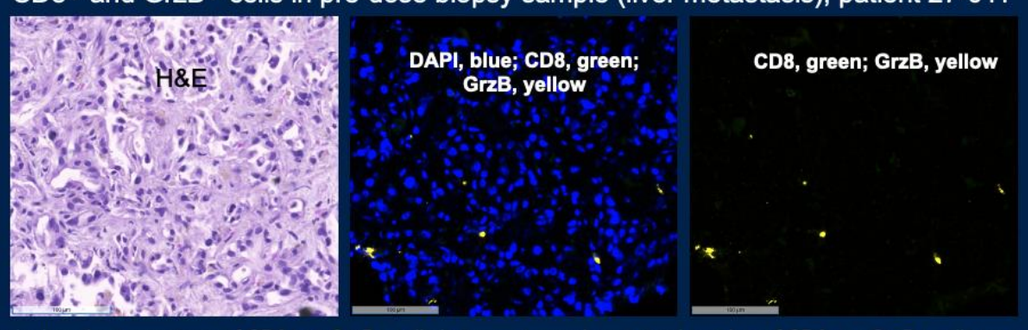
Immunophenotyping of Pre- and Post-Dose Tumor Samples



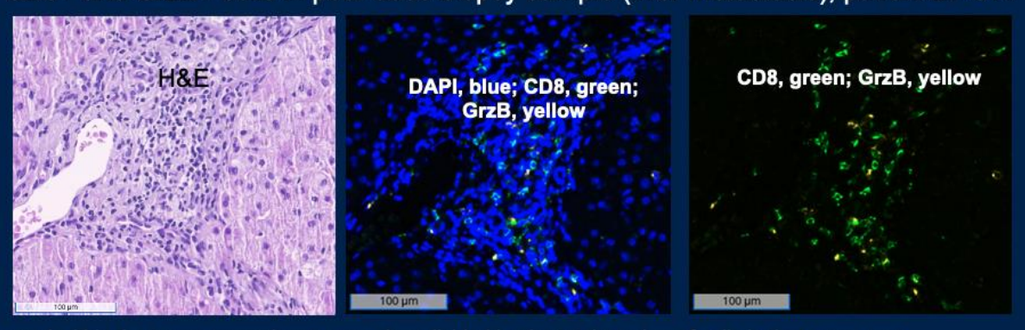


The percentage of CD8+ and Granzyme B+ cells was substantially increased with elraglusib/GnP but not with GnP only

CD8+ and GrzB+ cells in pre-dose biopsy sample (liver metastasis), patient 27-011



CD8+ and GrzB+ cells in post-dose biopsy sample (liver metastasis), patient 27-011



To calculate the percentage of CD8+ or GrzB+ cells in tumor parenchyma, total number of CD8+ or GrzB+ cells was counted within the tumor parenchyma area, then divided by the total number of cells in that same area.
Abbreviations: Elra, elraglusib; GnP, gemcitabine plus nab-paclitaxel; GrzB, Granzyme B; NE, not evaluable; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease

And then obviously the tissue sample that we saw and this patient, as a reminder, did not get the did not get a response to stable disease, right? But he went on and study for over 20 months. And you can see on the far right figure here, you see all the infiltrations of the T cells and the Granzyme B+ cells suggesting activated T cells, as well as the CD56+ positive natural killer cells.

And the other thing we noticed was a decrease in MDSCs, myeloid-derived suppressor cells, which is actually bad in the microenvironment and I think the drug helps clear that as well. So I think we need to do kind of more work in this in looking at tumor analysis from what we have. But I think like this suggests that the mechanism may lead to what we are thinking as tumor reprogramming of the immune microenvironment. So I'll leave it at that, if that would help.

Daniel Schmitt

I think that's very helpful. I think the data is very compelling. And if you equilibrate, so the non-MD you have, you look at a more restricted patient population to sort of compare and contrast to the other major studies. And all of a sudden, the delta and median OS improves, the hazard ratio goes down. And clearly, the effect of the drug is being shown.

Deva Mahalingam

Yeah. And obviously as for physicians, we don't like to compare between trials because it's not a good idea to do that.

Rachna Shroff

Yeah.

Deva Mahalingam

But we have a comparison at least between our own patient population that we enroll in the randomized study and I think that should be the take home message. But we can certainly do a little bit better by trying to be a bit more stringent as we do more stringent as we do a registration-type trial meeting...

Daniel Schmitt

It's the double-edged sword of running a randomized controlled trial just so you have a control. And then they say, well, how do you compare it to another trial?

I think always – it's always a bit of a challenge to make sure that the data is represented in the most scientifically rigorous way. And I think from my perspective, the data speaks for itself. So, Rachna, your patients, you had patients on the trial. Can you give us a little bit of perspective on what you saw in the trial and what's your take away on the data you're seeing here? What's the meaning...

Rachna Shroff

I will say, I think because I was able to see a number of patients that were on this trial and see – I mean, first of all, I think there's also something to be said, and this was kind of already alluded to that it's not easy in pancreas patients to just add more therapy on. I mean, definitely with FOLFIRINOX, but even which gem and nab-paclitaxel and I think what was really great is, is that I didn't – it wasn't necessarily – I mean, you showed the safety data at your presentation, but there really wasn't anything that made it complicated to be able to put patients on this trial and offer them this drug, which I think is really, really important, because the point that was made earlier, pancreas patients are really – it's a complex disease and there's so many facets to their care and how they do that has nothing to do with the drugs that we're giving them. And so, I think the ability to give them something that doesn't necessarily add to the cumulative toxicity is really important.

But I also think that looking at that patient population that was able to get the first cycle is really key. And Colin and I were looking at that data just before we got on stage. And we were saying, I mean, that's really meaningful and impactful. And yes, that absolutely is not it was not statistically designed to look at that specific patient population and you take all of that in terms of the data purity component of it. But I think at the end of the day in the real world and in the clinic, there are patients across the spectrum in terms of bad players and bad biology, and all of them are getting FOLFIRINOX or gem nab-paclitaxel. I mean, that is the real world statement.

But at the same time when you then account for what is probably that initial drop off that that group of patients that perhaps had a lower albumin or had other poor prognostic types of things that make them the more aggressive biology or the types of patients that would have just done poorly, unfortunately, regardless, and then you take out that noise, if you will, and you look – I mean, then you really see, I think, the magnitude of the impact of the drug and what it can potentially do. And I think that's the punch the punch line to me.

Daniel Schmitt

So, this is something that – I don't want to put words in your mouth, but I've been in oncology for 20 years as well. And I look at the profile of this drug and what I'm hearing from the data today, both in terms of – this is

all about patient care. Right? And so, we have this almost benign. I don't want to overblow it, but we have patients who feel better. They do have some toxicity, additional toxicity, but not dose limiting or treatment limiting and with a significant outcome in terms of their overall survival.

So, Toni, weigh in here. Shoot some holes in this. What did you see in your patients? And give us your perspective on elra and the potential for where you see this going in the treatment of pancreatic and maybe beyond.

Toni Saab

Yeah. I mean one has to start with as you've heard, pancreas cancer is the toughest nut to crack. It is a tough one. And so, we all see these patients, quite a few of them, and we know how tough it is to actually get them through treatment and get them to live beyond the one year mark.

We certainly are doing much better today than we were before, but we're not even close to any other. This is the only cancer that's still in the single digits. I mean, depending what you look at. It's about 8%. Some would say 12%, five-year survival. No other cancer like that. So this is a cancer that desperately needs improvement.

So going to this, it's a balancing act. There's no effective therapy that doesn't add a little bit of toxicity. It doesn't exist and it's not supposed to exist because it's actually modifying something in the system. So you will see a little bit of toxicity, added toxicity. But that has to be balanced out. I think one of the problems with how we measure toxicities is we also don't account for the time the patients spend on treatment. So sometimes when treatments are more effective, you're spending more time on chemotherapy, and so you see some cumulative toxicity later on rather than earlier on. These would be related to the chemotherapy. That's not a bad thing. These are things we can control as long as they don't impair the quality of life of patients.

And then the same thing with your experimental agent, when you add an experimental agent to a standard therapy, you don't want to see the toxicities from the standard therapy get amplified to the point where the patient cannot go through the treatment. And at the same time, you don't want to have the toxicities that essentially make it difficult for the patient to even be able to go on that experimental treatment. So here we're not seeing that significant added toxicity that would be concerning for us to say, this seems like a goal. This is a goal. This is – the patients are able to tolerate it well. And when you're talking about patients who are feeling better, and you can't quantify that on a clinical trial. This is something that as we patients in clinic, my patient comes in the door and we're sitting there and we're talking, gained 3, 4 pounds, feeling better and I'm doing more things. I'm able to go back golfing. In Arizona, there's a lot of golfing. All these things, this is what we hear from our patients and that happens in the first month of treatment. So before even I see the scan, I'm like, wow, this looks like this patient is going to do well.

And to the point where you're bringing that first cycle patients that are able to get that first cycle, it is so predictive that if those patients are able to go through the treatment as we want them to, as we hope they do, these are the patients that do the best. And yes, there are certain characteristics here that if you adjust for a little bit more the numbers, the delta would continue looking more favorable. And, of course, you don't want to do that.

But the point of it is that one of the – as, again, Rachna and others have alluded to is you don't want to compare to other studies at this point of time. You created your own control because this patient population is very heterogeneous. Every study looks different if you want to look at the control arm. That's why you have a control arm, to make sure you adjust for the patient population you are accruing, you are enrolling on the study.

So, the differential in survival is actually pretty impressive. In pancreas terms, this is a big differential. And the tail of the curve that's forming actually is even more impressive. The fact that you have a doubling of the landmark survival is pretty impressive itself.

Now, I will tell you historically, when we use gemcitabine many, many, many eons ago You would never see a patient reach the three years mark or the two years mark.

When gemcitabine and nab-paclitaxel or Abraxane, you know, came through. We were excited about the fact

that about 5-plus percent of the patients were able to survive three plus five years. I mean, this sounds crazy, right? I mean, you're thinking like, okay, you know, how does that make sense in today's world? But this is in pancreas cancer. That's a lot of improvement already. And now we're seeing this lift further up.

Now, of course, you know, the main question is when you look at the data and when you look at our individual patients, we were seeing these results individually from patient to patient. But it's important ultimately to see the data. That we presented today.

And the data definitely confirms this – these things we're seeing like, okay, you know, we're seeing responses in both. But those patients that are going on elra are actually staying on longer and they're living longer than we expect them to be. And that data confirms it. The study confirms that once you're done and this makes sense.

I mean, if you look at the world we live in today, the world of immune therapy, immune modulation, you see a little bit of a disconnect between how many more responders you're seeing and those that flip that waterfall plot down, versus how long they're surviving? So if you look at liver cancer, you look at biliary tract cancer, you see sometimes those staying close together and then they start opening up at the end. And that's the immune therapy effect.

That's the immune modulation effect, which is leading patients to live longer because now the immune system around their cancer is healthier, is able to actually maintain or check or keep the cancer in check. And so this is what we're seeing here as well.

So I think, you know, ultimately what we observe in clinic, all of us, as we treat those patients. You know, we see the individual patients doing as well. But it's so good to see this actually – this data coming out with the control arm and these curves looking as good as they are and that, say, starting to really look favorable in terms of survival. So, I think that overall, this sums up kind of my impression of the individual and the data from the trial.

Daniel Schmitt

Yeah. It's remarkable to hear. Well, I guess it's not remarkable to hear that in different situations such as Colin's, whose got it on the back on the FOLFIRINOX, or the rest of the panel that has it on the back of a gem/abraxane is reporting sort of the same phenomenon where patients feel better and are doing – not only are they doing better, they're feeling better with a drug. So, go ahead.

Colin Weekes

So, I think what this drug does, the safety profile we're talking about, it now runs for combinability. It becomes a platform that you can add to, right? So, if you think about like the RAS inhibitors, for example, right? You can think about how you can potentially add this to that.

We've sort of touched on the immune system, right? And if you look at pancreas cancer, drug development, immunotherapy is not working, right,. But maybe we have some hints that there's a backbone here that you add on to. So, I think these are all important things to think about, is that at the end of the day, I think there's a platform here that's – that you can build upon that we didn't have that platform, I think, prior to what we saw today.

Toni Saab

Absolutely. I mean, I totally agree. I think these are building blocks and we can continue to amplify on these building blocks.

And once you start modulating that environment around the tumor, it's a winning proposition for pancreas cancer. That's a – again, that's another – one of the toughest nut to crack, is that tumor microenvironment in pancreas cancer and how all the immune therapy, previous immune therapies, more traditional immune therapy studies have failed. That's because you had that fortress just around these cells that you cannot penetrate.

Now, as you actually start modulating that environment and invite those favorable cells, now then you can start thinking about these combinations. So you establish that first platform and you add on to it, but not to

undermine the fact that already, by itself, it's already lifting up. At least that's what we see on the study. They're already lifting up the capacity of these patients actually to survive.

I mean, that's a positive study. I can't – I mean, I don't know about you guys, but I can't recall the last real positive study that we've seen in pancreas cancer since NAPOLI-3, which really didn't change the landscape much, just stacking on more chemotherapy with that cytotoxic wall. But this is one of the, if not the first biologic, immune-based therapy that its biology and immunology together in this that essentially drove the study to be positive. We haven't seen that for a long, long time in pancreas cancer.

Rachna Shroff

And you don't typically see the type of curve, the type of OS... ...that kind of relatively quick separation and durable separation. That's not a typical overall survival curve...in the world of pancreas cancer. And so I think that's – it's notable and – I mean, especially when you look at that efficacy evaluable after four-week population, even that hazard ratio. That's not a hazard ratio.....we see in pancreas cancer.

Daniel Schmitt

Starting with a five.

Rachna Shroff

Yeah I mean, we're usually happy with 0.7, 0.8. And so that – I mean, those are really, those big.....ratios for the fact that in the world of pancreas cancer, those are notable things, I think.

Daniel Schmitt

So in terms of combined ability, we've got two trials, we've got a pilot trial or a small three arm trial that you're running with FOLFIRINOX. We've got a – I think this is an exceedingly reasonable sized trial for potentially a pivotal trial. We've got a...

Toni Saab

This is 50% of a Phase 3 trial, size wise. This is not...for Phase 3 trial. So, that's one of the largest Phase 2 randomized trials on record. So you're well-powered. You're very well powered.

Daniel Schmitt

Good. So in terms of other drugs coming, so we know that a lot of – there's a lot of visibility to the RAS inhibitors. We know that there's been some preclinical research or at least mechanistic understanding that those to the RAS inhibitor with a GSK-3 inhibitor may be combinable and potentially synergistic. How do you see those two and any other new drugs coming to the fore and what should we be looking for to combine our with?

Colin Weekes

I mean, you already are – you already – I mean you do have a study that's looking at a – at an immune checkpoint inhibitor plus elraglusib, right, and nab-paclitaxel.

Daniel Schmitt

It's in the drafting stage, yeah. And note, hasn't hit the first patient yet.

Deva Mahalingam

Yeah. So, I'm going to say that I think that the low-hanging fruit would be, obviously, in terms of checking to see the kind of modulating microenvironment with all the checkpoint inhibitors, is what I think Colin was referring to. And I think that trial is going to be – and was a key trial, right, from the point you're talking about?

Daniel Schmitt

Yeah, there's one in draft.

Deva Mahalingam

In draft. Yeah. So that's obviously another key that would add anything more in terms of the overall survival. But I think the rationale of it is certainly of interest. We have seen preclinical data that would show that this – the two drugs could work just based on the docking proteins somewhere, the RAS, and especially the RAF proteins are hitting the de-escalating events. So I think we could kind of see that would add more in terms of not just response which you see a lot with the RAS inhibitors but also survival. And we know that the RAS inhibitors could also be limited in terms of the duration of response and whether this could added more in terms of survival as well. And anything to add anything else.

Colin Weekes

I would say also that the RAS inhibitors are...The RAS inhibitors are... so the RAS inhibitors would be important for that process.

And the MAP kinase pathway, which is what RAS targets, its engagement with GSK-3 is also very important in EMT. So you can see – you could potentially see how combined those two drugs might even further augment this – the conversation around EMT and potentially overcome resistance to the RAS inhibitors in patients who don't have the particular EMT phenotype that the RAS inhibitors would work. So there's many ways to think about how you combine this with RAS inhibitors with different group of things. But there's other drugs, too.

Daniel Schmitt

So what else would you...we are very excited about what we're seeing for patients right now with these backbones, but obviously there's other combinations or potentially other histologies or subtypes. I mean, where should we be looking at is next steps for putting this drug out and we always talk about risk benefit to the patients. In this study, we show clearer significant clinical benefit with minimal clinical risk, I would say. Where else do you think that this would be applicable?

Rachna Shroff

You mean outside of pancreas? Is that what you're...

Daniel Schmitt

Well, with any other histologies or any other patients that you see beyond first line metastatic/pancreatic, is there...

Colin Weekes

So, I think within pancreas cancer, any of the patients who have localized disease, I think, these combinations potentially make sense of that setting. But I think this conversation about EMT is important for other GI lung disease as well. And so, there's I think, now you have evidence that it's combine-able, so we could think about looking at the other GI cancers; colon cancer, gastric cancer, biliary cancer, so I think, there's – you know, many places you may be thinking about combining with RAS, lung cancer becomes also a setting where RAS inhibitors are important in terms of disease modifying.

Rachna Shroff

Yeah, I mean, thinking about the multifaceted mechanism of action. I mean, I actually think there's a broad swath, in which.....you could think about this and to your point about combine-ability, regardless of the chemo backbone or whatever that combination is that is being used to say, gastric cancer, biliary cancer, or whatever, I think, that EMT component as well as the immunomodulatory effects. I think, those two things right there make a number of different tumors definitely within GI, but even probably outside of GI as well, feasible.

Toni Saab

I mean, if you think about this as your playground. You've already shown a proof of principle that your playground seems to be safe and seems to be effective, but you have to confirm that. So, I wouldn't undermine the fact that a stand-alone right now, you have enough justification to move to the next level of to move to the next level of confirmation. But that doesn't mean that you don't also think about the opportunity. Because now you've shown a proof of concept on where one, you have an agent that adds value, significant value to patients which you hope to confirm even further with larger studies. But at the same time start creating a path to the

future, whether combining with RAS inhibitors, with other immune based strategies, whether you expand. So, you start building your – around your safe and effective playground.

So, I think you already have quite a bit to move forward to the next level. But at the same time also start thinking strategically about, all right, the RAS inhibitors, they make a lot of sense to combine with that or even all these, right. Because they all modulate different aspects of the immune system. This is creating a positive media. Takes it from a very negative media to a very positive media. And so you create a playground where you can actually work with multiple different options, including stacking multiple options on.

Now, the two don't necessarily have to essentially go stacked up one on top of the other. They can all go in parallel, and they should. Because, ultimately, if you think about it, even with the RAS inhibitors. Even with the RAS inhibitors, we're not achieving more than 20%, 25%, maybe 30% if you want to really go with this vision of an imagination of a response. And many of these responses are not durable in pancreas. In others maybe, but in pancreas it's not.

So, there's a big challenge in pancreas that remains even with the most promising elements. And that's what I think you cannot as you said, as Colin said, you can't just think about one strategy. But one strategy right now. This is a valid and valuable strategy to move forward with. We start thinking about the other building blocks that are going to come.

Colin Weekes

What about IV versus oral?

Toni Saab

So, you know, this weekly seems fine. Weekly seems fine. Oral would be optimal if you can move to an oral formulation, it certainly is optimal. It will make it easier on the long run because, you know, you think about the long-term benefits of this agent, right? Because it seems that the benefits continue long term.

When you think about strategies where chemo can drop and you continue on your agent. This is where an oral agent would make it even more attractive. On the long, long term, right, because that's what you're aiming for. When you start thinking about combinability with other strategies. When you start thinking about the other area, EMT becomes even more important is in the early stage of the disease, where you can actually improve significantly the likelihood of these patients to survive the cancer. Today, only 30%, maybe 20% to 30% do survive their cancer, actually, perhaps less than that, if you can change the whole landscape in the earlier stages. So this is just the beginning.

Daniel Schmitt

So to Colin's point and great minds, I like to think, I was going to answer the oral question as well because I'm not sure if everybody is aware, but we do have an oral development program and we've got a lead formulation that's a tablet that shows greater than 95% bioavailability in preclinical testing, which is something that we are bringing along for further development. And I think that the earlier stage patients and longer duration of treatment in a home setting certainly is attractive on all the right levels.
I'm wondering ...

Toni Saab

And remember, a lot of these toxicities are transient, it can happen early. So there is a long-term potential. We're not seeing any long-term issues with this agent. We do see them with chemo. We're not seeing them with elra, which makes it ideal for our long-term strategy. Even one can think that as it is a modulator as well that you can go across multiple lines of therapy. So you don't have to stop it if gem/abraxane stops working, you can move to the next treatment and change your chemo, but continue the elra.

Colin Weekes

So, to that point, the trial that I have opened right now is patients get FOLFIRINOX for six months and then go on maintenance 5-FU plus the elraglusib. And then when the tumors grow back out, they go back onto FOLFIRINOX and elraglusib. And what I can tell you is that we see that in the maintenance therapy alone -- so it's maintenance elraglusib plus 5-FU. So we are seeing patients continue to have response in that setting and then when they do grow back out, we also see the reintroduction of response. So, to Toni's point, it is

feasible to do.

Daniel Schmitt

So I'm open to opening it up to the audience if there's any questions. I guess my first question is, all right, so if we were to stack these out and we want to do the next studies, should we be looking at first locally advanced or should we be doing more metastatic work? Or if you had to send in a note, Rachna, what would be the next step for you, where would you like to see this in your – what patients are coming in that you say, wow, I'd really like to have them on?

Rachna Shroff

I mean, I think the localized patient population is a really important population to the point around EMT and the way that this drug works, and I think – again, and just speaking to the fact that it's a tolerable regimen and that sort of thing. I mean, I think locally advanced is a really complicated field, just the definition of and what the approach is. And I think it's hard to do a really clean is. And I think it's hard to do a really clean and clean study when you're looking at a drug in terms of understanding what the right and meaningful endpoint is there without trying, again, kind of factoring in the heterogeneity that comes into that population. So I would say probably more the localized that is potentially operable, whether that be respectable, borderline respectable, I think that's a really interesting space to look at because of the way that this drug works.

Daniel Schmitt

And, Deva, in your practice, where do you – have done a great job with this but...

Deva Mahalingam

I think the low-hanging fruit is obviously to move this into a registration type trial in the front line setting in pancreatic cancer with the kind of strategically deciding... you're going to need over 500 patients for the study. And then, what kind of eligibility criteria would you want to include to kind of allow – prevent that kind of early drop that we saw? So that's the first thing you're going to invest your dollars in doing.

And then Toni mentioned the building blocks, right? The building blocks would suggest maybe you start bringing this earlier on in pancreatic cancer treatments early. The second building block is that some of the trials that you're already talking about, where you would add an immunotherapy to the things that are already established to see whether this adds anything more. And that building block can go across multiple histologies, right?

And it's just a matter of like where you want to put your resources. I'm sure many investigators will be reaching out to you guys to say, can you run investigator initiated trials in this phase? I already have found it, there with multiple histologies. So – but money is obviously – it's going to dictate how you're going to do these trials so – and who you're going to partner up in as well.

Daniel Schmitt

There is no shortage of people knocking on the door right now.
So...

Colin Weekes

I would say – so I totally agree with the early disease setting. That's I think – for me as an investigator, that's where I think it's important. But I think as a company, the important thing is to do the registration trial, right? And I would actually also focus on FOLFIRINOX, because, as I said before in this conversation, their drugs have not been combinable with FOLFIRINOX. And some of the – like the agents that we're talking about have overlapping toxicity with FOLFIRINOX, right? So a lot of just, you know, MAP kinase pathway inhibitors are going to have GI toxicity, which is common toxicity for FOLFIRINOX.

So, if you can carve out a space where you have a drug that combines with FOLFIRINOX, that's a space that you're going to own. And then, I would take that and do all these other things that we're talking about.

Toni Saab

Yeah. You have to get this this agent to the patients. So your strategy really has to rely first on a registrational strategy, which, means that this is how you get it to the patients. Otherwise, this drug will not be accessible to the patient ultimately. I mean, if these and there's no reason not to believe that these trends will continue, then that's added value again to patients in the near future if this study goes and runs as you're – again, as you're building all these other pieces and putting them in place.

The landscape in pancreas cancer is I mean, if you look at any other cancers, there are like, 20 million competing studies at the same time in pancreas cancer, good luck to find one. So the space is empty. Well, you can open it wide. Now the RAS inhibitors are trying to rush into it, but they're not even close yet. And we're talking about first line, changing the first line landscape.

You got to hit the biology early and hit it hard. That's the only way you're going to make a big difference in patients' lives. And then, what we continue to see across all these malignancies is that, yes, you can see a lot of benefits for agents being tested later in lines. But that biology in first line matters the most. A lot of patients lose the opportunity to see another agent, half of them after the first one, and then it goes downhill very quickly from there. This is why you need to really hit hard at the beginning. And that's a great opportunity, actually, to – this is again, this is a rare positive study in pancreas cancer.

Daniel Schmitt

So, Mike Moyer has the microphone. Is there any questions? I have...

QUESTION AND ANSWER SECTION

Analyst: Albert Lowe
Question – Albert Lowe: Albert Lowe at Craig-Hallum. What portion of first-line patients do you treat gem/abraxane versus FOLFIRINOX or NALIRIFOX? And then, what portion of these patients do you think would be good candidates for the elra combination?

Toni Saab

I'll take this one. It's on a clinical trial. It doesn't matter. If my clinical trial has gem/abraxane, that's the standard of care for all the patients. There's no, frankly, good data – so I'll get to the NALIRIFOX issue. But there's no good data that suggests that FOLFIRINOX is any better than gem/abraxane outside the BRCA1 or BRCA2, which is a very small proportion of patients. They're pretty similar. That's across the board, whether you're here in Japan. In Japan, in fact they favor gem/abraxane over FOLFIRINOX. And so, it's a wash. So, I really don't think that that's frankly an issue. It used to be a few years ago, people were very much entrenched into one camp or the other. And then, the data that's coming including real-world evidence suggesting you guys get over it. Chemotherapies, chemotherapy, it's all the same. It doesn't add much value anymore to the patients.

Chemotherapy is chemotherapy. It's all the same and doesn't add much value anymore to the patients. Let's move on. NALIRIFOX, interesting, study was positive. I was part of that study, and so it was positive. Slightly positive, I'd say marginally positive, but very tough regimen to tolerate. And that's why it hasn't picked up. If you look at the market in the United States, NALIRIFOX is less than 2%, if not less than 1% of the overall market. That's because it's sheer torture for patients, frankly.

Daniel Schmitt

Anybody else with a different perspective?

Deva Mahalingam

I agree. I think in academic institutions with experienced investigators, I think there is a balance. I think there's a mix between the two regimens with some nuances about which one they would lean towards to. In community practices, I think there's a lot more gemcitabine paclitaxel than in the academic setting because they feel that it could be better tolerated. And so, I think just depending on where you are.

So, I think that it balances out to about 50/50, I would say. And then many patients who don't are not able to get a combination treatments just on single agent, gemcitabine, or single agent, 5-FU. So you have to keep

that in mind as well.

Daniel Schmitt

So, questions. Chris?

Analyst: Christopher Liu

Question – Christopher Liu

Thanks. Chris from Lucid Capital Markets. First, congrats on the data. Just a couple of questions. So, first for Dan. When do you plan on exploring sort of a biomarker strategy? We saw some potential biomarkers here today and what kind of registrational study look like? And then for the panel, in this dataset, we've kind of seen a lower median OS, slightly lower median OS than what slightly lower median OS than what we've seen in historical studies for the control arm that the data here today kind of explains some of that. You mentioned low albumin, something I noticed was a high CA19-9. Does that adequately explain that? And then lastly for Dr. Mahalingam, we saw – there was one slide with a biomarker with CXCL2. Do we have the exact numbers for the median OS in that biomarker subset?

Daniel Schmitt

Do you want to take...I'll take the first one. I think that – we do have a biomarker strategy in development. Some of that was presented in a poster this afternoon. That was very well-attended, by the way. But in terms of a registration study, I think that that is dependent on our discussions with the regulators and asking them, in light of this data, what would be required.

So, we have mapped out the options from a whole Phase 3 to sort of more of a confirmatory trial. We have – but we want to talk to the regulators and see what they're thinking, particularly in the light of the kind of compelling data that's been shown here today. I mean from the company perspective, I ask the question, how long should you hold this away from patients who really need it to do a couple hundred more patients? So, we will have those discussions and it it'll be an agreement between us and the FDA and EMA. And so next is the question. The control arm.

Toni Saab

So, that's one of the most dangerous exercises in futility is to actually compare studies, different studies each other. That's one of the – in fact, that's one of the biggest weaknesses in having single-arm studies, because they all look quite fluffy, they look great, and they fail and they go into the Phase 3. Some of them don't as much. And so that's why having a control arm, especially in pancreas (sic) pancreatic cancer, especially in pancreatic cancer is very important because it controls for the patient population that's included in the trial. Because that's a very heterogeneous patient population.

So albumin can explain part of it, selection bias. You know, some people like FOLFIRINOX where perhaps they picked, you know, patients in that early phase of the study that may not, you know, fill the perfect bill. But at the end of the day, all what matters is that delta. That's what you measure yourself on to.

You're not picking the winner, right? Like you do with the single-arm study. You're flipping a coin, kind of half a coin, I guess. But you're flipping a coin to pick who goes here and who goes there? You have no control over it. So that's the cleanest way to actually have a signal. So the only clean comparison here is between arm A and arm B. That's the only comparison that's valid, frankly.

Rachna Schroff

Yeah. I mean, I would just even add to that that, you know, in the way that modern day drug development happens and just the, you know, the necessary speed with which companies have to move to be able to try to stay ahead of the game, as well as also make sure that they're getting their drugs out to the – to their patients. You know, more and more often than not, we see a Phase 1 study that potentially has a signal and then turns into expansion and becomes a single-arm study. And we all get really excited.

And I think to Toni's point, I mean, I really actually give this study kudos for doing a large randomized Phase 2 trial because, I mean, it takes a lot of work and it takes a lot of investment and a lot of resources, you know, financial as well as others to be able to do it.

But to this point, it is the only way that we, who treat this cancer every day, can look at this and say, "This actually means something." I think that's really – it's impactful because we have that clean control.

Deva Mahalingam

And to your biomarker question, I think this is still very exploratory. So I can't give you – I mean, because if you are just looking at the, like, for example, that was just one of the cytokines we looked at. And we are seeing that if you have a higher level, it's associated with an improved survival only in the elra GnP and not the GnP only arm. So we're looking at a subgroup within a subgroup of one biomarker, right? And we do see multiple biomarkers that are in that trend. And I think as we get more of the data analyzed, it might be easier then to start looking at kind of true survivals or anything. And maybe someone else, maybe Taylor might know it because I know she was doing some of this machine learning stuff as well. Did you see – was that survival? Was that an actual median overall survival that you saw in terms of the CXCL2 data?

Biomarker Consultant

They're all conclusive – oh, thank you. And so, right now, I'm using machine learning. And so right now I'm using machine learning and multivariate models to actually try to combine those and improve on what we see with CXCL2.

And so, I think there is some really complicated signals there and we can improve on that, but even just with CXCL2 alone, we're seeing a really clean biomarker and I did cross validation to basically see if you randomly sample this patient cohort. Is it a stable signal? Because I think that's the problem with a lot of machine learning analysis is, you look at your cohort, you make the machine learning or mathematical model and then it looks great, but you reapply it and then it's like, okay, well that doesn't really necessarily translate and so we did this cross validation study to make sure that it was a stable result and CXCL2 is rock solid.

So the hazard ratio across all these different cross-validation fold was solid. And then even looking back at some of our Phase 1 data, we similarly see these cytokine signals. And so, I think it's really conveying you can look at a patient, look at their immune environment and say, are they a patient that is going to have an anti-cancer effect when you add that GSK3 inhibition. So you can kind of encapsulate what does that patient's immune system look like at that time? And is GSK3 inhibition the right kind of perturbation to push them towards anti-cancer effect?

Daniel Schmitt

RK, go ahead.

Analyst: Ramakanth Swayampakula

Question - Ramakanth Swayampakula

There were a couple of safety measures, safety issues that popped up in the presentation. Visual impairments and the rates of neutropenia. Are this a real impediment in terms of adoption or these things could be taken care of with certain prophylactic therapy that it should not really impact anything?

Deva Mahalingam

So I'll start with the visual disturbances, as we call it. It's more an irritation because it's a GSK-3 beta in normally has a signaling pathway in the rods and corners of the eyes. So we see this color and light changes perception that are usually transient. And I think it's also to do with the Cmax of the drug or the concentration of the drug as it hits the peak, which is why it's usually transient and in most cases, I think it just last a few hours. And so patients usually describe it as a lightning or darkening of the room or something like that.

And so I do not see that as an impediment in terms – for patients that is, right? The neutropenia was – it just kind of, we just noticed more neutropenia. But as we did the trial, as you can see, it never translated to febrile neutropenia and sepsis because that's really what kind of impact to patients in terms of things. So we are – every time they come in for their weekly checks, we are seeing that neutropenia levels. But it never – patients were coming in and said I feel fine. But all the physicians tend to do with just maybe adjust the doses of

chemo along the way as they are treating the patients just to balance out for the neutropenia.

Colin Weekes

Yeah, I would say in my study to answer those questions too, we do see patients having visual changes. The dark – like, it's like a blue or black hue. That's their vision is And that lasts for like I've had patients up to 24 hours but like so they get chemotherapy one day. The next day they wake up and it's gone. And it does persist over time. But it's not a thing that sort of alters lifestyle. And then, I agree with the neutropenia, that can be managed.

Ramakanth Swayampakula

So the second question for me is, on the PFS data that we saw today, it was similar between the two arms. But were there any. But were there any observations in terms of quality of life which would tell you that even though it's the same, but the quality of life is better, especially with the elra and GnP?

Deva Mahalingam

Yes. So in the trial, if someone progressed for whatever reason, even if it's a small lesion that maybe popped up on a scan, and that's a progression, right? Clinically, the patient is doing well, but we have to follow study protocols. And I don't think in the study we allowed for patients to go on, which what we do in a lot of the immunotherapy trials. We'll say, okay, you can keep going beyond what we call progression. And I think that's what we are seeing with the immunomodulatory signal is that patients are actually getting this kind of post progression benefit. And we had patients who actually had progressed and then decided not to get second line treatment. As you know, 50% of patients get second line therapy and we saw them living at 10 and 12 months on. And so, they were kind of sitting around for six months, like not getting any treatment, but still surviving. But that's the choice of a patient can make, right? So I think that that I saw that in patients where they were clinically well, but by protocol they're off study, you know.

Analyst: Silvan Türkcan

Question – Silvan Türkcan

Thank you. I'm Silvan Türkcan, Citizens. I have a question to the company. Did you consider, obviously there, unfortunately, in pancreatic cancer, there will be a lot of progressors. Would it make sense to rechallenge with elra? And did you consider adding an exploratory cohort maybe to a pivotal trial, so that it could be maybe line-agnostic eventually as you read out the pivotal trial?

My second question is maybe for the whole panel. As you scale up in the past with obviously some of these chemotherapy trials that got pivotal trials, what are your prescriptions for a pivotal trial here as we expand to more patients, to more sites? Obviously, you mentioned we already 50% there in terms of patient population. But what are some of the pitfalls that we should consider maybe enrollment criteria or something to replicate the benefit we've seen here? Or are there any threats to potentially making it smaller? Thank you.

Colin Weekes

Yeah, I guess my – the last the last latter question, I think it's really – the site selection is really important. Because I think you want to have sites that, so if you're using let's say FOLFIRINOX because your chemotherapy backbone, like they have experience with managing patients on FOLFIRINOX or gem/abraxane, right. There's nuances to both of those things. And then I think you want to have, you know, so it's been shown in, if you take patients who have Whipple surgeries for pancreas cancer, right. It's been shown that the amount of Whipple surgeries that a place does, the better the outcomes are, and the less deaths are associated with that.

I think the same thing applies here, right? So, we talked about metastatic disease, but the more experience that the center has, and it's not just the doc. It's actually the nursing staff, all the ancillary staff that goes into taking care of those patients. The more experience those – that those, that center has with this disease population, the more likely the outcome is going to be, you know, more closer to the truth. Right. It's going to be a greater estimate of the truth. Right?

So I think in this particular study, you see that when you eliminate those patients, that the first step, in the

initial tail that falls off, right. When you eliminate those patients, when you have an outcome that looks pretty promising. Right?

So how do we get to eliminate those patients? And that's where the study center – choosing your sites, that's how you eliminate those patients that fell off initially because I'm going to pick true – so if you say that patients have to be ECOG 0, 1, 2, or 3 to go on to the study, right? That's – there's an objective way to do that, but it's really subjective, right? It's what I say ECOG 0, 1 is, right? And if I say, okay, well, I just want to see if I can just push this patient on the study. They're truly ECOG 2, but I said they were 0, 1, right? That ECOG 2 patient that I said was 0, 1, that's the patient that falls off in the first part of the study. So you really want to be selective about who – who's doing the study, right?

And then also you want to have experienced investigators like him who says, okay, we see neutropenia, but what does it really mean, right? So you understand that maybe neutropenia is present, but it's not the rate limiting step in this conversation, whereas if you have a non-experienced leader of a trial, that stuff gets sort of muddied as well. So I think it's really – it's – yeah. You just got to be very careful about who you select to do your stuff.

And so sometimes having more sites to be fast isn't the right thing to do, right? And I think in pancreas cancer, that really is the case where we seem like if you – if we were to go over all the studies in pancreas cancer where there's muddied water is because there's – there – it's a number of sites that do certain thing like we were talking about treating advanced disease. If you look at those studies, they're a mismatch of outcomes. And a lot of it is because they wanted to do these things quickly.

So they had a lot of sites that don't know how to take care of pancreatic cancer patients. And then you get outcomes that you can't really replicate. And then you say, okay, well, I don't know to do this information. So, I think it is really important about being selected and thought too much, right?

Well, I think it's experience is what I really say.

Deva Mahalingam

With this data, even if we are required to do a registration type trial, I think there would be a lot of interest globally to be a participant of this trial, right? That's the first thing. As a physician, and when the patient comes in to see me and I'm thinking of putting them on a trial and I know that they are on the fence, right? Ultimately, I'm looking at the patient and he's saying, please give me hope. I want to try and get into this trial, and I'm going to try and get that patient into the trial, which is where the subjective nature comes in, because ultimately we want to give the patient the best option, even if we might think that it's kind of iffy, right?

So, I think you're going to see this in the global trial. And the only way you can control things is to play with the eligibility criteria and be stringent where you can with some flexibility. And I think that's going to be how we design the protocol, how we kind of put the right language in and then let it be. This is a global trial. You're going to see the differences. But you're right, we need to pick the global trial in institutions that have higher volumes of pancreatic patients, so that they know how to manage these patients as opposed to like the odd one key in there.

Yeah. That's an interesting point, right? Do you think that we could try and get a – and I think this is something that Colin has talked about in his trial, where even after a break of the chemo, the elra continues and then the chemo comes on. And whether we would re-challenge this, there's no data to support re-challenging of elra if someone has progressed kind of clearly on elra, but to your point like, you know, and I think,, Tony mentioned it earlier, as whether you could just keep elra going, even if you bring in another chemo backbone in the second-line setting to achieve that improved survival as well.

Analyst: Kaveri Pohlman

Question – Kaveri Pohlman

Hi. This is Kaveri Pohlman from Clear Street. Thanks for all the insight and for taking my question. Just a couple from me, so what minimum magnitude of OS benefit or OS difference would you like to see when we move from a – this study to a bigger trial? And the second one, you know, it was discussed since it's a – it has an immunotherapy effect with a longer tail in terms of survival, which we have also seen in PFS, but here we

are seeing the effect most prominent in the OS. Is there any reason why that is specifically in the OS metric alone and if you have seen any similar pattern with any other drugs before? Thanks.

Deva Mahalingam

Yeah. I'll maybe take the second question first with the tail-end, right? So, we have seen it with checkpoint inhibitors to start with. And for example, one of the trials that is now – if you look at the KEYNOTE-048 Trial which is a head-and-neck cancer trial, I mean, that trial – the randomization was pembrolizumab with fluorouracil and cisplatin versus cetuximab, which is a standard of care before that. And you could look at the data and you'll see that the overall response rates in the PFS were comparable between the arm, but then the pembro added the kind of tail end.

So, we're starting – we saw – we kind of saw that in the checkpoint inhibitor. We already got this kind of post-progression survival, you could just you say, and there are other trials in lung cancer that the KEYNOTE-042 and the – the KEYNOTE-042 and the CheckMate 057 and there are so many numbers I can't remember. But even in the second line trials, we're seeing the same pattern improve the overall survival and then, I think so we are seeing this in kind of immunomodulatory kind of things and that's why I think we were trying to get at with this trial as maybe we're seeing the tai lend because of that. And I think your first question was to do with, what was it again?

Kaveri Pohlman

The minimal magnitude of OS benefit that you would like to see?

Deva Mahalingam

Yeah. So, I think three months, I think we were three months on that thing and I think discuss and even said anything at three months the difference would be both significant and meaningful in pancreatic cancers and that would usually translate with a hazard ratio kind of less than 0.7.

Daniel Schmitt

So the three months corresponds to the trial overall at this point and the trial still ongoing. The four months corresponds to the - those patients who could get beyond one cycle of treatment. So, again, to - I think it was Tony and both Rachna and I were saying there hasn't been a major advance in this area. These are major advances.

Colin Weekes

Even the three months is not - the three months is a major advance. I mean it really is.

Daniel Schmitt

So, I'm going to get one last question.

Kaveri Pohlman

Let me ask one more question. Just a hypothetical maybe. If this drug were to be available to you tomorrow, what percentage of patients would you give it to initially? And are there any patient population who you would avoid giving it this combination based on its risk benefit profile?

Deva Mahalingam

I would give it all, if the – if based on the data, never mind whether you have the FOLFIRINOX or the gemcitabine at least - but at least now we have the gemcitabine/abraxane data. I would give all my patients gem/abraxane with this drug because of the survival benefit that you see. I'm waiting to see college data, which I think would come up probably it means FOLFIRINOX would do the same thing that'd be great.

But in terms of – I would be happy to do add that to either chemotherapy arm if I can see the tail end survival go longer. I may not see the PFS on their kind of more responses or anything like that. But if patient is going to live better and do better clinically without any additional side effects, then I think I can convince a patient to do that, whichever drug.

Colin Weekes

I would give it to every patient. So my study is done enrolling. It's a much smaller trial, so it's not going to be like this. But based upon what I've seen, I would give it to all patients. And I'm actually currently developing studies for neoadjuvant studies with FOLFIRINOX in this combination. So I'm all in, so I'm a little bit biased, I guess.

Daniel Schmitt

Chris? You're the last man standing, my friend. Go ahead.

Christopher Liu

Lucid Capital Markets again. Thanks for letting me ask my question. So for the patients who can get to at least one full cycle of treatment where you had that four months difference, has any analysis been done into what's enabling those patients to get to that point? So what's the difference between the safety population and the one month population, that delta of patients, is it the albumin or – we done anything.

Deva Mahalingam

As we talked about, it's very subjective on how we put people on to the trial. Right? So you have this group of patients. And there could be other factors. We know that there's certainly a certain subgroup in pancreatic cancers that are highly aggressive, highly resistant to the current standard chemotherapeutic agents. So I think that's certainly one of the population that we see the drop off. And then, I think the other one is just performance status. The patients are usually when they come in, have declined from where they were even very quickly or when issue was space of three to six months, they have had weight loss, symptoms related to the cancer. And I think that accounts for some of the patients who start off and then decide if you weaken that, I don't know whether I can do this chemo and I just want to come off the study or they would decline, right, very quickly. So we've seen all of that. And there's no way of kind of figuring out who that is upfront apart from being more stringent about patient selection. That's the only thing.

Christopher Liu

Thank you.

Daniel Schmitt

Very good. Well, thank you. I think we've run our time tonight. And I appreciate everybody, your time and attention, and the time and attention of these gentlemen who have more than enough appointments to take care of. But appreciate your support and the fact that you're using the elra and taking care of patients. So, with that, we're going to wrap up and bid everybody good night. Thank you.