Givastomig: Mature Clinical Data and Path to Registrational Development

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Operator Introduction

OPERATOR

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Opening Remarks

SRISHTI GUPTA

Chief Executive Officer, NovaBridge Biosciences

Welcome, and thank you for joining today's webcast to discuss the updated Phase 1b givastomig data presented at ESMO. A year ago, we were encouraged by the early activity we were seeing with givastomig. Today, with substantially more follow-up, we have a much deeper understanding of the durability, safety and overall clinical profile of the program. Today's discussion is about more than an updated data cut. It’s about how a much more mature dataset has changed our understanding of the program and increased our confidence in its future development. With additional follow-up, the key objectives of the Phase 1b study have now largely been accomplished. We have characterized the durability and consistency of clinical benefit, selected the 8 mg/kg dose for registrational development, and used the data generated through this study to inform our Phase 3 strategy. What is particularly encouraging is that our confidence in the clinical profile of givastomig has increased as the dataset has matured. We continue to see evidence of durable clinical benefit, with responses that can persist and, in some patients, deepen over time. The data also continue to demonstrate clinical activity across CLDN18.2 expression levels, including lower-expression tumors, supporting the broad potential of the program. To summarize, this mature dataset has allowed us to better characterize durability, establish the registrational dose, and support an FDA-agreed global registrational study protocol. With that, I'd like to introduce our Chief Medical Officer, Dr. Philip Dennis, who will review the updated clinical results, discuss the key findings from the mature dataset, and explain how these data informed selection of the 8 mg/kg registrational dose and support our planned registrational development strategy. Following Phil's presentation, he'll be joined by Dr. Sam Klempner, Associate Professor of Medicine at Massachusetts General Hospital and lead investigator of our Phase 1b study, who will provide an independent clinical perspective on the durability of the findings, their relevance for patients with gastric cancer, and the potential implications for the treatment landscape. Phil, over to you.

Clinical Data Presentation

PHILIP DENNIS, M.D.

Chief Medical Officer, NovaBridge Biosciences

Thank you Srishti. Before getting into the data, it's helpful to step back and consider what a successful therapy needs to deliver in frontline gastric cancer. Efficacy is critical, but so are broad patient applicability, manageable safety and the ability to integrate into routine clinical practice. Many CLDN18.2-targeted approaches involve tradeoffs between these dimensions, and this slide helps put that landscape into context. Against that backdrop, let's turn to givastomig. With the additional follow-up we're presenting today, we can now assess the profile of givastomig with greater maturity, including the depth and durability of response, safety and activity across CLDN18.2 expression levels. So let's walk through what the updated dataset tells us. Next slide please.

When we initiated this Phase 1b study, we believed that a successful frontline therapy would need to demonstrate four things. First, broad patient applicability, second, durable clinical benefit, third, a manageable safety profile, and fourth, practicality for routine clinical use. Earlier in development, many of these questions remained unanswered because the dataset was still relatively immature. What makes today's update different is the amount of follow-up we now have available. With nearly 18 months of median follow-up in the selected 8 mg/kg cohort, we can now move beyond simply asking whether the drug is active. We can now begin to assess whether responses are durable, whether safety remains manageable over prolonged treatment, whether activity extends across CLDN18.2 expression levels, and whether the overall benefit-risk profile supports broad frontline use. As I walk through the data, I'll come back to each of these four attributes because they provide a useful framework for understanding how the program has evolved as the dataset has matured. But first, it's worth briefly revisiting the mechanism and why we believed this approach had the potential to address those four attributes. Next slide please.

Givastomig combines 18.2 targeting with conditional 4-1BB t-cell activation. The design seeks to amplify anti-tumor immunity within the tumor microenvironment while maintaining a safety profile suitable for frontline use. The key question has always been whether that design translates into durable clinical benefit and manageable safety. The updated Phase 1b dataset provides increasing confidence that it does. Of course, mechanism alone doesn't determine clinical impact. Ultimately, that needed to be evaluated in the Phase 1b study, which was designed to answer several key development questions. Next slide please.

The Phase 1b study was designed to not only establish safety and characterize activity, but ultimately to answer three questions that would be critical for registrational development. First, what dose should advance into registrational development? Second, is activity observed across a broad CLDN18.2-positive population? And third, does clinical benefit remain durable with longer follow-up? Importantly, the study enrolled patients across the CLDN18.2-positive spectrum rather than focusing exclusively on the high-expression cohort. The updated dataset provided important information on dose selection, durability, safety and patient population that helped inform registrational development planning. With that framework in mind, let's turn to what we've observed clinically, beginning with the breadth of activity across the CLDN18.2-positive population. Next slide please.

One of the most important findings in this dataset is the consistency of activity across CLDN18.2 expression levels. Strong activity was observed in patients with CLDN18.2 expression in greater than 75%, which is where currently approved CLDN18.2-targeted therapy is primarily focused.

Importantly, activity was also maintained in lower-expression tumors. At the 8 mg/kg dose, which we have selected for registrational development, objective response rates were 82% in the CLDN-high population and 75% in patients with CLDN18.2 expression between 1% and 74%. Disease control approached 100%, and nearly every efficacy-evaluable patient experienced some degree of tumor shrinkage. Activity was also observed across PD-L1 subgroups. Importantly, these findings have persisted as the dataset has matured, with nearly 18 months of median follow-up in the 8 mg/kg dose. While these are early-phase data, the consistency of activity across expression levels gives us increasing confidence that the opportunity may extend beyond the currently defined high-expression treatment segment. Beyond response rates alone, we also wanted to understand the consistency and magnitude of these responses. Next slide please.

Response rate is important, but we also wanted to understand the breadth and depth of activity across the study population. What we observed was evidence of activity across CLDN18.2 expression levels as well as PD-L1 subgroups. Beyond the responses themselves, we saw substantial depth of response at the selected 8 mg/kg dose, with a median tumor reduction of 62%. Perhaps most notably, 68 of 69 efficacy-evaluable patients experienced some degree of tumor shrinkage. That level of consistency suggests the activity we're observing is broadly distributed across the population rather than driven by small subsets of patients. In our view, these findings strengthen the overall response-rate signal and provide important context for what comes next. The key question then becomes whether those responses translate into durable clinical benefit over time. With nearly 18 months of median follow-up in the selected Phase 3 dose cohort, we are now in a position to begin answering that question. The key question then becomes whether those responses translate into durable clinical benefit over time. Next slide please.

If I had to identify the single most important takeaway from this update, it would be durability. Earlier in development, we knew givastomig was generating responses. The key question was whether those responses would translate into durable clinical benefit over time. With nearly 18 months of median follow-up at the selected 8 mg/kg dose, we now have much greater visibility into that question.
What we're seeing is more than merely a response-rate story. The median duration of response is now 15.2 months. The median progression-free survival has reached 16.9 months. Fourteen patients remained on treatment at the data cutoff. Importantly, responses often continued to deepen after the initial response and today's dataset looks better than it did a year ago. That's exactly what you hope to see from a therapy intended for prolonged frontline treatment. What gives us confidence is not simply that we have observed responses. It's that those responses translated into durable disease control as the dataset has matured. It's also worth noting that despite nearly 18 months of median follow-up, only 13 progression events had occurred, while 18 patients remained censored and 14 patients were still receiving treatment at the time of the analysis. In frontline metastatic gastroesophageal cancer, generating responses is important, but sustaining responses over time is what ultimately matters most to patients and physicians. For us, that is one of the most encouraging aspects of this dataset.
The signal became stronger rather than weaker as follow-up matured. That additional follow-up significantly increased our confidence in the durability of benefit, supported selection of the 8 mg/kg dose for registrational development, and helped establish the foundation for the FDA-agreed global registrational study protocol. But, durability is only meaningful if patients can remain on treatment long enough to realize that benefit. That brings us to the safety profile, which I will cover on slide #8.

Greater follow-up also means substantially more drug exposure. We were pleased to see that, as exposure increased, no new safety signals emerged and we gained a much clearer understanding of the safety profile. No Grade 4 no Grade 5 givastomig-related adverse events were observed and rates of immune-related adverse events generally appeared comparable to what would be expected with

immuno-therapy plus chemotherapy as a backbone for frontline metastatic gastric cancer. The most common treatment-related adverse events include nausea, vomiting and fatigue, all of which occurred without a need for titration or active infusion monitoring. No Grade 5 treatment-related adverse events were observed. Importantly, the safety profile needs to be viewed alongside the durability data we just reviewed. Patients remained on treatment for extended periods of time, providing meaningful insight into the long-term tolerability in a frontline setting in metastatic gastric cancer. The only increased immune related toxicities observed compared to nivolumab plus chemotherapy is gastritis. Gastritis is a biologic consequence combining a checkpoint inhibitor, nivolumab, with givastomig, a CLDN 18.2/ 4-1BB immune amplifier. Most events are ≤Grade 2. Grade 3 events are rare. Gastritis typically develops after a tumor response is already documented. The 8 mg/kg dose is associated with lower overall and lower Grade 3 incidents, while maintaining a compelling efficacy and durability profile. The majority of events for gastritis are manageable with established intervention strategies including temporary cessation of the immuno-therapy assets, institution of high dose steroids followed by a slow taper. This approach commonly leads to resolution of symptoms to where patients can be rechallenged with givastomig. Standardized management algorithms were implemented and refined during Phase 1b trial. As a result, the duration of gastritis has decreased over the course of the phase1b trial. And as the dataset has matured, 8 mg/kg emerged as the dose that best balanced efficacy, durability and safety. Next slide please….

As we bring the data review together, we believe the updated dataset accomplished the key objectives of the Phase 1b program. We observed compelling clinical activity across tumors with CLDN18.2-high and CLDN18.2-low expression. With longer follow-up, we gained increasing confidence in the durability of benefit, with responses that persisted and often deepened over time. We established a manageable safety profile that supported prolonged treatment and did not reveal new concerns as exposure increased. And collectively, those findings enabled us to confidently select the 8 mg/kg dose for registrational development. Importantly, the maturity of the dataset also supported agreement with the FDA on a global registrational study protocol, including the patient population, study design, comparator arm, endpoints, as well as statistical powering. Taken together, we believe the key objectives of the Phase 1b study have now largely been accomplished. We've spent the last several slides discussing the data from the company's perspective. To help put these findings into clinical context, I'd now like to welcome Dr. Samuel Klempner, Associate Professor of Medicine at Massachusetts General Hospital and the lead investigator of the Phase 1b study. Dr. Klempner is a gastrointestinal medical oncologist with a clinical and research focus in upper GI cancers, specifically gastroesophageal cancers. He has been closely involved with the development of givastomig and has a unique perspective on what these results mean for physicians treating patients with metastatic gastroesophageal cancer, the importance of the durability signal, and where givastomig may fit in with the evolving treatment landscape. Sam, thank you for joining us.

Clinical Discussion

PHILIP DENNIS, M.D. and **SAMUEL KLEMPNER, M.D.**
Lead Investigator, Phase 1b Study; Associate Professor of Medicine, Massachusetts General Hospital

Phil - Sam, thank you for joining us. For the first question, Sam, you've been involved with this study since early in development and have seen the data evolve over time. Let me start with a very broad question. As you've seen the data mature, what has stood out to you most about the updated results?

Sam - Yeah, thanks, Phil. I would say a few things have stood out, and it has been nice to see longer follow up in this data mature. So, one, it's nice to see the initial reporting of the response rate continued to hold, but really in the world of effective frontline therapies and increasingly effective therapies, what we want to see is durability. And so I think that to see the response rate translate to durable disease control and durable responses and translating into PFS and early OS reporting, is really the things that have continued the enthusiasm for me as an investigator, you know, treating these patients in front of me. Everybody likes to see their tumor getting smaller. But it's really the durability that tends to move the needle in this disease. And so that's been, I'd say, at the very high level, some of the things that have stood out to me with the more mature data set.

Phil - So, have you seen the, in terms of the durability, have you seen patient subgroups, um, benefit all, what patients seem to benefit most, or do you think, well, all benefits are obtaining, uh, some benefit?

Sam - Yeah, I think it's, ultimately, it will take a very large number of patients to tease apart, but it's encouraging in some respect that there is not a biomarker group that's clearly driving the benefit. For example, I think it's pretty clear from looking at the waterfall plot that the activity is across the entire Claudin spectrum, not only seen in the very top expressors. Uh, similar to PDL-1 expression, you know, it's not like all of the responses are in the CPS high patients. The more encouraging story, I think, is that the early data suggests that the combination is active across the entire spectrum of PDL-1 and an extremely broad spectrum of Claudin expression, you know, going from one plus in one % or more of tumor cells is basically 80% of all gastroesophageal cancers. So, in some respects, it's been the lack of a clear cluster that's driving the benefit, that is one of the more encouraging things to me. Of course, you know, much larger numbers will maybe required to see some trends, but, uh, this has been one of the more encouraging findings, I would say.

Phil - As the PFS data has matured, with now almost a year and a half of follow up, what are your expectations for overall survival, given the current data, with ORR and PFS? I know it's a projection, but given the association of these endpoints with OS, what's your sense of what overall survival might end up looking like?

Sam - Yeah, I mean, I'm optimistic. I think when we start to see PFS pushing past a year easily and in some cases here, closer to a year and a half. Uh, we start to get optimistic about overall survival, especially as we've seen some later line claudin therapies, demonstrate activity as well, so there's the potential for sequential claudin targeting like we do with HER2. So we may really start to push this, you know, into the two year range, I mean, 20 months, 18, 20 months, and beyond, I think would get someone really excited in a larger data set for an overall survival. But maybe, who knows, maybe even, maybe even better, but with PFS that's beyond a year, you know, we know what we get out of later line therapies in general. So, I would be looking, hopefully, into the, you know, well into the 18 - 20 month kind of range, uh, optimistically.

Phil - Thanks. Um, I, earlier in the presentation, I spent some time discussing safety, uh, as well as efficacy and the rationale for selecting 8 milligrams per kilogram for, uh, a registrational study. Now, what's your perspective on the benefit risk profile of this selected dose?

Sam - Yeah, I think as the data you presented, you know, there is experience at 8 and 12, and certainly the shorter follow-up at 12 is not something that particularly bothers me in terms of assessing the overall kind of totality of the data. It is a balance. You know, these are patients who are having very good responses, and it's perhaps slightly higher response rates in the higher doses, but certainly we also see

slightly higher numerical rates of toxicity, including gastritis at 12 milligrams per kilogram. So, although in my own experience, having treated, you know, more than 30 patients on this trial, I would say the manageable, uh, toxicity has been similar at 8 and 12 in my own experience. So, we're not always looking for the highest dose, especially with agents that have an immunologic mechanism, component to their action. It's really the durability. So, we have to have a balance of tox and efficacy that allows patients to stay on therapy for extended periods of time. And so to me, I think it's very reasonable thinking along the 8 milligram per kg as sort of the dose that perhaps offers the best balance from a patient perspective. But it's encouraging to see that both doses are clearly active. And I would agree that the 8 mg per kg is worth continued development.

Phil - So if we, if you look at the totality of the toxicity profile and think about what you would expect with Nivolumab and Fall Fox alone, what's your overall assessment of what the addition of Givastomig does to that profile?

Sam - Yeah, I think, you know, one of the presidential symposiums at ESMO, a couple of the discussants made some really good points about the limitations of CTCAE, uh, capturing events. And I would agree that it's an imperfect system, but it is the system we have. And actually looking ahead at CTCAE version 6, there's some meaningful improvements that provide some chronicity along to the grading. So, I think it will actually help the grading be more reflective of the patient experience and ultimately that's what matters in the real world. I would say that to answer your question, um, you know, chemo has a known toxicity, immunotherapy with Nivolumab has a known toxicity, and Givastomig in the monotherapy trial has some single agent adverse events as described in original phase one. When we put them all together, I think as an investigator, we look to see if, is there cooperative or synergistic toxicity? Are we, you know, enhancing the toxicity profile of one of the existing components? And I would say, in my experience, we don't see any worsening, uh, chemotherapy related toxicity from the additional Givastomig and we haven't seen a clear signal in emergence of other existing immune related adverse events from Nivolumab, for example, I don't see significantly more hypothyroidism or skin related toxicity, things that we know from Nivolumab. The one that stands out, and I think, is no surprise. Um, is really the GI side effects, the gastritis in particular. I'd say as the data has matured, um, you know, most of the events continue to be low grade in the current system, so low grade 2 or less, and there is not a new safety signal, but it is, it is the gastritis, uh, that continues to be the one side effect with this combination regimen that just requires, uh, attention and education and monitoring. And I think it can occur across a wide spectrum of clinical manifestations, the majority of which are manageable in my own experience.

Phil - And what do you just personally, in terms of, again, given the, your vast experience with this combination, can you comment on how the management has changed, or do you think it's improved over time? Where are we now, as compared to the beginning of the phase one study?

Sam - Yeah, I think we're understanding sort of the kinetics of side effects, um, and having greater confidence in sort of these early descriptions. So, I guess I'll add a little bit of color to that. So, uh, with Zolbetuximab for example, with larger experience, we learned very clearly that the toxicity is is very early, often with the very first dose or the first couple doses of drug. And that can be a barrier and deterrent for some patients because they have a toxicity before they know if they're having a benefit. And sometimes it's hard to have that discussion with people if they're not feeling well. The gastritis, uh, with more mature data, you know, in my own experience, the time to onset is after, well after the patients have had at least one or two scans. And so, it's very helpful in the discussions because patients have a sense of whether they're benefiting from the combination. And I think, uh, when patients

understand or have some objective evidence that they're responding to the combination, they're certainly invested and inclined to try to adjust around any side effects that may be upcoming. So, in some ways, this has been, um, a nice thing to see, sort of the greater understanding of the timing and sort of onset of this, uh, adverse event profile in some ways itself is a bit favorable in terms of having patient discussions, and that is one piece that I think has really started to come out more clearly with longer follow-up. We also have a greater experience in managing the side effects because we have followed these patients for longer. So, we have, um, an experience of, you know, re-challenging and continuation of other components of the therapy during management of gastritis, which I think is another nice component to the combination is that it's modular, uh, meaning that you have chemo, checkpoint inhibitor, and Givastomig. And this is different than some other agents like the ADCs, which are either given as single agent or in some of the ongoing trials combination, but the ADC is being asked to do a lot of the work. So, if you hold the ADC in some of the later line studies, the patients are getting no therapy at all. Where here, if we have to hold Givastomig for a period, to manage gastritis, for example, there is still ability to continue components of therapy. And I think that's important for practical management of this disease.

Phil - Great. Thanks. I just want to touch on the topic of rechallenge that, um, obviously, that's an optimal outcome that if a patient develops gastritis, and they have the immunotherapy components withheld for a short time while their symptoms improve and they're treated appropriately. How do you see rechallenging rechallenge evolving over time? Right now, we have slightly more than half the patients that can be rechallenged. You see that improving over time with better management?

Sam - Yeah, I think so. I would say it's a discussion with patients. Obviously, they're going to bring their own perceptions and how the toxicity may have impacted them to the discussion, and that's very important. And we have discussions of re-challenge with chemotherapy components that also have similar themes. Uh, I would say, in general, the rechallenge has been, uh, at five milligrams per kilogram, although I have rechallenged patients, uh, at full dose, uh, as well. And my own experience, which, I think, is probably 3 to 5 patients with rechallenge, we, I think maybe I've had one person who developed recurrent gastritis that was manageable with, with hold. And so I think, again, we need larger numbers of patients to sort of get a little more granular data around the chances of recurrent gastritis, but thus far in my own experience, rechallenge is something that if I think the patient is clearly benefiting, and the toxicity has improved to, you know, kind of grade one, kind of like how we would think for other immunotherapy related toxicities, I feel pretty comfortable having that discussion and thinking towards re-challenge, particularly if it's relatively early on, like the first six months of someone's therapy where the, uh, ideal activation of the sort of immunologic component of this combination uh, may still drive a lot of the benefit, I would seriously consider it in patient discussions.

Phil - Great, thanks. Um, maybe as a closing, again, finishing with a broader question, um, knowing you're involvement in leadership in the study, if you compare where the program is today versus a year ago, let's change most in your own thinking about Giva, uh, and its future potential.

Sam - Yeah, it's a good question, and, uh, you know, be nice to play this back in, like, five years and see how close I was to feeling the same way. I think the longer follow up has been quite nice, and I've been involved in the program for a few years now. I think we have really seen no major changes in terms of particularly toxicity, and I'm feeling more confident across sort of a spectrum, but I don't think there's a specific result that drives this, but if I look at the entire space as a whole, I think there is some clear, positive differentiating factors. One, as I mentioned, is that the modular components make this very manageable over the course of someone's frontline therapy, which is something that some other agents

and approaches can't really offer. I think the ability to have data all the way down to the very low Claudin expression and PDL-1 negative patients is something that we have not really seen yet. And even the Illustro data set, really, the benefit was primarily in the high Claudin and PDL-1 positive. So that's quite different than the Givastomig dataset where the activity looks consistent across the entire Claudin and PD1 spectrum. So that is a nice thing. And then, to sort of continued validation of Claudin as a target has been something that is very, very clear. I mean, at ESMO, we saw two late line phase 3 trials from ADCs that continued to validate the idea of pushing on Claudin. And then we will see data from additional phase threes, but the mechanism is also different, and I think that that is important. I view Givastomig as a potential way of solving the 41 B, 41 BB, agonism question that has been a very active area of science and has very good scientific rationale, but hasn't been a problem that we have solved clinically. Um, meaning the naked 41BB agents, you know, were limited in toxicity, and so a spatially delivered 41BB agonist, uh, seems to get around that, you know, I forgot to mention in the toxicity that one thing that doesn't happen, at least in my experience, is really hepatotoxicity. So, we don't seem to be plagued by some of the problems of the naked 41BBBs. And I think, um, that is probably reflected in some other companies trying, uh, bi-specific 41 BB formulation, such as PDL-1 by 41 BB and others. And I think that's been a nice thing to see in the space is that we may, or you guys may have partly solved, if not solved, the ability to deliver 41 BB, because it's always been an attractive immunologic approach. It's just been limited by toxicity. So maybe I got a little bit off on a tangent, but I think that that is something that, you know, has been a nice thing to see.

Phil - Well, appreciate it, Sam. This has been a great conversation. We appreciate your insights and your leadership on the study. Thank you.

Sam - Thanks a lot.

Phil - As we discussed, the key takeaway is that these increasing mature data set has strengthened our confidence in the attributes we set out to achieve. Broad activity, durable clinical benefit, a manageable safety profile, and an optimized benefit risk profile at the selected 8 milligram per kilogram dose. With that context in mind, I'd like to turn the discussion back to Srishti to talk about the strategic implications of these findings and how we think about the opportunity ahead for Giva. Srishti, over to you.

Thank you, Phil. And thank you, Sam, for helping put these findings into clinical context.
Before we move to Q&A, I'd like to leave you with a few key takeaways from today's discussion.
A year ago, we were encouraged by the early activity we were seeing with givastomig.
Today, we have substantially more follow-up and a much deeper understanding of the durability, safety and overall clinical profile of the program.
Perhaps most importantly, the dataset has strengthened as it has matured.
With longer follow-up, we continue to see durable clinical benefit, a manageable safety profile and activity across the CLDN18.2-positive spectrum.
The updated dataset has also given us the information needed to select the 8 mg/kg dose and continue advancing our registrational development plans.
As the CLDN18.2 treatment landscape continues to evolve, we believe the profile emerging for givastomig is increasingly important.
The combination of durable clinical benefit, activity across CLDN18.2 expression levels and a favorable benefit-risk profile gives us confidence that givastomig has the potential to differentiate itself and play a meaningful role in the treatment landscape.
There is still important work ahead, but we believe the program is increasingly demonstrating the attributes we hoped to see when the study was first initiated.

So, for NovaBridge, this ESMO update represents an important milestone.
We have a more mature dataset, a clearer understanding of givastomig's clinical profile, and greater confidence in the path forward.
With that, Tara, we'd be happy to take questions.

Analyst Question-and-Answer Session

Great. Thank you, Srishti. So yes, at this time, we'll be conducting a question and answer session with our speakers. So please hold for a brief moment while we pull for questions. So our first question comes from Dana Graybosch at Leerink. Please go ahead, Daina.

Daina - Hello, um, a few questions for me, but maybe we can start on toxicity. Uh, maybe a few uh, there. So on the poster, if I look at the 8 mg per kg, uh, there's quite, you know, the numbers of Giva delay, interruption, and discontinuation. You reported at 55, 23, and 26%. So three questions there for the company and Dr. Klempner. One, you know, are those the same patients that we're seeing interrupt and discontinue? Or do we tend to have, you know, one of those, uh, uh, one of those happenings, you delay, or you discontinue, just trying to understand the totality of the number of patients that have any of these, um, treatment related changes to their dose? Two, I think you talked about two things make you encouraged about this toxicity, and I wonder if you can quantify it. One, how this number changed, let's say, from the first 15 patients enrolled to the second 15 or however you want to cut it to help us quantify that the management improve these numbers. And three, you talked about these coming late, but you don't have on here sort of a duration of treatment or exposure. To have any quantification about sort of when these dose changes happened, uh, in the, in the treatment course. Um, thank you for that.

Srishti - Thanks, Daina. Thanks for the questions. Um, so maybe I'll hand it over to Phil for the first part of the first question around understanding sort of the definitions, uh, the, and the totality and the patients, how they, how we, how we uh, define them in the toxicity table for the poster. So Phil, do you want to jump in on that?

Phil - Sure, thanks. So, I'll start with some definitions. So dose interruption is defined literally as an interruption of the infusion, right? So patients, um, start their infusion of their different drugs, right? As Sam mentioned, several modalities. In the course of that infusion, if they develop an infusion related reaction, then the infusion could be interrupted, medications can be provided, and the infusion can continue, often at a slower rate. But the clinical impact of those types of interruptions is typically quite low. Dose delay indicates that a patient who is intended to get a cycle of treatment has a delay in that cycle of treatment. And this is not uncommon, again, given two different immunotherapy agents combined with a chemotherapy regimen as well, that is quite complex and has its own set of toxicities. And for perspective, in terms of dose delay, checkmate 649, which is a study that led to the approval of Nivolumab and chemotherapy, had dose delay incidents of 67%. So it's actually quite common to really experience that. And maybe I want to, since Sam has lived through this by treating the patients, I would like to know, Sam, if you could just comment on that experience of dose delay and dose interruption.

Sam - Yeah, sure, happy to. So, a few things. One, uh, this is a problem in line of site for all clinical data sets. You know, it would be wonderful to see by cycle the rates of one component being held. We almost never see that even in big registrational base trees, even though the data exists. So this is partly, um, the way that AEs are captured in the CTCAE and partly just management of the data sets. I'd say clinically, obviously, I've treated a large number of patients with this drug at least 30 or 40 people. And yes, there are some of the same patients who have delayed ultimately leading to a discontinuation, but many

patients, that is, that is definitely not the case. I think it can't answer fully from the data, uh, which patient, if it's the exact same patients who interrupted the discontinued, but I agree, interruptions happen all the time. It's, you know, even if a patient is going away for the 4th of July to have family barbecue, you know, sometimes these things get recorded as an interruption, which is not held for a toxicity reason. Although, you know, in the table, this is treatment related adverse event, but those can be really a huge spectrum. So, I think it's incomplete to try to draw conclusions from that, uh, to answer your earlier question about the evolution of the toxicity and any formal metrics to understand that. Um, I'll let Phil comment, but, you know, in my own experience on this trial, I think the recognition and management has led to a materially different ability to maintain people on components of the therapy, including Givastomig. And I think I've maybe only discontinued completely, one or 2 people out of my entire cohort. Some of that is experience with these types of drugs, some of that is, you know, the excellent support that we have at big tertiary centers. Um, but I do think it is materially different from the initial 15 to this 71, you know, patient data set.

Phil - if I could just add to that, um, so the discontinuation rate that we show in our poster, uh, is accurate, and it reflects, for example, three incidents of infusion related reaction that happened within the first eight months of the combination study. We have not had an occurrence of an infusion related reaction that's led to discontinuation since then, due to the simple fact that we now have premedications, and we didn't have them at the time that those events led to discontinuation. So, the way if you exclude those patients or discontinuation rate is 16%, uh, and if we look at patients who discontinue because of gastritis, it's 13%. I will emphasize also that the timing of gastritis is getting shorter and shorter. If we look at grade 3 events that have happened over the course of the last year, the average time of grade 3 events is now less than 10 days. So, we are decreasing if patients experience gastritis, especially grade 3, which are very rare, right? The clear majority of cases are grade 2 or less, are grade 3 incidents at the dose that we're taking forward, registrationally, 8 milligrams per kilogram is 6% grade 3 events, and we know that those very rare events now luckily are happening for a much shorter period of time. And that's due to better management, early diagnosis, early intervention, slow steroid taper, and really just judicious management.

Srishti - Thanks, Phil, and then maybe to answer Daina's last question, you know, from the phase one data, what are we gleaning or how can we, you know, sort of make a comment on the duration of treatment? Um, and the direction of that. I, even though we may not have been exact, obviously, the phase 3 will be important for that, but how are you thinking about the duration treatment?

Phil - So the, um, I guess the one of the ways that to think about this practically is that we know that, um, for patients who do have, um, dose delay, uh, we know that the impact of that now is, is, is less, right? We know that the impact is arguably not, uh, it doesn't, uh, cause patient detriment, right? In other words, we know that patients who develop gastritis do not do worse. We know that treatment, you know, delaying for a couple of cycles, letting gastritis quiet down over a matter of a few weeks does not adversely affect outcomes. In the phase 3 study, uh, we are, uh, we recognize the burden of, um, really the safety issue for patients in a larger geographically diverse, um, network. But again, our phase one experience has informed earlier recognition, diagnostic criteria, and intervention guidelines. Um, we will plan on investigator education, standardized treatment management protocols, um, that are now included in our phase 3 um, study as we get ready for that. So we really, uh, we want to ensure that patients, um, maintain treatment, uh, but if they do have to, uh, withhold treatment due to gastritis, which again, is very important point. It develops 4 to 5 months in after a tumor response is typically initiated, that those patients can have that resolve, and as we now have experienced in Sam's institution, actually, I believe, can restart 67% of patients now on Givastomig after an episode of gastritis. So we

think that as with this implementation, especially in our phase three, gastritis will have a very minimal burden in such a registrational study.

Srishti - Thanks, Phil. Um, Tara, can we go to another analyst and then maybe come back if Dana has further questions?

Tara - Yeah, absolutely. So our next analyst that we have on is Andre Maldonado at HC Wainwright. Andres, please go ahead.

Andres - Hi guys, congratulations on the progress and thanks for taking my question. Um, I'll start with two, one for the company, one for Dr. Klempner. I guess let's start with Dr. Klempner. Um, you know, if the randomized data holds up, can you paint a picture of which patients would you reach for Givastomig first and maybe which would you still favor, Zolby, or another kind of chemo, um, chemo immunotherapy option alone? And then for management, you know, just curious, um, on how many patients, you know, with Claudin 18.2 low and PDL-1 low, um, just curious if you can give us a little bit more color on how they're doing. And, you know, essentially, you know, that seems to be an importantly, particularly important, um, uh, you know, population for Givastomig. So essentially the question is, you know, how will the phase 3 really establish that benefit in those low patient expressors rather than, you know, just being driven by that overall result by the high expressors. Thank you.

Srishti - Thank you, Andres. Dr. Klempner handing it over to you for the first question.

Sam - Sure, uh, I'll be part of question. So, um, who will I give the drug to if it was approved? So, I think, you know, in some ways, the market is speaking a bit, you know, the adoption of Zolby and implementation in the US has been dramatically smaller than the predicted patient population just from the prevalence of the biomarkers. And I really do think that that is driven by, uh, the early toxicity and the perception of patients. It's just unlucky for them that, the very high rates of nausea actually come with vomiting during the infusion, so it's, it is unfortunately a big turnoff for patients to want to come back. And as Pill alluded to, I think, while Givastomig certainly has a known toxicity profile and it can impact patients, the timing is a big deal because if you have a patient who's been on therapy for 6 weeks, 3 months, and they've had 2 scans, and they know that their tumor is shrinking, as most patients have, they are very incentivized and motivated to ride out and um, and manage actively any side effects. And that just doesn't happen with Zolby. So I think, I suspect Lucerna will be a positive phase 3 trial in the PDL-1 positive, Claudin high population that they're targeting. Even if that is the case, if Givastomig were also a positive phase 3 trial, I think that it would cannibalize a large portion of the Zolby market. Um, and I've, I've participated in the phase 3 Zolby trials, participated in the ADD, you know, (inaudible) studies, uh, and those ADCs will may come to the first line. I think they're problematic, uh, to combine with chemotherapy in first line and asking an ADC to completely replace, uh, (inaudible) is is still a relatively high bar. This was my comment about sort of a modular features of having 3 drugs and a standard backbone chemo that everybody's comfortable with. So, short answer, I think it would claim most of the frontline patients because the prevalence of Claudin one plus and 1% are more is like 80% of every patients that walk in the door. Your question about, you know, splitting the data by Claudin levels and PDL-1 levels. I mean, as you know, the numbers are a little bit limited. There is data from the 71 patients presented at ESMO, looking at, you know, Claudin above 75 and 1 to 74. Um, but it is limited by by small numbers and some overlap, which perhaps is encouraging that there doesn't appear to be a big difference there. The other thing is that there's actually not that many PDL-1 negative patients in my experience. Um, About 15, 20% of gastric cancer. So it's always a hard subgroup to pull apart. Um, but I

don't think that there's any suggestion so far that says there's a clear difference in activity or there's a clear population that is driving the benefit. Ultimately, that could be true in the setting of phase 3, and there's always some patients that tend to do better, but it's not always limited to biomarker, you know, sometimes GE Junction does better than worse than gastric in many of our data sets, and some of these are not clear biology or whether it's other features that tend to co-migrate with those anatomic restrictions. Short answer, hard to answer, hard to give you a clear answer on a subgroup that's driving the benefit, but, you know, a phase 3 trial would have the numbers to give a little bit more confidence around point estimates for some of those subgroups.

Srishti – Phil, do you have anything to add on?

Phil - Just very, very, two quick add-ons, to address. The first is that, uh, 55% of our patients, uh, at 8 milligrams per kilogram, had peritoneal metastasis, a notoriously difficult group of uh, patients to, to manage. And so I think that's an important prism to also look through our current data. And finally, we do recognize those double lows, if you will, even though they're very rare to Sam's point. Um, low for PDL-1, low for Claudin, and, uh, we are, we have a cohort in our ongoing phase one, combining Giva with chemo alone, with no checkpoint inhibitor because a checkpoint inhibitor is not indicated in that, uh, group of patients. And we're seeing very promising early data. So we hope to, again, as a lifecycle management, we hope to be able to move into a PDL-1 negative group as well.

Srishti - Thanks, Bill. Tara, are there other questions?

Tara - Yes, so we have one more from Daina Graybosch at Leerink, Daina you can go ahead.

Daina - Yeah, thanks for another follow-up. I wonder if you could just give us some more context on the upcoming registration trials, sort of where you are in finalizing that protocol with FDA and global regulators and when you expect to begin to study.

Srishti - Thanks, Phil, do you want to jump in on some of the agreed upon points with the FDA so far?
Phil - Sure. So, uh, we we've had several very productive meetings with the FDA. We've got alignment on key portions of the design. We've stated publicly. We have two paths for accelerated approval, for ORRR and PFS. It's clear that the FDA wants overall survival as an endpoint that will be required for full approval. Again, we've gotten full endorsement of our regional distribution, the statistical details of the study. So we're very encouraged by that. Uh, and we're in the process now of finalizing, uh, some some final features, uh, to really ensure uh, the studies built for success.

Srishti - So yeah, today's focus data was really on the data set. We're finalizing the execution plan, based on where we have feedback from the FDA, and we'll update on the trial start as soon as possible. But as Phil says, given Giva's long-term clinical commercial value, we want to make sure that we design an execution plan that maximizes its ability to get to patients. So we look forward to updating on the timeline. Tara, I think if that covers live questions, were there any questions that came in via the platform?

Tara - Nope, that's all we have time for, so I'll turn it back to you for some closing remarks.

Srishti - Perfect. Thank you so much. Thank you, Phil, and thank you, Sam. Also, thank you everyone for joining both in the evening as well as in the morning. Um, If there's one thing I hope you take away from today, is that Givastomig has reached an important point in its development. We now have a

substantially more mature clinical data set. We have a greater understanding of the benefit risk profile and the regulatory feedback that we'll need to inform the path forward. So this gives us a very strong clinical development and regulatory foundation to advance Giva into a registrational path forward. We're really excited about what lies ahead for the program and we look forward to keeping you updated on the progress. Thank you again.