Thank you and welcome to the Alkermes plc conference call and webcast to discuss new clinical data and updates from our ongoing ARTISTRY-1 clinical trial of ALKS 4230, our investigational agent in oncology. These data are being presented as a mini oral presentation at the European Society for Medical Oncology 2020 virtual meeting.

Please note that during today’s call we will reference slides that are available on the webcast. If you have not done so already, please go to the Investors section of our website, Alkermes.com, to access the webcast player. A PDF of the slides will be made available on our website following the conclusion of this call.
During this presentation, we will be making forward-looking statements based on our current expectations relating to, among other things, the clinical development of ALKS 4230 and the potential therapeutic value of ALKS 4230. These forward-looking statements are neither promises nor guarantees and are subject to a high degree of uncertainty and risk. Please see slide 2 of the Investor Presentation accompanying this webcast, our press release issued this morning, and our most recent annual and quarterly reports filed with the SEC for important risk factors that could cause our actual performance and results to differ materially from those expressed or implied in the forward-looking statements. We undertake no obligation to update or revise the statements provided on this call as a result of new information or future results or developments.

Our prepared remarks today will include recent data from certain ongoing clinical trials in our ARTISTRY development program. This dataset will evolve as patient enrollment continues and as more patient data becomes available, and may not be indicative of future data or the final study results from such ongoing trials or results of future clinical trials.
With me today for the prepared remarks are:

Craig Hopkinson, our Chief Medical Officer and Executive Vice President of Research and Development,

and special guest, Dr. Ulka Vaishampayan, Professor of Internal Medicine, Division of Hematology and Oncology at the University of Michigan, and Lead Investigator of the ARTISTRY-1 clinical trial.
After the prepared remarks, we’ll open the call for Q&A with Dr. Hopkinson. Now, I’d like to turn the call over to Craig.
Thank you, Sandy, and good morning everyone.

I'm delighted to be on the call today to share important new ALKS 4230 data being presented at ESMO with the clinical and investor communities. Efficacy, safety and tolerability data from the ARTISTRY development program have been accumulating in both the monotherapy and combination settings and now provide a clearer picture of ALKS 4230's potential clinical profile and utility.

In addition to the dataset being presented at ESMO as a mini oral presentation, this morning we will also provide an update on our ARTISTRY-1 monotherapy melanoma cohort, including data on an additional response that occurred subsequent to our ESMO data cutoff. As outlined in the press release we issued this morning, with two partial responses already observed in the first 6 evaluable patients in the monotherapy melanoma cohort, we have met the protocol-defined criteria to expand this cohort for further enrollment. We believe this is an important indicator of ALKS 4230's monotherapy activity profile.

This morning, I will begin with an introduction to ALKS 4230 followed by an overview of our clinical development program for ALKS 4230.

Dr. Vaishampayan will then share clinical data from ARTISTRY-1 that were presented at ESMO, after which I will elaborate on the most recent monotherapy response data, and discuss enrollment trends and next steps for the ALKS 4230 development program.
ALKS 4230 owes its roots to Proleukin or Recombinant Human IL-2, one of the first immunotherapies approved for metastatic melanoma and renal cell carcinoma that demonstrated complete and durable anti-tumor responses due to its activation of CD8+ T cells and Natural Killer cells associated with cancer-fighting immune responses.

Broader adoption of the therapy has been limited by its tolerability profile, notably vascular leak syndrome and severe hypotension.
ALKS 4230 was designed to retain the therapeutic benefits of recombinant human IL-2 by selectively activating anti-tumor effector cells while mitigating the IL-2-associated expansion of immunosuppressive regulatory T cells, or T regs, and activation of vascular endothelial cells.

4230 is a stable fusion protein, consisting of IL-2 and the alpha subunit of the high-affinity IL-2 receptor. This design allows ALKS 4230 to preferentially bind to the intermediate affinity IL-2 receptor located on CD8+ T cells and NK cells– shown here on the right. At the same time, it is sterically occluded from binding to the high-affinity receptor, which has been associated with certain undesirable effects of IL-2.

ALKS 4230 is administered as an inherently active drug, does not require any metabolic conversion, and does not degrade to native IL-2.

For a more detailed discussion on 4230’s mechanism, I encourage you to refer to our SITC investor presentation from last year, available on our company website.
Our design concept for 4230 has been validated in preclinical models – which showed the desired pharmacokinetic and pharmacodynamic cell expansion profile, superior anti-tumor efficacy compared to recombinant human IL-2 as monotherapy, and enhanced anti-tumor activity in combination with a variety of immunotherapies including anti-PD-1, anti-CTLA-4 and the angiogenesis inhibitor, lucitanib.

These data support further exploration of ALKS 4230’s potential clinical utility, as monotherapy and in combination with a variety of immunotherapies and other cancer treatments.
The clinical development program for ALKS 4230 is progressing on multiple fronts.
In our ARTISTRY development program, we have two ongoing phase 1/2 studies, as well as a recently-initiated phase 2 study.

ARTISTRY-1, evaluating ALKS 4230 administered intravenously, is the most advanced in enrollment and the subject of today’s data presentation.

ARTISTRY-2 is our subcutaneous dosing study, and is evaluating the safety, tolerability and efficacy of 4230 in both once-weekly and once-every-three-week dosing regimens.

Both of these studies are evaluating ALKS 4230 as a monotherapy and in combination with pembrolizumab.

We also recently announced the initiation of ARTISTRY-3, a phase 2 study to further evaluate the clinical and immunologic activity of ALKS 4230 monotherapy on the tumor microenvironment in advanced solid tumors. Findings from this study may help us answer important mechanistic questions and identify the tumor types for which ALKS 4230 could offer the most clinical benefit.

In addition, our phase 2 ION study, being conducted in collaboration with the Fred Hutchinson Cancer Research Center, is ongoing.
Today we will focus on ARTISTRY-1.

The intent of this study is to evaluate the anti-tumor efficacy, safety, tolerability and pharmacodynamic effects of ALKS 4230, in both monotherapy and combination settings. There are 3 parts to the study.

Data from Part A, the ongoing monotherapy dose-escalation phase, led us to the identification of the 6 µg/kg/day dose as our recommended phase 2 dose, or RP2D, last year.

Part B is a monotherapy dose expansion phase evaluating ALKS 4230 at the RP2D in refractory melanoma and refractory renal cell carcinoma, which are the approved indications for recombinant human IL-2. For both of these tumor types, patients often have limited treatment options following disease progression on PD-1 therapy.

Understanding the single-agent activity of ALKS 4230 is an important aspect of its clinical profile and will help inform the potential therapeutic contributions of 4230 in possible combinations.

Today Dr. Vaishampayan will review ARTISTRY-1 study data as of the data cut of July 24th, 2020, that is being presented at ESMO. As I mentioned earlier, since the time of that data cut, a subsequent partial response was observed in the monotherapy melanoma cohort. With this second partial response in that cohort, we achieved the protocol-defined response criteria for the Simon two-stage design enrollment, triggering expansion of the melanoma cohort to enroll up to a total of 41 patients.

I will speak to this in more detail later on this call.
I will also note that patients in the Part B monotherapy expansion stage are eligible to roll over into the Part C combination stage of the study at the investigators’ discretion, following four cycles in good standing or upon progressive disease.

Turning to Part C of ARTISTRY-1, this part of the study is evaluating two biologically active doses of ALKS 4230 in combination with pembrolizumab in a variety of advanced solid tumor types. The 3 µg/kg dose is being evaluated in PD-1 approved tumor types in both refractory and treatment naïve patients, as well as certain PD-1-unapproved tumor types and a cohort of monotherapy rollover patients. These basket cohorts are designed to provide important signal seeking information and help inform future development strategies. The 6 µg/kg dose of 4230 is also being studied in combination with pembro in dedicated Part C cohorts in melanoma, non-small cell lung cancer and head and neck squamous cell carcinoma.

Anti-tumor response and duration of response assessments are based on RECIST 1.1 criteria and investigator-assessed, immune-related response, or iRECIST criteria. Unless otherwise noted, the safety data for all cohorts and the efficacy data for the monotherapy cohorts are from a data cutoff date of July 24th, while the efficacy data for the combination cohorts are from a data cutoff of August 7th.
As we have advanced through development of ALKS 4230, we have been accumulating evidence supporting our design hypothesis. In ARTISTRY-1, ALKS 4230 has shown:

Dose-dependent, selective expansion of effector cell populations with negligible expansion of T regs.

Monotherapy efficacy activity, with evidence of disease stabilization and partial responses in melanoma, which will be discussed by Dr. Vaishampayan shortly.

We have also seen durable and deepening responses for 4230 in combination with pembro, in both anti-PD1 approved and unapproved tumor types.

In the combination cohorts, we have seen clinical benefit – including stable disease or partial responses – in patients who entered the study with difficult-to-treat, progressive disease. Certain of these patients have remained on treatment for more than 6 months, with some remaining on treatment for more than a year.

And we have seen a clinically manageable safety profile with the most frequently observed treatment-emergent adverse events consistent with anticipated effects of immunotherapy, and no incidents of vascular leak.
Now, to provide an update from our ARTISTRY-1 clinical trial from the ESMO Virtual Congress, I’m pleased to introduce the ARTISTRY-1 lead investigator, Dr. Ulka Vaishampayan.

Dr. Vaishampayan is a professor of internal medicine within the division of hematology/oncology at the University of Michigan. Her research is primarily in translational drug development and early phase clinical trials in cancer with a focus on genitourinary malignancies.

Welcome, Dr. Vaishampayan, and thank you for joining us today.
Thank you, Craig, and good morning everyone.

Today, I will focus on new data from the Part B monotherapy cohort of patients who received the RP2D of 6 µg/kg of ALKS 4230 and the Part C combination cohorts of patients who received the 3 µg/kg dose of ALKS 4230 together with pembrolizumab.
Shown here on slide 15 are the patient baseline characteristics for the data set being presented at ESMO. A total of 15 patients were enrolled in the monotherapy cohorts and 67 patients were enrolled in the 3 µg/kg combination cohorts. At the time of enrollment, all patients had rapidly progressing disease. All of these patients were pretreated, with the majority having received multiple lines of prior therapy.
This slide outlines the safety data observed for these cohorts, as of the July 24th cutoff date, unless otherwise noted.

ALKS 4230 given in combination with pembrolizumab did not demonstrate any additive toxicity to that established with pembrolizumab alone.

The side effect profile across the monotherapy and combination cohorts was generally consistent with what one would expect to see with cytokine therapy, such as fever, chills and low-grade hypotension. Importantly, no signs of vascular leak syndrome—the hallmark toxicity associated with high-dose IL-2—were observed.

In the combination cohorts, two deaths were reported in patients with pancreatic cancer. One death was due to the underlying cancer and assessed as unrelated to treatment with ALKS 4230. The other was due to inanition, or starvation, and assessed as related to both study drugs. No deaths were reported in the Part B monotherapy cohorts.
Turning to efficacy data, I’ll first review the overall response data from the monotherapy expansion cohorts. Efficacy data presented here are as of the cutoff date of July 24, 2020, unless otherwise noted.

In this cohort, 15 patients, 6 with melanoma and 9 with renal cell carcinoma, received the 6 µg/kg dose of ALKS 4230. This swimmer’s plot shows the overall responses and the duration in those patients.

At the time of the data cut, out of the 5 evaluable melanoma patients who had received 1 or more scans, 3 patients had stable disease or better. Among these 3 patients, one had a confirmed partial response, and remained on ALKS 4230 monotherapy as of September 1st, and the other two demonstrated stable disease on at least two consecutive scans and have since rolled over into Part C.

Let’s now take a closer look at the patient who had a confirmed partial response.
This is a case study of a 66-year-old female patient who was diagnosed with metastatic urethral mucosal melanoma in 2017. The patient completed one year of nivolumab in September 2018, followed by one year without any treatment. Her disease recurred in September 2019 and was progressive at the time of her enrollment into ARTISTRY-1 in October 2019.

Within the first 2 cycles of ALKS 4230 monotherapy, this patient experienced stable disease and her tumor began to shrink. She achieved a Partial Response by week 20 of treatment and a deepening of the response was observed through week 39 of treatment. As of her July 27th scan, her tumor had reduced by 39%.

Further, the patient’s serum lactate dehydrogenase, or LDH, a known marker for treatment response in melanoma, normalized at Week 5, and has remained within the normal range.

This patient experienced grade 3 transient hypotension, which was managed with IV fluids.

As of September 1st, this patient remained on ALKS 4230 monotherapy for more than 11 months.

I will also pause here to point out that this patient experienced iritis, an inflammation of the eye, which is an immune-related SAE. Immune-related adverse events like this are consistent with the anticipated effects of cytokine administration and may be a leading indicator of ALKS 4230’s activity.

Taking a step back, the early responses observed with ALKS 4230 as a monotherapy treatment are an important element of its potential clinical utility.
Now we will shift our focus to the combination cohorts of ARTISTRY-1. Data presented from Part C are as of the cutoff date of August 7th, 2020, unless otherwise noted.

This swimmer's plot shown here on slide 19 shows all 67 patients, representing more than 10 different tumor types, who received ALKS 4230 3 µg/kg in combination with pembrolizumab. Of the 67 patients, 52 had evaluable scans as of the data cut.

Responses were observed in both the PD-1 approved treatment naïve cohort, shown here in red, and the PD-1 unapproved cohort, shown here in bright green. Patients in these cohorts were heavily pretreated and had progressive disease upon entry to the study. Overall responses seen as of the cutoff date are indicated on this slide. Responses were seen in multiple tumor types, and I will speak to some of these cases in greater detail.

First, let's look at the patients from the PD-1 unapproved cohort.
Here is a waterfall plot on slide 20 of the best response by target lesion for the 35 evaluable patients from the PD-1 unapproved cohort. The area between the two gray horizontal lines indicates stable disease per RECIST criteria. As evidenced by the arrows, as of the data cutoff date of August 7th, 2020, eight patients continued on therapy with maturing data.
Now, let’s focus specifically on the ovarian cancer patients from the PD-1 unapproved group. This swimmer’s plot on slide 21 shows the 14 ovarian cancer patients enrolled in this cohort, 13 of whom were evaluable at the time of the data cut. These patients entered the study with progressive ovarian cancer and were generally heavily pretreated.

Of these 13 evaluable patients, 9 patients showed stable disease on their first scan, as indicated by the orange boxes.
Among these patients, six received a second scan by the data cutoff and five of these six patients experienced stable disease or better during the course of the treatment with ALKS 4230 and pembrolizumab, including one patient who demonstrated a tumor burden reduction of 76%. All 5 of these patients received prior platinum-based chemotherapy and were assessed by the investigators as platinum-resistant. Some had also received prior bevacizumab and/or a PARP inhibitor. Of these five patients:

- 3 patients – noted as patients OC 1, OC 2 and OC 3 on this slide – experienced clinical responses, including one confirmed complete response, one confirmed partial response, and one unconfirmed partial response.
- The other 2 patients— noted here as patients OC 4 and OC 5—achieved stable disease and had tumor shrinkage of 22% and 18%, respectively, as of the August 7th data cut, and had remained on therapy for more than 14 weeks and 21 weeks, respectively.
- As of August 7th, 4 of these 5 platinum-resistant ovarian cancer patients continued on therapy.

Next, I will go into greater detail on two of these patients, marked as OC1 and OC2 on this slide.
Shown here on slide 23 are details for a 48-year-old female patient who enrolled in the study with a diagnosis of high-grade, progressive ovarian cancer, which was BRCA wild-type. She had received 5 prior lines of therapy.

This patient initiated ALKS 4230 in combination with pembro in January 2019. At cycle 4, she demonstrated a partial response with a 60% decrease in target lesions, along with a complete normalization of her CA-125 levels, which is an established prognostic indicator in ovarian cancer.

At cycle 10, the patient had a complete response with a 70% decrease in target lesions, which was confirmed at cycle 12.

Throughout her treatment period, the patient tolerated therapy well and did not experience any serious adverse events.

As of August 7th, the patient had a sustained complete response and remained on study.
The next case study is an 83-year-old female patient with ovarian cancer, which was BRCA negative. She had received 2 prior lines of therapy, and had progressive disease when she entered ARTISTRY-1 in February 2020.

At cycle 2 of treatment, the patient demonstrated stable disease with a 6% decrease in target lesions. Her tumor continued to shrink with treatment, and at cycle 8, she had a 76% decrease in target lesions.

As of the August 7th data cutoff, the patient had not experienced any serious adverse events and remained on therapy.
As we think about the treatment landscape for ovarian cancer, the standard of care for first-line treatment is multi-modality, involving both surgery, and platinum-based chemotherapy, with or without bevacizumab and a PARP inhibitor as maintenance therapy for patients who are BRCA positive. It is important to note here that there are no anti-PD-1 treatments approved for ovarian cancer.

Following first-line platinum-based chemotherapy, many patients may become platinum resistant, and their disease often progresses within 6 months after completion of therapy.

Unfortunately, there are limited treatment options for patients with platinum-resistant ovarian cancer. Non-platinum chemotherapy has low response rates and is associated with short progression-free survival. The median overall survival for platinum-resistant ovarian cancer is less than 12 months.

Given the high unmet need for this patient population, I am really encouraged by the responses seen so far in ovarian cancer with ALKS 4230 in combination with pembrolizumab.
Let’s take a closer look now at the responses we have seen in other tumor types. Clinical responses associated with significant tumor burden reduction were observed in 4 additional patients in Part C. This includes one patient with triple-negative breast cancer, one patient with pancreatic cancer, and two patients with esophageal cancer.

Also, as shown by the orange boxes on slide 26, a number of these patients, all of whom entered the trial with progressive disease, experienced prolonged stable disease for two or more consecutive scans while on treatment with ALKS 4230 in combination with pembrolizumab.

I will now discuss the two esophageal responses.
This case is a 54-year-old female patient who had an adenocarcinoma of the gastroesophageal junction. This tumor type is anti-PD1 approved, however, this patient had no prior checkpoint inhibitor therapy. She had received four prior lines of therapy, before entering the study in January 2020.

At cycle 6, she had a confirmed partial response with a 43% decrease in target lesions. At cycle 8, her response deepened to a 48% decrease.

The patient experienced grade 2 treatment-related joint pain, which was managed with medication. As of August 7\textsuperscript{th}, the patient remained on study.
The next case is an 82-year-old male patient with esophageal squamous cell carcinoma. Unlike the previous esophageal patient, this patient's tumor type is not approved for treatment with anti-PD1 therapies.

He initiated ALKS 4230 combination treatment with pembro in March 2020. At cycle 4, his target lesions had decreased by 23%, and at cycle 6, he had a partial response awaiting confirmation with a 36% decrease in target lesions. This patient experienced transient grade 3 treatment-related AEs, including neutropenia and lymphopenia, and no serious AEs.

As of August 7th, the patient remained on study.
The responses we have seen with ALKS 4230 in combination with pembrolizumab in these non-ovarian tumor types are also encouraging, with reductions in target lesions of up to 66% and patients continuing on ALKS 4230 therapy for up to 74 weeks as of the August 7th cutoff. These data support further clinical evaluation of ALKS 4230 in combination with pembrolizumab.

Of note, the 66% reduction in tumor size was observed in a patient with triple-negative breast cancer. This patient’s case was presented last year at SITC and she has continued on treatment for more than a year and a half with a sustained and deepening response.

It is important to note that these patients, except for the one pancreatic patient who unfortunately passed away, are doing well on treatment and remain in the study.
In summary, these data provide encouraging evidence of antitumor efficacy for ALKS 4230 as both a monotherapy and in combination with pembro, with a safety profile generally consistent with the anticipated effects of cytokine therapy, but with no reports of vascular leak syndrome, which is otherwise a hallmark toxicity of high dose IL-2 treatment.

The most frequently observed adverse events regardless of causality in both the monotherapy and combination cohorts were transient fever and chills.

In terms of efficacy, we saw durable and deepening responses to ALKS 4230 as a monotherapy in melanoma and in combination with pembrolizumab in a diverse set of difficult-to-treat tumor types.

The data presented here provide new insights into the potential clinical value of ALKS 4230 as a novel treatment option in oncology and I believe future research for its use as monotherapy and in combination with other therapies is certainly warranted.

With that, I will turn it back over to Dr. Hopkinson.
Thank you, Dr. Vaishampayan for your review of the data today, and for your participation in the ARTISTRY-1 study.

In addition to the review you just heard on ARTISTRY-1, as I mentioned at the start of the call, since the date of the data cut for the ESMO mini-oral presentation, an additional melanoma patient in the monotherapy cohort achieved a partial response, awaiting confirmation.
This 74-year old male patient with sino-nasal mucosal melanoma had prior nivolumab treatment and had progressive disease at the time of enrollment into the ARTISTRY-1 study in June 2020.

At cycle 4 of monotherapy treatment with ALKS 4230, this patient demonstrated a 39% tumor shrinkage. As of September 1st, he remained on treatment.

Interestingly, both partial responses observed to date with ALKS 4230 monotherapy have been in patients with mucosal melanomas who had received prior PD-1 therapy. Mucosal melanoma is considered a particularly aggressive form of melanoma and is often not discovered until an advanced stage. Treatment options for this subtype of melanoma are very limited.
The recruitment of subjects in the monotherapy stage of ARTISTRY-1 follows a Simon two-stage study design, commonly used for phase 2 studies in oncology for practical and ethical considerations. The first stage was designed to enroll up to 21 patients in each of the melanoma and renal cell carcinoma cohorts. If protocol-defined response criteria are achieved in this first stage of 21 patients, the applicable cohort is expanded to recruit up to an additional 20 patients.

With two partial responses observed among the first 6 evaluable patients in the monotherapy melanoma cohort, the protocol-defined response criteria for expansion of this cohort were achieved, and up to an additional 20 patients will be enrolled in this cohort for a total of up to 41 patients.

These data are consistent with our design hypothesis for ALKS 4230 and the known monotherapy activity of recombinant human IL-2 in melanoma. We are encouraged by this evidence of single-agent anti-tumor efficacy for ALKS 4230 and look forward to enrolling more patients to further evaluate ALKS 4230 as monotherapy.
Across the ARTISTRY development program, overall patient enrollment has been accelerating despite certain COVID-19-related disruptions. Since January, we have enrolled 103 patients across the program, doubling our total number of enrolled patients. We believe these enrollment trends are an important indicator of investigator enthusiasm around the program.

In ARTISTRY-1, as of September 9th, 2020 – we had enrolled 38 patients in Part A, 26 patients in Part B and 91 patients in Part C, including full enrollment of the Part C PD-1 unapproved cohort. Following a delay related to COVID, our ex-U.S. sites have recently re-opened and are already contributing to enrollment, particularly in the Part B monotherapy cohorts.
One of the most distinctive features of the ALKS 4230 clinical development program is the potential for subcutaneous dosing. ARTISTRY-2, our subcutaneous study, is ongoing in its dose escalation phase for both the once-weekly and once-every-three-week dosing options. As of September 9th, 2020, we had enrolled a total of 43 patients in the study. We believe that we are narrowing in on the recommended phase 2 dose for subQ and hope to share updates from that study later this year.

Taking a step back, we have made significant progress in this development program, both in terms of new data accumulation and patient recruitment. I am particularly gratified that the responses we are seeing are occurring in patients that have failed multiple prior lines of therapy and may have few remaining potential treatment options. Each response is meaningful and I would like to express my sincere appreciation to the patients and investigators that have participated in the development program to date. We look forward to updating you on our progress as the program continues.
Thank you, Craig and Dr. Vaishampayan. We will now open the call for questions. Operator?