

ALKS 4230 SITC Conference Call Script

November 8, 2019



ALKS 4230: An Investigational Selective IL-2 Fusion Protein

2019 Society for Immunotherapy of Cancer (SITC) Meeting
Investor Presentation

November 8, 2019



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Sandy Coombs

Welcome to the Alkermes plc webcast to discuss ALKS 4230, our lead investigational agent in oncology. I'm Sandy Coombs, Vice President of Investor Relations at Alkermes. With me today are Craig Hopkinson, our Chief Medical Officer and Senior Vice President of Medicines Development and Medical Affairs and Mark Namchuk, our Senior Vice President of Research, Pharmaceutical and Non-Clinical Development.

Please note that during today's webcast we will reference slides that are available on the Investors section of the Alkermes website.

Slide 2

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Forward-Looking Statements

Certain statements set forth in this presentation constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: achievement of the design rationale for ALKS 4230; the potential therapeutic benefit of ALKS 4230; and clinical development plans for ALKS 4230, including the ARTISTRY-1 and ARTISTRY-2 clinical studies and the collaboration with the Fred Hutchinson Cancer Research Center. The company cautions that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks, assumptions and uncertainties. These risks, assumptions and uncertainties include, among others: the preliminary ALKS 4230 efficacy and safety data presented as part of the SITC Investor Presentation may change as more patient data becomes available and may not be predictive of final results of such clinical studies, results of future clinical studies or real-world results; ARTISTRY-1 and ARTISTRY-2 clinical study data may be interpreted by the U.S. Food and Drug Administration ("FDA") in different ways than the company interprets it; the FDA may not agree with the company's regulatory approval strategies, including its clinical study designs and conduct or the sufficiency of the results thereof to support approval; clinical development activities may not be completed on time or at all; the results of the company's clinical development activities may not be positive; regulatory submissions may not occur or be submitted in a timely manner; the FDA may make adverse decisions regarding the company's products; and those risks, assumptions and uncertainties described under the heading "Risk Factors" in the company's most recent Annual Report on Form 10-K and in subsequent filings made by the company with the U.S. Securities and Exchange Commission ("SEC"), which are available on the SEC's website at www.sec.gov and on the company's website at www.alkermes.com in the "Investors—SEC filings" section. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation.



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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. The risk factors included in slide 2 of the Investor Presentation accompanying this webcast, in our press release issued this morning, and in our SEC filings 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 preliminary data from certain clinical trials. These data may change as patient enrollment continues and as more patient data becomes available, and may not be indicative of final data from such trials or results of future clinical trials.

Slide 3

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Agenda

- **Introduction to ALKS 4230**
- **ALKS 4230 Non-Clinical Data Overview**
- **ALKS 4230 Clinical Development Program and Preliminary Results**
- **Summary and Next Steps**



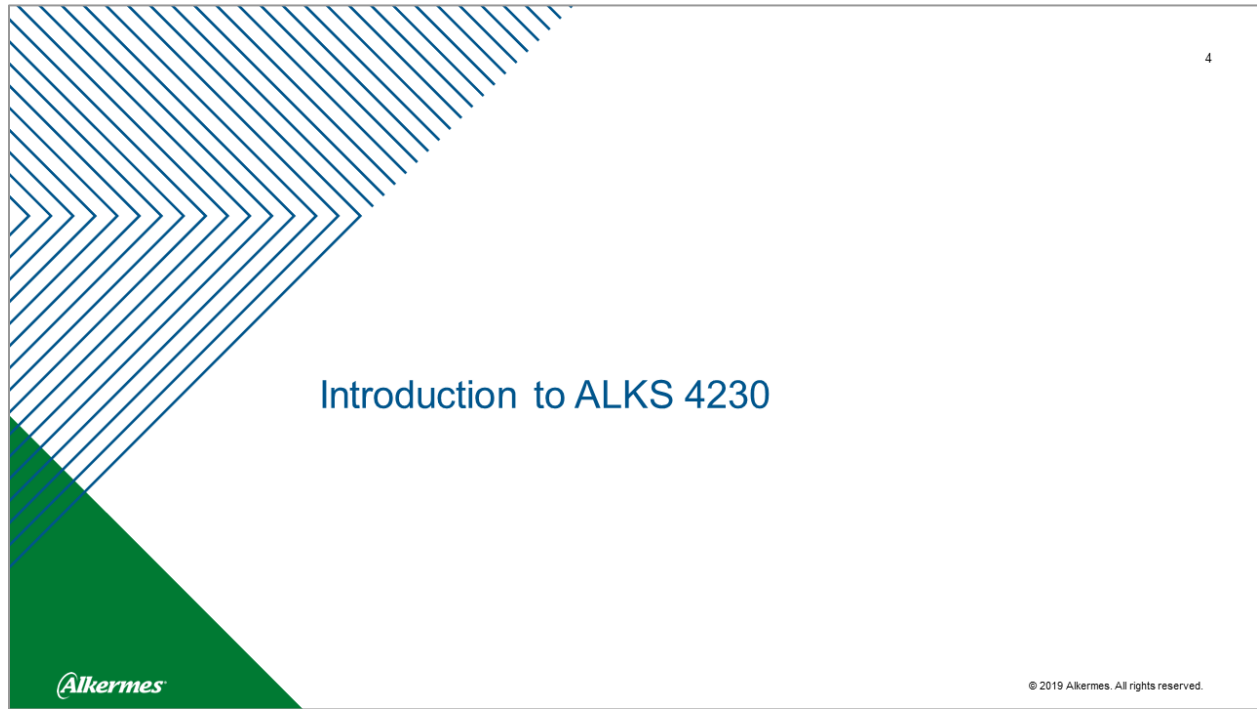
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Mark Namchuk will start with a brief overview of the IL-2 mechanism, followed by an introduction to ALKS 4230, and a brief discussion of certain ALKS 4230 non-clinical data.

Craig Hopkinson will then discuss preliminary clinical data emerging from our ARTISTRY clinical studies and provide an update on ongoing programs.

Now, I'd like to turn the call over to Dr. Mark Namchuk.

Slide 4



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Introduction to ALKS 4230

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Thank you, Sandy and good morning everyone. I'm going to spend the next 10 to 15 minutes introducing you to ALKS 4230. I will discuss both the molecular biology and the design concept that led to the genesis of 4230 and also some of the underlying nonclinical data that encouraged its advancement into clinical development. My colleague, Craig Hopkinson, will then discuss some of the preliminary clinical data from the ARTISTRY program.

IL-2 Therapy Has Proven Anti-Tumor Efficacy, but is Associated With Serious Toxicities

- Recombinant human IL-2 (rhIL-2), known as PROLEUKIN® (aldesleukin), is approved for metastatic renal cell carcinoma and metastatic melanoma based on complete and durable remissions
- IL-2 potentially activates the high-affinity IL-2 receptor found on vascular endothelial cells, resulting in poor tolerability and toxicities
 - Black box warning for vascular leak syndrome, pulmonary edema, hypotension, heart toxicities and more
- Toxicity profile of IL-2 significantly limits its broad use, despite its established anti-tumor efficacy

PROLEUKIN® (aldesleukin)
for injection, for intravenous infusion
Rx Only

WARNINGS

Therapy with Proleukin® (aldesleukin) should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with a normal thallium stress test and a normal pulmonary function test who have a history of cardiac or pulmonary disease.

Proleukin should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

Proleukin administration has been associated with **capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.**

Proleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of Proleukin therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

Proleukin administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

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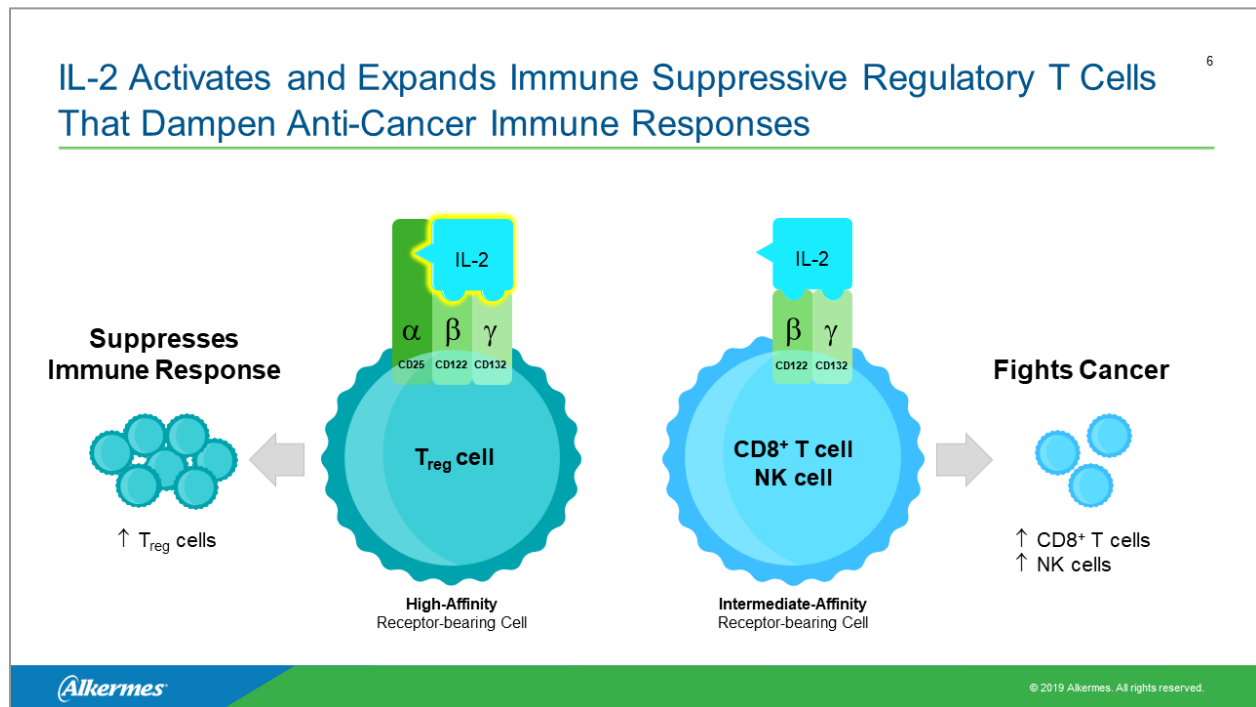
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ALKS 4230 owes its roots to one of the first immunotherapies that delivered durable responses, namely Proleukin or Recombinant Human IL-2, which is an approved treatment for metastatic melanoma and renal cell carcinoma.

Broader adoption of the therapy has been precluded by its side effect profile, notably vascular leak syndrome and severe hypotension, which are, in part, driven by IL-2's activation of vascular endothelial cells.

Slide 6

IL-2 Activates and Expands Immune Suppressive Regulatory T Cells That Dampen Anti-Cancer Immune Responses



In addition to its toxicity profile, another limitation of IL-2 is its expansion of immune suppressive regulatory T cells, which I will refer to going forward as T regs.

As shown here in illustration, there are two different types of IL-2 receptor complexes: referred to as the intermediate-affinity and high-affinity receptors.

The intermediate-affinity receptor is a dimeric receptor, composed of beta and gamma subunits, and is commonly expressed on CD8+ T cells and Natural Killer, or NK, cells.

The high-affinity IL-2 receptor is trimeric, with the alpha subunit located alongside the beta and gamma components. It is expressed on immunosuppressive T regs and vascular endothelial cells.

When IL-2 binds to the intermediate-affinity receptor, shown here on the right, the binding initiates a cascade of intracellular signaling that leads to the activation and proliferation of CD8+ T cells and NK cells, which are associated with cancer-fighting immune responses.

However, IL-2 also activates and expands T regs by binding to the high-affinity receptor, as shown here on the left. These cells act as a brake on the immune system and dampen immune responses, thereby limiting the anti-cancer effect of CD8+ T cells and NK cells.

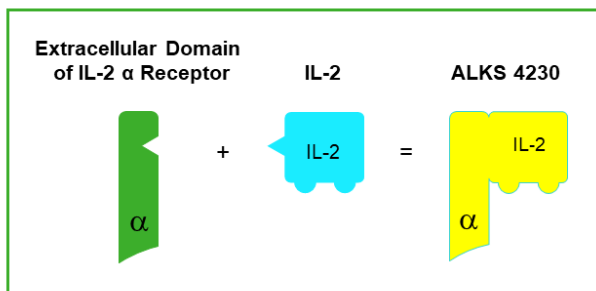
In order to optimize the anti-tumor effects of IL-2 signaling, one would want to selectively expand the tumor-killing effector cell population of CD8s and NKs, while avoiding the activation of immunosuppressive T regs.

Slide 7

Our Goal: Design a Molecule That is Stable and Inherently Selective for the Intermediate-Affinity IL-2 Receptor

ALKS 4230 Design Intention:

- Selectively expand cancer-fighting CD8⁺ T cells and NK cells to potentially improve anti-tumor efficacy
- Prevent IL-2-derived expansion of T_{reg} cells to minimize inhibition of immune response
- Mitigate certain side effects of IL-2, including vascular leak syndrome



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Our goal for the ALKS 4230 program was to create a molecule that exclusively binds to the intermediate-affinity receptor and avoids binding to and activating the high affinity-receptor – thereby selectively expanding effector cell populations while *preventing* the IL-2-derived expansion of Tregs.

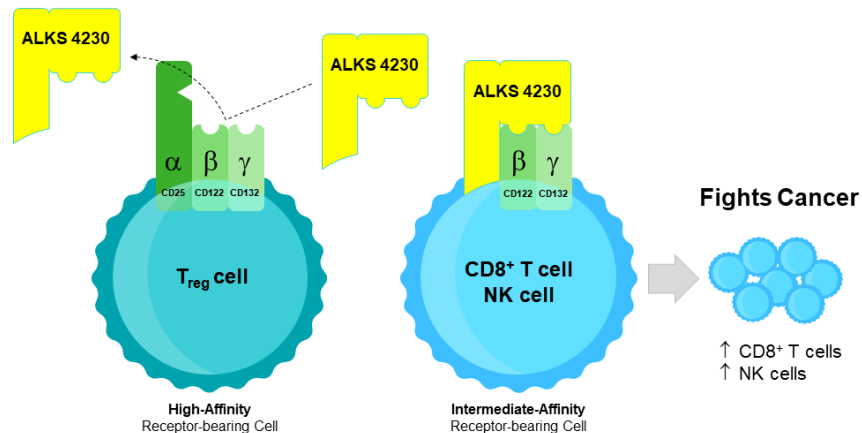
Our design hypothesis was that this profile could lead to improved anti-tumor efficacy by minimizing the immune suppressive impact of T reg expansion and also mitigate the known side effects of IL-2, particularly around vascular leak.

In designing 4230, our approach was to create a molecule that could take advantage of the *natural differences* between the two receptors. To do so, we leveraged our proprietary fusion technology and protein engineering capabilities to fuse IL-2 to the IL-2 alpha receptor subunit. The resulting molecule is a stable fusion protein inherently selective for the intermediate-affinity IL-2 receptor that does not require metabolic activation and never metabolizes to become native IL-2.

Slide 8

ALKS 4230 is 'Sterically Occluded' From Binding to the High-Affinity Receptor

8

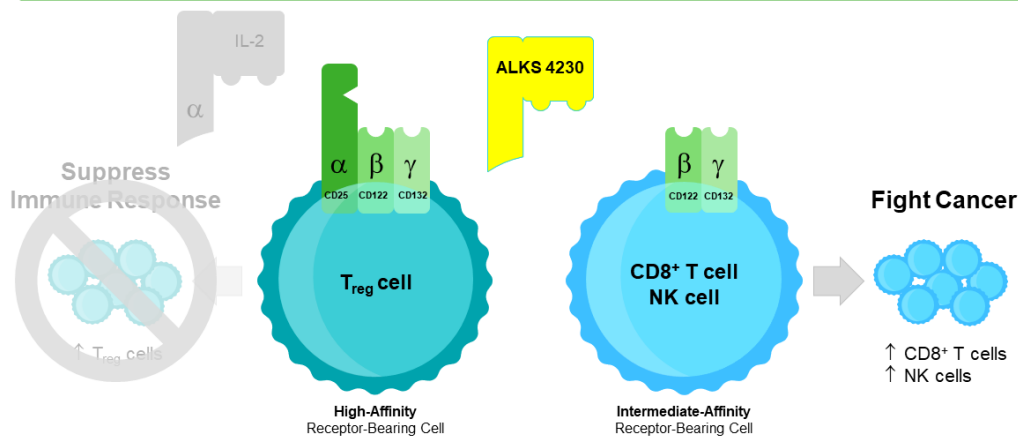


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ALKS 4230 is 'Sterically Occluded' From Binding to the High-Affinity Receptor

8



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So, going back to our illustrated depiction of IL-2 receptor binding...
 ...the fusion of IL-2 with the alpha subunit continues to allow binding of ALKS 4230 to the intermediate-affinity receptor, driving the expansion of CD8⁺ T cells and NK cells, that are immunostimulatory.

However, ALKS 4230 is blocked from binding to the high-affinity receptor, due to its size and shape, resulting from the addition of the fused alpha subunit. This phenomenon is known as steric hindrance or steric occlusion. By blocking 4230's ability to bind to the high-affinity receptor -- by design -- we limit the expansion of Tregs.

Slide 9



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ALKS 4230: Design of a Stable Fusion Protein

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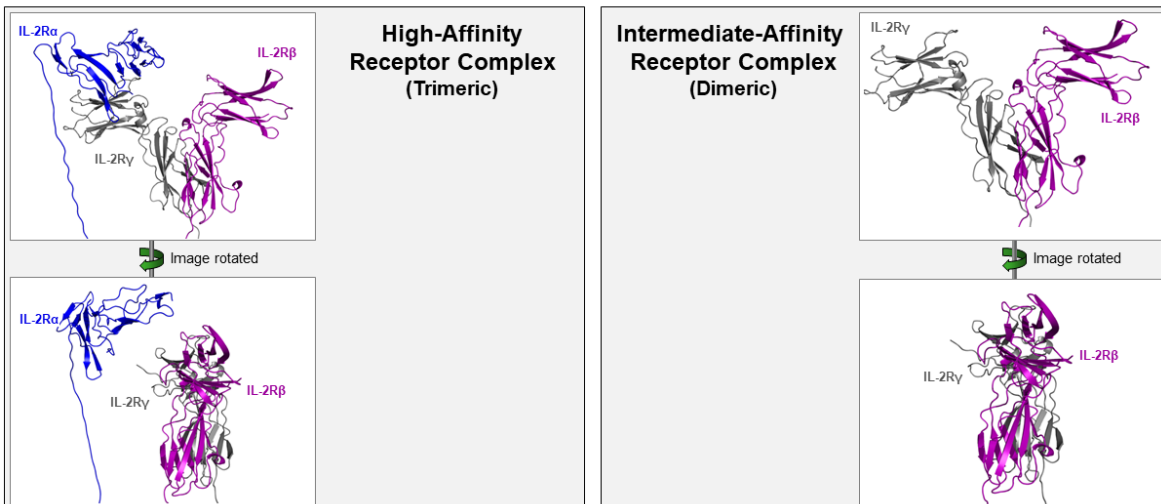
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Let's take a look at this concept in high-resolution crystal graphic structures.

Slide 10

10

IL-2 Binds to Both IL-2 Receptor Complexes



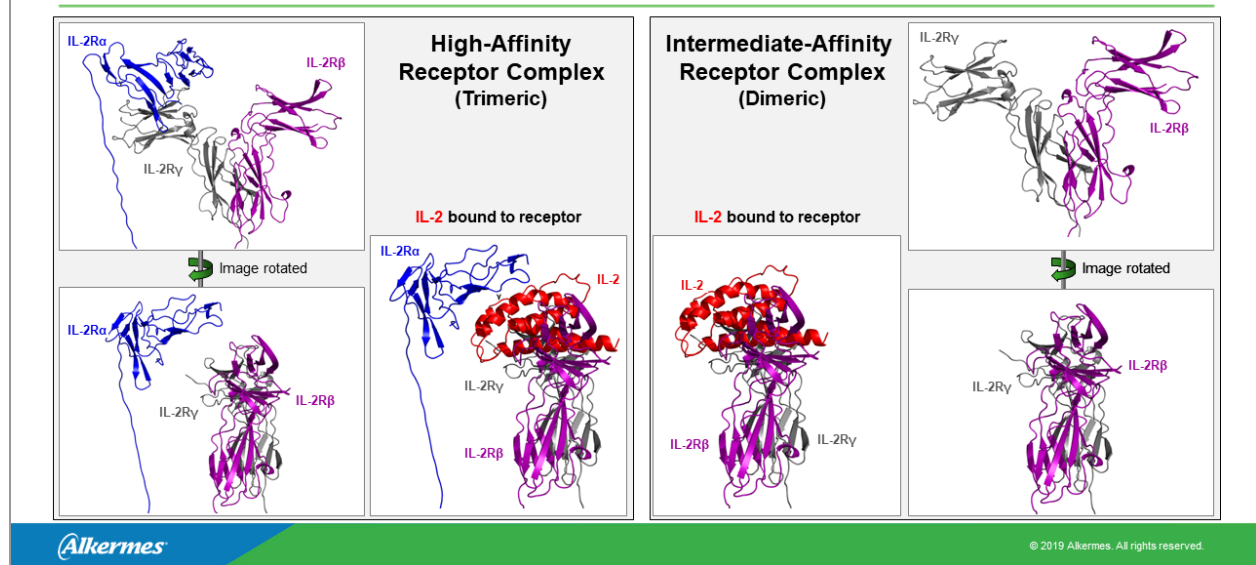
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Shown here on slide 10 are ribbon diagrams of the x-ray crystal structures of the high-affinity receptor complex on the left hand side of the slide, and the intermediate-affinity receptor complex on the right. The IL-2 alpha receptor subunit is shown in blue, the beta subunit in magenta and the gamma subunit in gray.

The images on the bottom of the slide depict the same receptor complexes, rotated slightly – which allows us to see the cleft created by the subunits where IL-2 will eventually bind.

IL-2 Binds to Both IL-2 Receptor Complexes



Let's take a look now at how IL-2, shown in red, interacts with both receptor complexes.

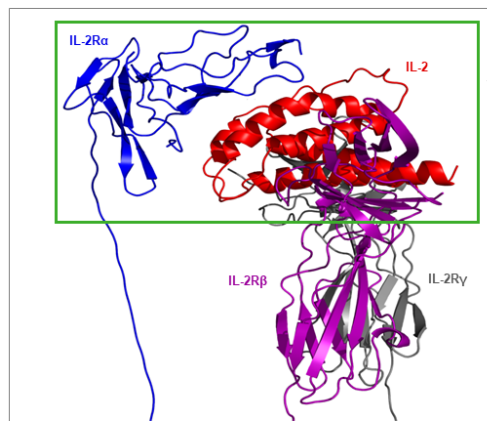
Looking first to the left side of the slide, at the high-affinity receptor complex...you can see that IL-2 fits nicely into the cleft formed between the blue alpha subunit and the beta-gamma subunits. The interaction between the surface of IL-2 with each of the 3 subunits, like a key fitting tightly into a lock, drives the increased affinity of IL-2 for the high-affinity receptor.

On the right-hand side of the slide, you can see IL-2 binds to the beta-gamma subunits, but without the blue alpha subunit in place, the cleft that we saw in the high-affinity receptor is not present in the intermediate-affinity receptor.

Slide 12

Alkermes' PICASSO™ Technology Enables Facile Fusion of IL-2 With the Extracellular Domain of IL-2 Receptor α

12



IL-2 bound to
high-affinity receptor

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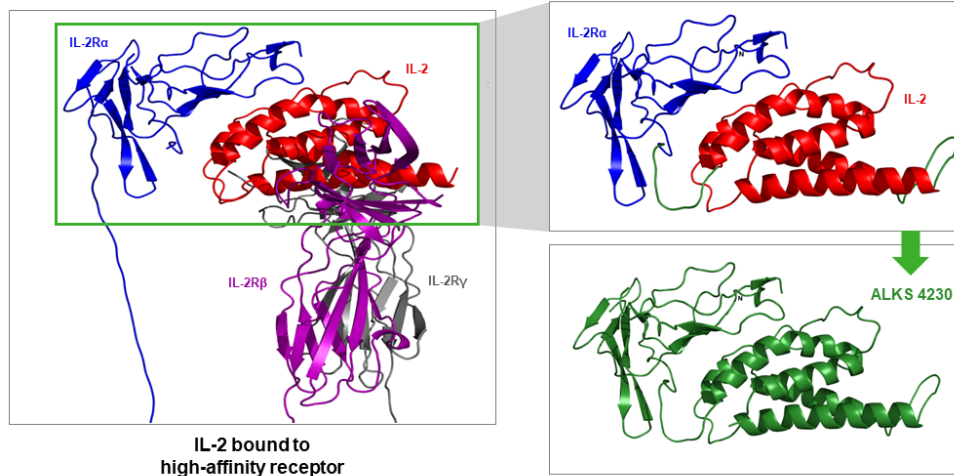
Now I'll spend a moment on how we designed ALKS 4230. Shown here is a closer look at the same image as what's on the previous slide, focusing on the interaction between IL-2 with its high-affinity alpha receptor subunit.

Going back to the idea of taking our lessons from nature – our goal was to design a construct that would allow us to take these 2 proteins, namely the alpha receptor subunit and IL-2, and fuse them to create a single stable polypeptide.

Slide 13

Alkermes' PICASSO™ Technology Enables Facile Fusion of IL-2 With the Extracellular Domain of IL-2 Receptor α

13



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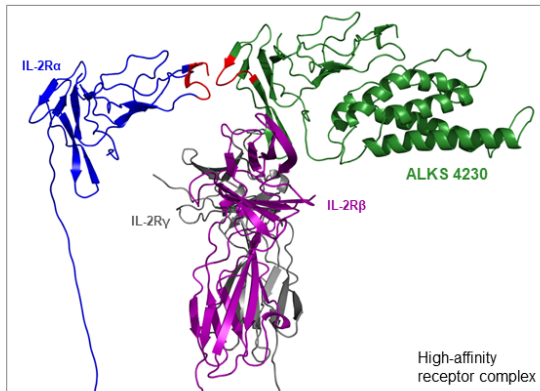
To do so, we utilized our proprietary PICASSO technology to enable circular permutation. We cleaved IL-2 to create a new opening with a C-terminus that is more proximal with the N-terminus of the alpha receptor subunit.

Looking now at the upper right image of the slide, we then inserted two small linker peptides, *shown in green*, allowing us to fuse and create a single contiguous polypeptide that retains the 3-dimensional structural characteristics of IL-2 and the alpha subunit. Shown in the bottom right image, we have the newly formed ALKS 4230 molecule.

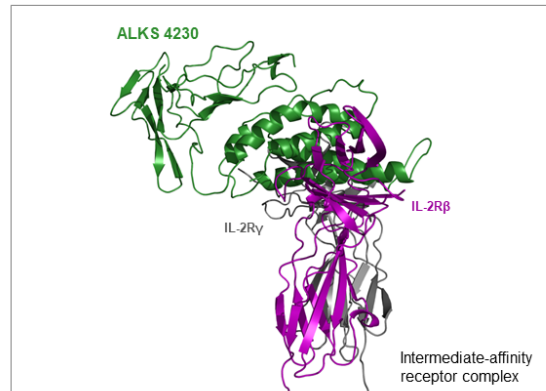
Slide 14

ALKS 4230 is Designed to Exclusively Bind to the Intermediate-Affinity IL-2 Receptor

14



ALKS 4230 is sterically hindered from binding to the high-affinity receptor



ALKS 4230 binds to the intermediate-affinity receptor

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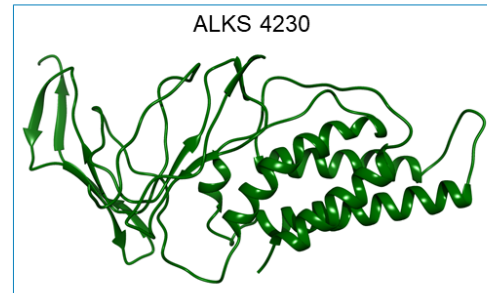
Now, taking the ribbon structure of ALKS 4230, shown in green on slide 14...

On the right hand side, you can see that ALKS 4230 has maintained its ability to bind to the intermediate-affinity receptor.

However, on the left-hand side, due to its size and shape, ALKS 4230 is sterically precluded from binding to the high-affinity receptor.

ALKS 4230: A Selective IL-2 Fusion Protein


- ALKS 4230 is an inherently selective, single polypeptide comprised of IL-2 and the high-affinity IL-2 alpha receptor chain
 - Immediately active upon systemic entry; does not require metabolic activation
- Designed to exclusively bind to the intermediate-affinity IL-2 receptor, thereby selectively expanding tumor-killing CD8⁺ T and NK cells
- ALKS 4230 is sterically occluded from binding to the high-affinity IL-2 receptor
- Designed to have negligible effects on T_{reg} expansion and activation of vascular endothelial cells



So to summarize, as a design concept, we wanted to build something that would be inherently selective for the intermediate-affinity receptor – thereby selectively expanding CD8⁺ and NK cells, with negligible effects on regulatory T cells, and potentially decreasing the side effects that limited the use of IL-2, such as vascular leak.

The resulting molecule, ALKS 4230, is a stable fusion protein that is immediately active upon systemic entry and never metabolizes to become native IL-2.

Slide 16



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ALKS 4230: Non-Clinical Data Overview

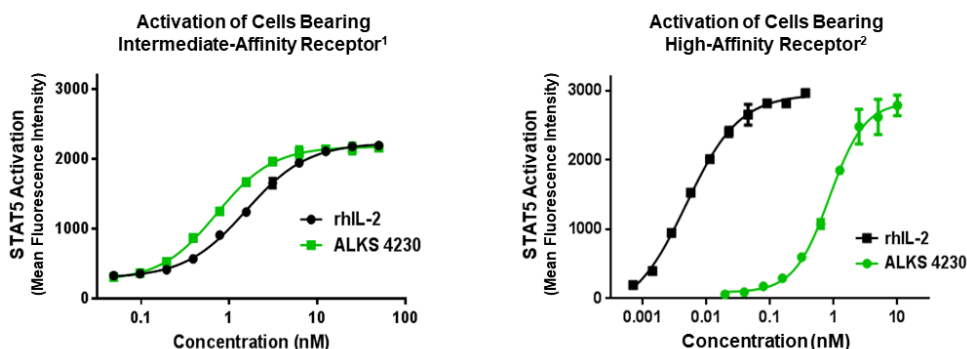
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Now I'll show you some non-clinical data that supports our design rationale and encouraged us to move ALKS 4230 into the clinic.

ALKS 4230 Selectively Signaled Through the Intermediate-Affinity IL-2 Receptor Complex

17



ALKS 4230 potency is shifted ~400-fold towards the intermediate-affinity receptor vs. rhIL-2

1. pSTAT5 Activation on Human HH Cells
2. pSTAT5 Activation on Human NK-92 Cell Line
rhIL-2: Recombinant human IL-2

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Here are in vitro data collected from human cell lines expressing the high-affinity and intermediate-affinity IL-2 receptors.

In this assay, we looked at STAT5, the first signal activated downstream of receptor engagement. The black line shows recombinant human IL-2 and the green line shows ALKS 4230.

In the left-hand graph, you can see that ALKS 4230 is nominally more potent than Recombinant Human IL-2 signaling through the intermediate-affinity receptor.

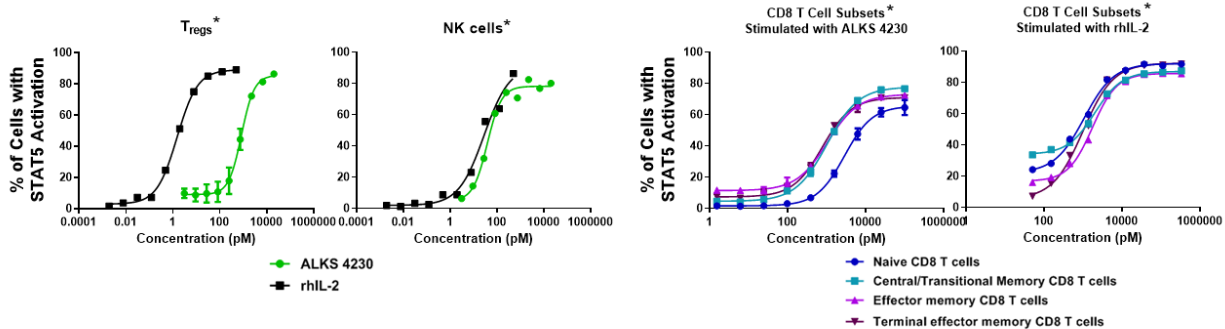
On the right-hand side, what you see is that we have driven a significant decrease in potency in the ability of ALKS 4230 to signal through the high-affinity receptor, in comparison to recombinant human IL-2.

These data support our design hypothesis of the selectivity of ALKS 4230 for the intermediate-affinity receptor.

Slide 18

ALKS 4230 Selectively Activated Human CD8⁺ T Cells and NK Cells Compared to T_{regs}, Unlike rhIL-2

18



ALKS 4230 and rhIL2- similarly activate important populations of CD8 T cells and NK cells;
But ALKS 4230 is ~400 times less potent in activating immunosuppressive T_{regs} compared to rhIL-2

* T_{regs}, NK cells and CD8⁺ T cells from healthy human donors
Ref: Rosentrater et al. Abstract 4281 presented at the American Association for Cancer Research 2015

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To further characterize the activity of ALKS 4230, we studied isolated primary human cells from healthy donors. While in the previous slide we saw the activation of STAT 5 in human cell lines that expressed the high affinity and intermediate affinity receptors, here we wanted to see how the selectivity for the receptors translated into activating immunostimulatory and immunosuppressive human cells.

We are again measuring STAT 5 activation, which as I mentioned earlier, is a marker of activation of the receptor.

In the left two graphs, you see that for activation of the Treg population, there is a big shift in potency between IL-2 and ALKS 4230. ALKS 4230 is almost 400-fold less potent in activating Tregs in comparison to recombinant human IL-2.

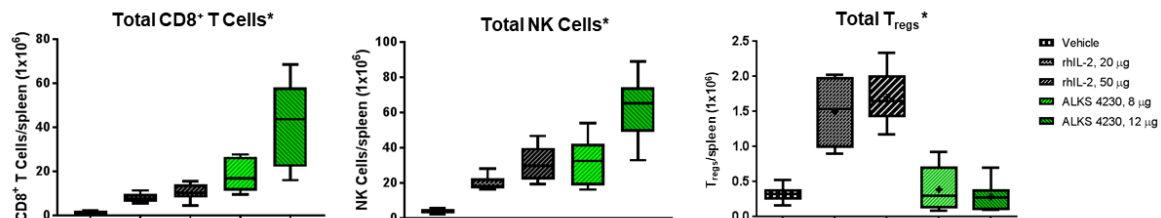
Moving to the graphs on the right – when we look to activation of natural killer cells as well as the important subsets of CD8⁺ T cells, including effector and central memory CD8s, ALKS 4230 is equally potent, if not a little bit more potent, in activating them as compared to recombinant human IL-2.

These data show that the selectivity for the intermediate-affinity receptor that we saw demonstrated by the data in the previous slide translated to the selective activation of CD8⁺ T cells and NK cells, with minimal activation of T regs.

Slide 19

ALKS 4230 Selectively Expanded CD8⁺ T Cell and NK Cells, With Negligible Increases in T_{regs}, *in vivo*

19



ALKS 4230 had a dose-dependent effect on CD8⁺ T cell and NK cell expansion

*Cell expansion study in healthy mice

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We confirmed our design hypothesis *in vitro*, but next asked ourselves, does this concept hold up *in vivo*?

Here on slide 19 is a snapshot of data looking at the pharmacodynamic response to ALKS 4230. Here we are looking at absolute cell numbers from the spleen of healthy mice. Recombinant human IL-2 is shown in gray and ALKS 4230 in green.

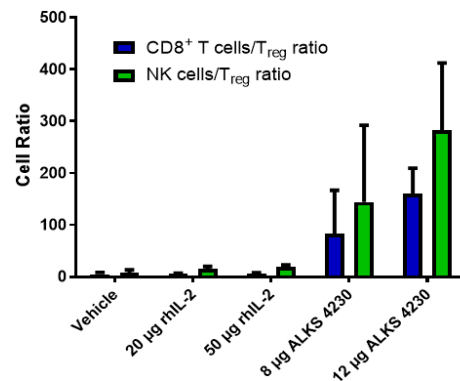
The left two panels show that both IL-2 and 4230 demonstrated a dose-dependent effect on the expansion of CD8⁺ and NK cells, with 4230 driving slightly more expansion.

But importantly, on the far right panel of the slide, recombinant human IL-2 drove significant expansion of the Treg population, as predicted, whereas ALKS 4230 demonstrated negligible effects on that immunosuppressive cell population.

Slide 20

ALKS 4230 Induced a Dose-Dependent Increase in Ratio of Effector Cells to T_{reg} , in Contrast to rhIL-2

20



12 µg ALKS 4230 induces a 160:1 ratio of CD8⁺ T cells/ T_{reg} , and a 283:1 ratio of NK cells/ T_{reg}

Effector cells are CD8⁺ T cells and NK cells; Cell expansion in spleens of healthy mice

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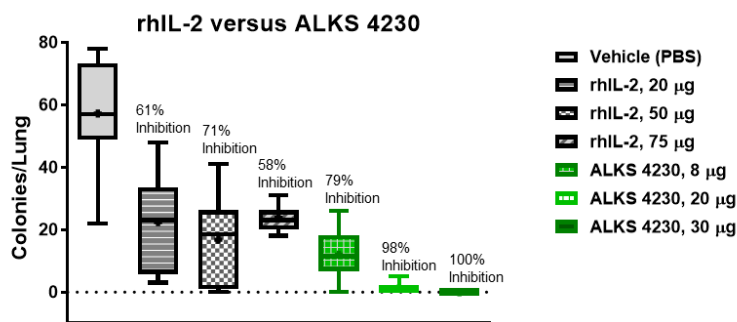
Here are the same data you've just seen, but plotted as a ratio. The blue and green bars depict the ratio of expansion of CD8⁺ and NK cells relative to T reg cells, respectively.

The data show that 4230 is in the vicinity of 100 to 300 times more selective in expanding the effector cell population versus the Treg population, as compared to recombinant human IL-2.

We saw similar selective expansion in non-human primates as well. For example, in non-human primates, 0.1 mg/kg ALKS 4230 dosed once-daily for five days resulted in an approximate 600% increase in CD8⁺ T cells with minimal changes in the number of Tregs.

ALKS 4230 Monotherapy Completely Inhibited Tumor Colony Formation in Murine Lung Cancer Model

21



Proof-of-principle that selective activation and expansion of CD8⁺ T cells and NK cells over T_{regs} may provide improved anti-tumor efficacy, compared to rhIL-2

Ref. Losey et al. Abstract 591 presented at the American Association for Cancer Research 2017

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Going back to our design hypothesis, we wanted to investigate whether the improvement in the ratio of effector cells to regulatory T cells could drive improvement in anti-tumor efficacy, when compared to IL-2.

Shown here is a B16-F10 model of lung cancer colonization in mice. What we are studying here is whether IL-2 or ALKS 4230 can prevent the formation of melanoma colonies in the lung.

On the graph, the vehicle is shown in the far left box. Moving to the right, shown in the next three gray boxes is recombinant human IL-2 dosed up to its maximum tolerated dose, followed by ascending doses of ALKS 4230 shown in the green boxes.

As seen in these data, the maximal efficacy achieved by recombinant human IL-2 was about 71% inhibition of tumor colony formation. Contrast that to the right-hand side panels where ALKS 4230 was also dosed up to its maximum tolerated dose for this model, and you see that at the two higher doses there was nearly complete inhibition of tumor colony formation.

These data suggest that improvement in the ratio of effector to Treg cell populations could potentially drive superior efficacy for ALKS 4230, when compared to IL-2.

Non-Clinical Data Summary

ALKS 4230 Features	Model
Preferentially binds and signals through the intermediate-affinity IL-2R	✓ <i>In vitro</i>
Selectively activates and expands circulating NK cells and CD8 ⁺ T cells	✓ Mouse, NHP
Negligible effects on T _{regs}	✓ Mouse, NHP
Demonstrated superior anti-tumor efficacy compared to rhIL-2	✓ Mouse

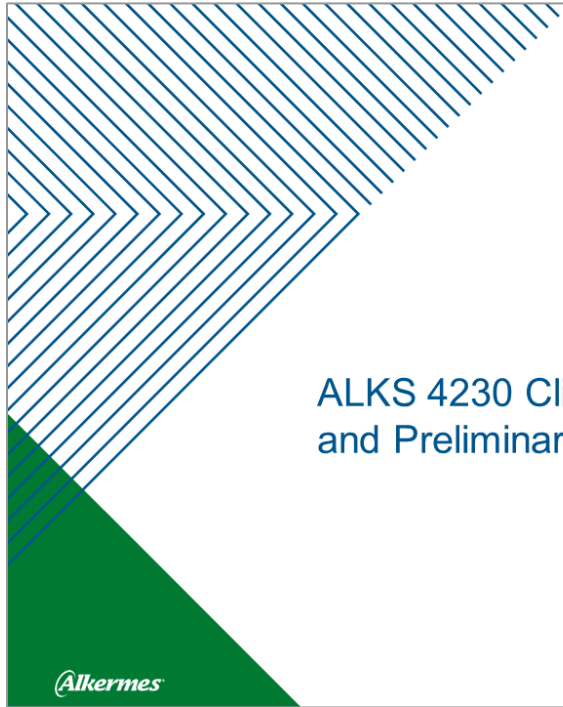
So in summary, our design concept was to create a molecule that would selectively bind to the intermediate affinity receptor. To do this, we took advantage of the natural differences between the structure of the high affinity and intermediate affinity IL-2 receptors to create a fusion protein, ALKS 4230, which inherently binds and signals through the intermediate affinity receptor.

Our non-clinical data in mice showed that this selectivity leads to expansion of the desired CD8⁺ and NK cell populations, with negligible expansion of regulatory T cells. We conducted equivalent research in non-human primates, where we saw a similar result and, as Craig will introduce to you in a moment, we've seen similar data to date in the context of human studies.

Finally, we were able to show that the selectivity of 4230 in the expansion of the effector cell population drove superior anti-tumor efficacy in a nonclinical model, as compared to recombinant human IL-2.

And with that, I'll hand the discussion over to Craig.

Slide 23



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ALKS 4230 Clinical Development Program
and Preliminary Results

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Thank you, Mark.

Overview of ALKS 4230 Clinical Development Program

ARTISTRY-1 Phase 1/2	IV dosing <i>Refractory advanced solid tumors</i>	<ul style="list-style-type: none"> • Part A: Monotherapy dose escalation • Part B: Monotherapy dose expansion • Part C: ALKS 4230 + pembrolizumab combination
ARTISTRY-2 Phase 1/2	Subcutaneous dosing <i>Refractory advanced solid tumors</i>	<ul style="list-style-type: none"> • 6-week monotherapy lead-in phase • Followed by ALKS 4230 + pembrolizumab combination <ul style="list-style-type: none"> – Evaluating once-weekly and once every three weeks dosing • Efficacy expansion phase planned
ION-01 Phase 2	IV dosing <i>Anti-PD-1 pre-treated HNSCC patients</i>	<ul style="list-style-type: none"> • ALKS 4230 + pembrolizumab combination • Assessment of tumor microenvironment from paired biopsies • Predictive biomarker assessments

HNSCC: Head and neck squamous cell carcinoma



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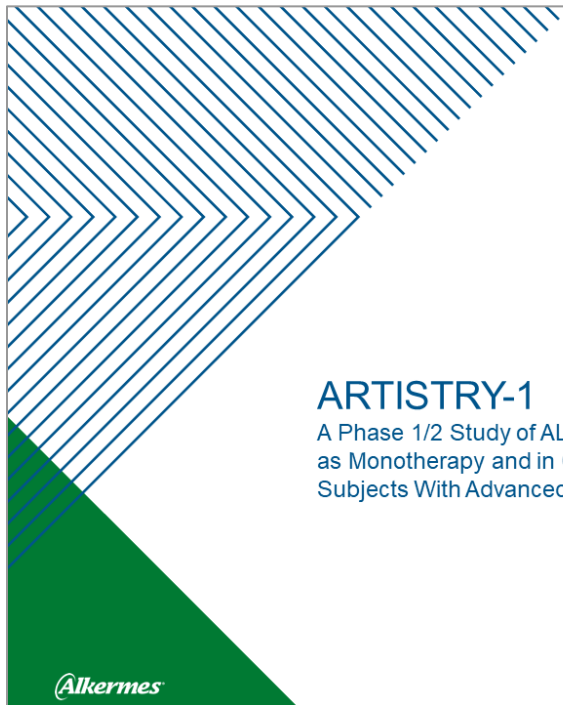
The clinical development program for ALKS 4230 is progressing on multiple fronts, with two ongoing phase 1/2 studies as part of our ARTISTRY clinical program, and a recently announced Phase 2 study in collaboration with the Fred Hutchinson Cancer Research Center, which will leverage the resources of ION, the Immune Oncology Network.

The study farthest along in enrollment to date is ARTISTRY-1, evaluating 4230 administered intravenously in both monotherapy and combination therapy settings. The preliminary data from this study are the primary focus of our update at SITC this week.

In addition, we initiated ARTISTRY-2 earlier this year. This phase 1/2 study is evaluating the safety, tolerability and efficacy of ALKS 4230 administered subcutaneously as both monotherapy and in combination with pembrolizumab, looking at both once-weekly and once-every-three-week dosing regimens.

In addition to ARTISTRY-1 and 2, we recently announced a research collaboration with the Fred Hutchinson Cancer Research Center. The collaboration includes a planned phase 2 trial, known as ION-01, which is designed to evaluate ALKS 4230 in combination with pembro in patients with advanced or recurrent head and neck squamous cell carcinoma who did not achieve complete remission with checkpoint inhibitor therapy. We expect this phase 2 study to begin in the coming weeks.

Slide 25



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ARTISTRY-1

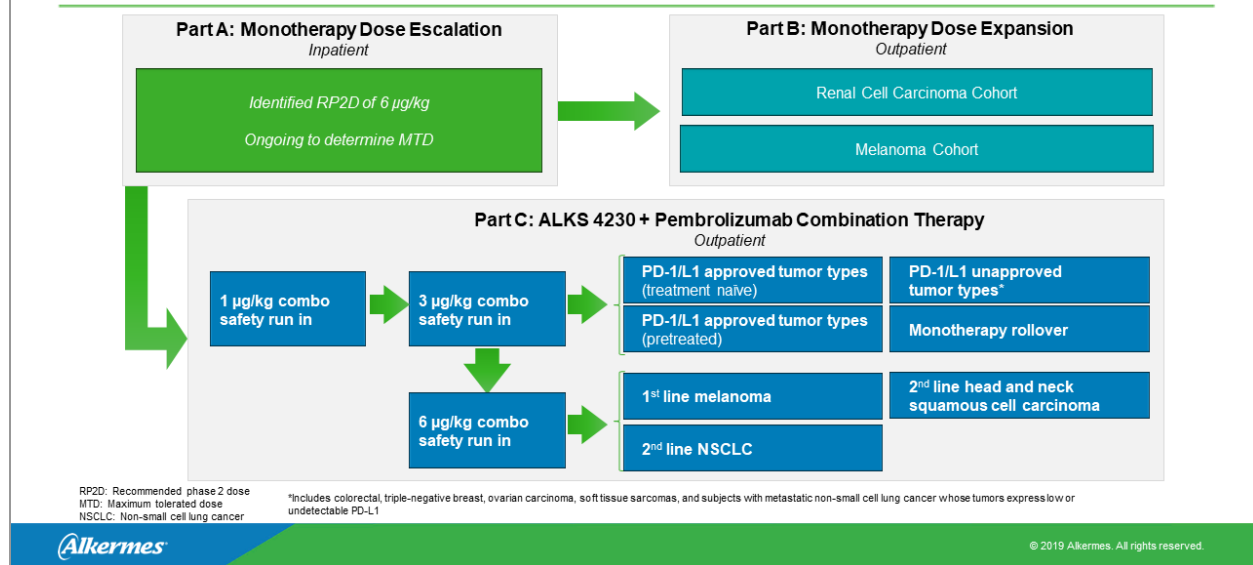
A Phase 1/2 Study of ALKS 4230 Administered Intravenously
as Monotherapy and in Combination With Pembrolizumab in
Subjects With Advanced Solid Tumors

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Turning back to the data being presented at SITC: the first poster we presented today contains preliminary efficacy and safety findings from ARTISTRY-1. Data presented in the poster and discussed on this webcast are as of the cutoff date of August 2, 2019, unless otherwise noted.

ALKS 4230: ARTISTRY-1 Phase 1/2 Study Design

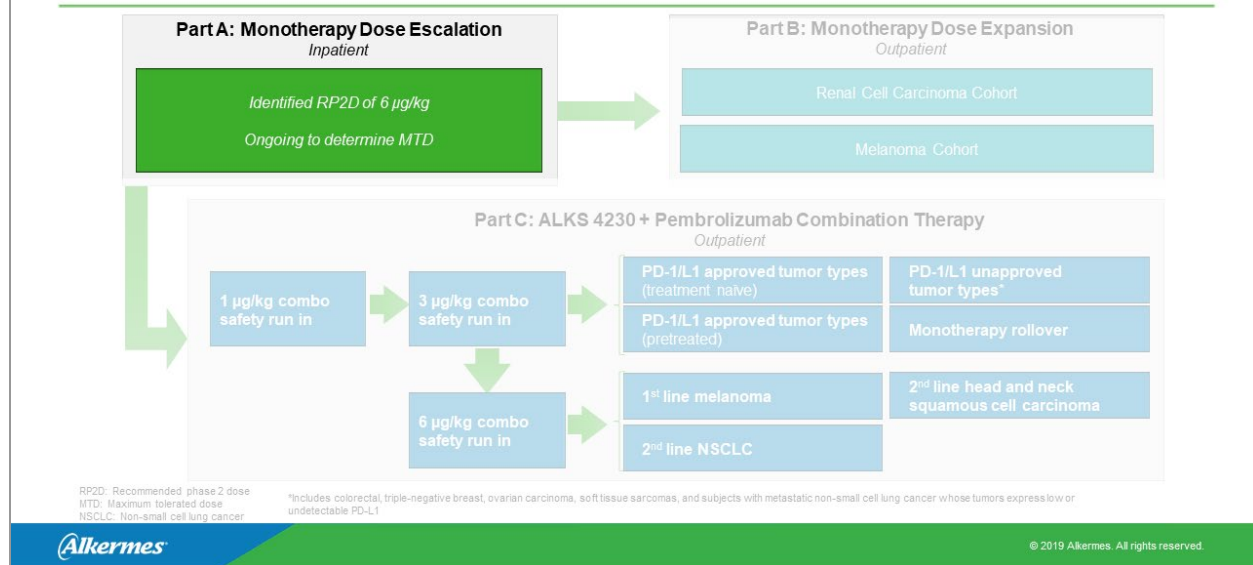


ARTISTRY-1 is a phase 1/2 study evaluating the safety, tolerability and pharmacodynamic effects of ALKS 4230 in patients with refractory advanced solid tumors, in both monotherapy and combination settings.

In ARTISTRY-1, ALKS 4230 is administered as a 30-min IV infusion dosed once-daily for five consecutive days. We selected this dosing regimen for this initial study to mirror the dosing of high-dose IL-2. While not optimized from a dosing perspective, this regimen allowed for a useful benchmark for pharmacodynamic effects observed with ALKS 4230.

ARTISTRY-1 is comprised of three distinct parts: monotherapy dose-escalation, monotherapy dose expansion and a combination therapy stage with the checkpoint inhibitor pembrolizumab.

ALKS 4230: ARTISTRY-1 Phase 1/2 Study Design



The Part A monotherapy dose escalation stage was designed to assess safety and pharmacodynamic markers, and to study the immuno-stimulatory effects of 4230, with the goals of establishing a recommended phase 2 monotherapy dose and identifying the maximum tolerated dose.

With expectations of potent biologic activity, we began dose escalating at low levels of ALKS 4230 in an in-patient setting. Most patients that enrolled in Part A were refractory patients with progressive disease and with very limited treatment options.

Slide 28

ARTISTRY-1 Part A Monotherapy Dose Escalation: Patient Characteristics

28

	Cumulative N	%	Median (Range)
Gender			
Male	23	64%	
Female	13	36%	
Age (yrs)			61 (35-82)
Tumor Type			
Melanoma	8	22%	
Prostate	5	14%	
Renal Cell	5	14%	
Other*	18	50%	
Total	36	100%	
Prior Lines of Therapy			3 (1-8)
0	1	3%	
1	4	11%	
2	8	22%	
3	8	22%	
4	7	19%	
5+	8	22%	

*Other: Breast, colorectal, clear cell of hypopharynx / submandibular gland, esophageal, gastric, lung, mesothelioma, pancreatic, sarcoma, leiomyosarcoma, ovarian uterine, and unknown primary

Patients who had received prior immune checkpoint inhibitor therapy:

- 7/8 melanoma patients
- 1/1 lung cancer patient
- 3/5 renal cell carcinoma patients

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Slide 28 provides a closer look at the patient disposition for the first 36 patients from the five completed dosing cohorts in the ARTISTRY-1 monotherapy dose escalation stage.

Upon entry to the study, these patients had advanced disease across a variety of solid tumor types, including melanoma, prostate and renal cell carcinoma, and had a median of three prior lines of therapy, including prior treatment with checkpoint inhibitors.

ARTISTRY-1 Part A Monotherapy Dose Escalation: Safety Summary

29

At escalating doses of ALKS 4230 up to 6 µg/kg:

Pyrexia (Fever) and Chills	Most frequently reported adverse events (AEs), regardless of relationship to ALKS 4230; Anticipated effects of cytokine administration <ul style="list-style-type: none"> Majority were Grades 1–2 in severity
Hypotension & Confusional State	Possible dose relationship; Grades 1–2 in severity
Grade ≥3 Treatment-related AEs	Only observed with 3 µg/kg and 6 µg/kg doses <ul style="list-style-type: none"> Neutrophil, lymphocyte, and white blood cell count decreased (n = 4, 2, and 2, respectively); pyrexia (n = 2); and aspartate aminotransferase increased, diarrhea, febrile neutropenia, neutropenia, hypoalbuminemia, hyperbilirubinemia, cholangitis, and jaundice cholestatic (n = 1 each)

- No vascular leak syndrome reported
- No Grade 4 or 5 treatment-related AEs reported

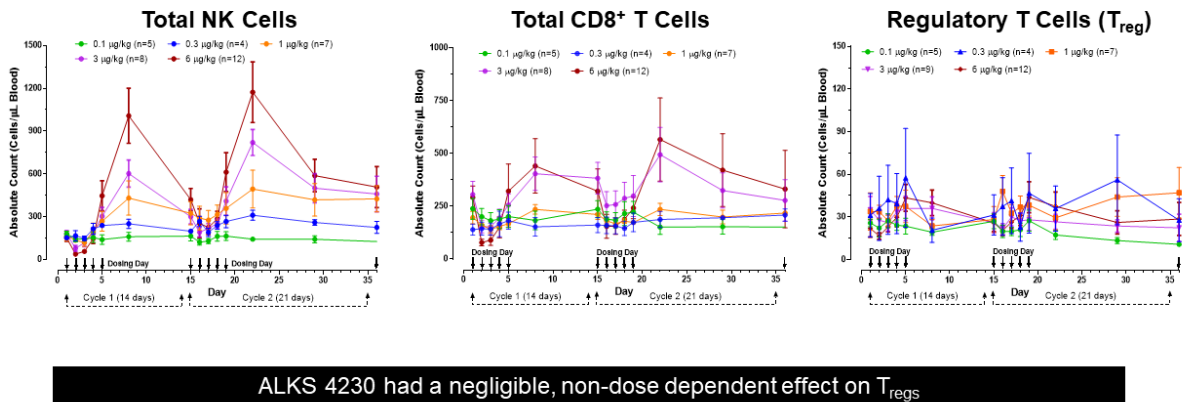
Data as of cutoff date of Aug. 2, 2019



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Slide 29 outlines the safety summary from Part A. The side effect profile across the five completed cohorts was generally consistent with what one would expect to see with cytokine therapy, such as fever, chills and low-grade hypotension. No Grade 4 or 5 treatment-related AEs were reported, and importantly, no signs of vascular leak syndrome—the hallmark toxicity associated with high-dose IL-2—were observed.

ARTISTRY-1 Part A Monotherapy Dose Escalation: *Dose-Dependent, Selective Expansion of NK and CD8⁺ T Cells*



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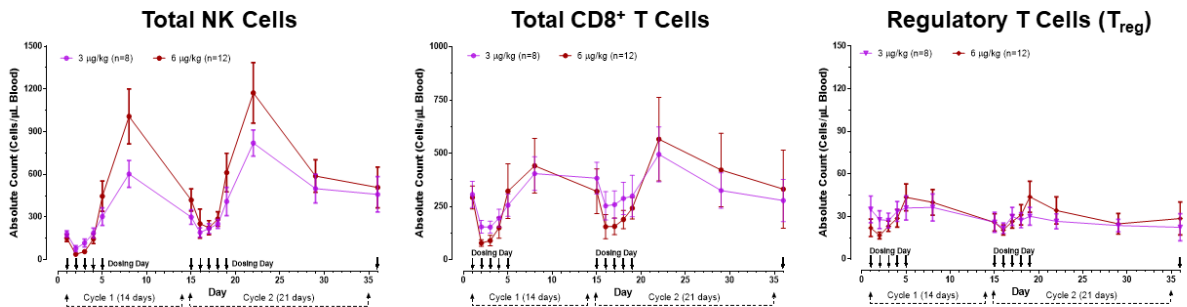
Data from the five completed dose-escalation cohorts, spanning doses of 0.1 to 6 micrograms/kg of ALKS 4230, demonstrated dose-dependent pharmacodynamic effects on the numbers of circulating NK cells and CD8⁺ T cells. ALKS 4230 had minimal, non-dose dependent effects on immunosuppressive regulatory T cells.

Note that the Y-axis scale on the Treg graph has been narrowed here in order to clearly visualize the individual dose levels and demonstrate the non-dose dependent effects.

Slide 31

ARTISTRY-1 Part A Monotherapy Dose Escalation: *Dose-Dependent, Selective Expansion of NK and CD8⁺ T Cells*

31



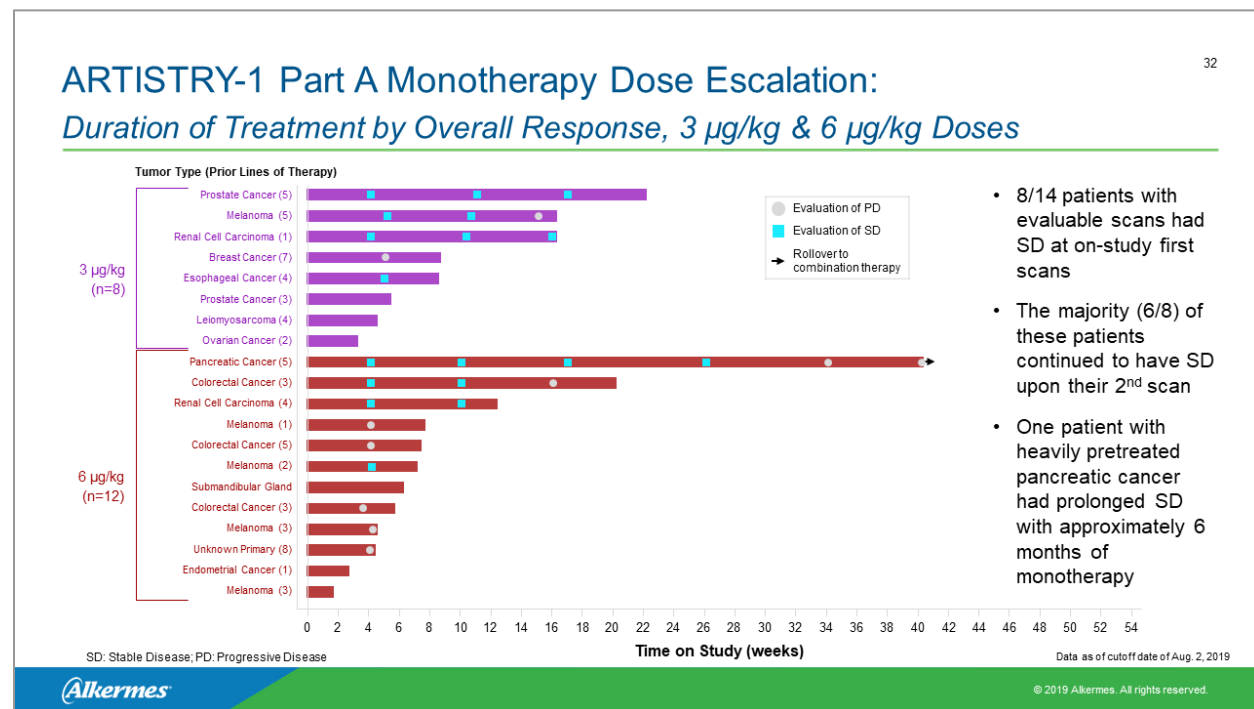
6 µg/kg selected as recommended monotherapy phase 2 dose in June 2019

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On slide 31, we focus in on the cell expansion for the 3 and 6 microgram/kg doses. Based on the biologic activity demonstrated and the safety and tolerability profile we observed for these two doses, we advanced them into the expansion cohorts for ARTISTRY-1, and in June of this year, selected 6 micrograms/kg as the recommended monotherapy phase 2 dose.

Slide 32



Turning to slide 32. This swimmer's plot shows the target lesion response in those patients who received 3 and 6 microgram/kg doses in the monotherapy dose escalation phase of ARTISTRY-1.

While we didn't expect to see much in terms of efficacy activity in this refractory, all-comer population, and the focus of Part A was primarily to collect PK, PD and safety data, we did observe disease stabilization starting at the 3 microgram/kg dose level.

As we reported earlier this year, 8 of the 14 patients who completed on-study first scans demonstrated stable disease on monotherapy treatment. Clinical benefit appeared to be maintained as the majority of these 8 patients continued to have stable disease upon their second scan. All patients have since discontinued therapy. One patient rolled over into the combination stage of the study prior to discontinuation, and I will speak to his case next.

ARTISTRY-1 Part A Monotherapy Dose Escalation:

Case Study: 70-Year-Old Male With Progressive Pancreatic Carcinoma

Diagnosis

Pancreatic Cancer

Diagnosed in 2015. Prior medical history: diabetes, hypercholesterolemia, hypertension, ischemic cardiomyopathy, myocardial infarction, lower extremity swelling, and GERD

Treatment

5 prior lines of treatment

Apr 2018 – Jan 2019

ALKS 4230 Monotherapy

6 µg/kg IV for 5 days every 3 weeks

Feb 2019 – Jun 2019

ALKS 4230 + pembrolizumab therapy

3 µg/kg ALKS 4230

On-Study Benefits

- Treated with ALKS 4230 for >1 year
 - Received monotherapy treatment for 10 months; demonstrated 6 months of stable disease
 - Rolled over to combination therapy for an additional 4.5 months, following progressive disease
- Maintained ECOG performance status of 1 throughout the study
- No drug-related serious adverse events
- Drug-related side effects of fever, chills and neutropenia
- CA 19-9 tumor marker reduced from 2571 U/mL (baseline) to 673 U/mL while on monotherapy

GERD: Gastroesophageal reflux disease; ECOG: Eastern Cooperative Oncology Group Performance Status

Data as of cutoff date of Aug. 2, 2019

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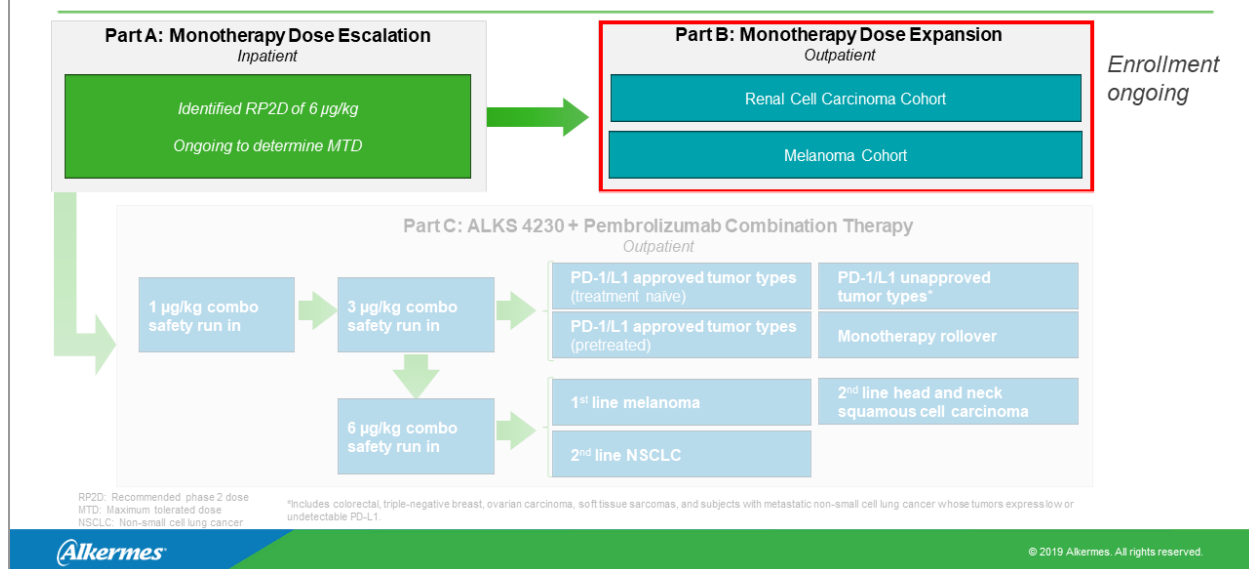
This patient, with heavily pre-treated, advanced progressive pancreatic carcinoma, had prolonged stable disease on ALKS 4230 monotherapy and went on to enroll in the Part C combination stage of ARTISTRY-1.

This patient is a 70-year-old male who was diagnosed in 2015 and had been heavily pre-treated with 5 prior lines of therapy. The patient enrolled in ARTISTRY-1 in April 2018 and received ALKS 4230 as a single-agent therapy at the 6 microgram/kg IV dose. The patient was able to stay on monotherapy for about 10 months, with stable disease maintained for approximately six months. Despite multiple comorbidities, he tolerated monotherapy treatment well, with drug-related side effects of fever, chills and neutropenia, but no drug-related serious adverse events.

During this monotherapy treatment phase, the patient's CA 19-9 tumor marker levels dropped from 2571 Units / ml at study entry to 673 Units / ml.

Following 10 months on monotherapy treatment, the patient rolled over to the combination stage and remained on therapy for an additional 4.5 months. Remarkably, he maintained his ECOG performance status of 1 throughout his time in the ARTISTRY-1 study.

ALKS 4230: ARTISTRY-1 Phase 1/2 Study Design



Based on data from the dose escalation stage, in June, we identified 6 microgram/kg of 4230 as the recommended phase 2 monotherapy IV dose. Data from this dose demonstrated the tolerability profile we set out to achieve for 4230 along with the desired lymphocyte cell expansion without corresponding IL-2-induced Treg activation in dose-escalation. Notably, the maximum tolerated dose of IV ALKS 4230 has not yet been reached, and we will continue to dose escalate until we reach MTD in order to establish the full potential dose range.

Based on identification of the recommended phase 2 dose, we initiated the phase 2 expansion portion of ARTISTRY-1 to evaluate ALKS 4230 as monotherapy in patients with renal cell carcinoma or melanoma who are refractory to prior PD-1 therapies. Following disease progression on PD-1 therapy, these patients often have very limited treatment options.

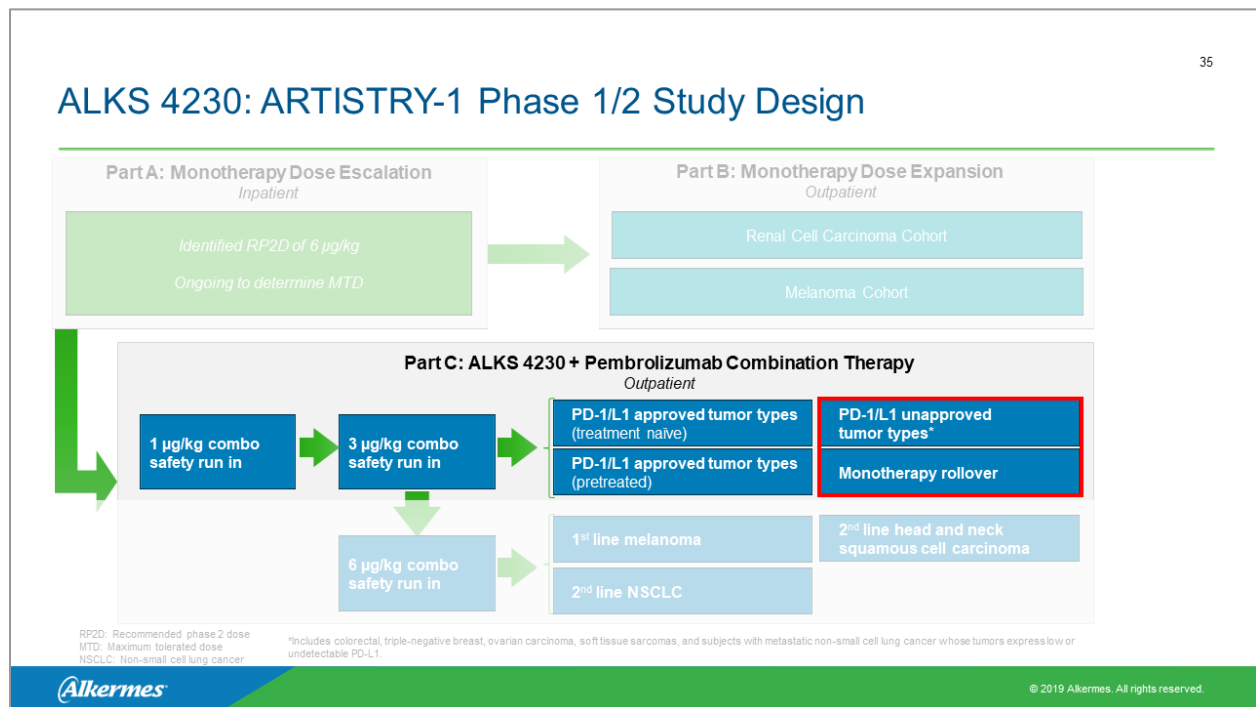
In this monotherapy expansion cohort, we will assess objective efficacy measures, and the safety and tolerability of ALKS 4230.

In this monotherapy expansion stage, following four cycles in good standing or upon progressive disease, patients are eligible to roll over into the combination with pembro stage of the study at the investigators' discretion. Given that most responses on high-dose IL-2 occur in the first 12 weeks of treatment, we believe we will be able to capture ALKS 4230's monotherapy activity in this study while addressing the realities of a competitive clinical study enrollment landscape and ethical considerations. Further, since all patients are PD-1 refractory at enrollment, the opportunity to revisit PD-1 following exposure to ALKS 4230 could provide interesting new data related to priming of the immune system.

We are actively enrolling this monotherapy expansion portion of the study in both inpatient and outpatient settings, and plan to present data at a future medical meeting.

Given the cell expansions we observed in Part A and the known monotherapy efficacy that high-dose IL-2 has demonstrated in these indications, our hypothesis remains intact that there is potential for ALKS 4230 to have monotherapy efficacy in renal cell carcinoma and melanoma.

Slide 35



In parallel to the ongoing monotherapy dose escalation and expansion cohorts, we have been steadily enrolling patients in the Part C combination stage of ARTISTRY-1, evaluating ALKS 4230 in combination with pembro in a variety of tumor types, in both in- and outpatient settings. Cohorts being evaluated include PD-1 approved tumor types in both refractory and treatment naïve patients, as well as in certain PD-1-unapproved tumor types.

Anti-tumor response and duration of response assessments in Part C are based on investigator-assessed, immune-related response, or iRECIST criteria, AND independent, central, blinded radiographic review per Response Evaluation Criteria in Solid Tumors, or RECIST 1.1 criteria. The scans are performed approximately 5 to 6 weeks apart.

Data being presented at SITC are primarily from the PD-1 unapproved cohort, as well as the previously mentioned monotherapy rollover patient.

Slide 36

ARTISTRY-1 Part C Combination Stage With Pembrolizumab: *Patient Demographics: PD-1/L1 Unapproved Tumor Types*

36

	Cumulative N	%	Median(Range)
Gender			
Male	9	36%	
Female	16	64%	
Age (yrs)			54 (34-79)
Tumor Type			
Ovarian	7	28%	
Colon/Colorectal/Rectal	7	28%	
Sarcoma	7	28%	
Triple Negative Breast Cancer	3	12%	
NSCLC (PD-L1 negative)	1	4%	
Total	25	100%	
Prior Lines of Therapy			3 (1-8)
1	2	8%	
2	7	28%	
3	6	24%	
4	3	12%	
5+	7	28%	



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First, let's look at the patient demographics from the cohort of PD-1 unapproved tumor types. A total of 25 patients with a median age of 54 enrolled and the majority of patients were female. Patients had a wide variety of tumor types including ovarian, colon, triple negative breast cancer and PD-L1 negative non-small cell lung cancer.

Patients had a median of three prior lines of therapy and were all progressive at time of enrollment.

SLIDE 37

ARTISTRY-1 Part C Combination Stage With Pembrolizumab:

37

Safety Summary: PD-1/L1 Unapproved Tumor Types & Monotherapy Rollover Patient

- Safety profile in combination with pembrolizumab generally consistent with monotherapy profile
- No emerging evidence of additive or synergistic toxicities in combination with pembrolizumab

Pyrexia (Fever) and Chills	Most frequently reported adverse events (AEs), regardless of relationship to ALKS 4230; Anticipated effects of cytokine administration <ul style="list-style-type: none">• Majority were transient and Grades 1–2 in severity
Hypotension	Grades 1–2 in severity
Grade ≥3 Treatment-Related AEs	Occurred in 7 patients, and include infusion-related reactions (n = 2), lymphocyte count decreased (n = 2), anemia, aspartate aminotransferase increased, confusion, dehydration, and fatigue (n = 1 each)

- No vascular leak syndrome reported
- No Grade 4 or 5 treatment-related AEs reported

Data as of cutoff date of Aug. 2, 2019

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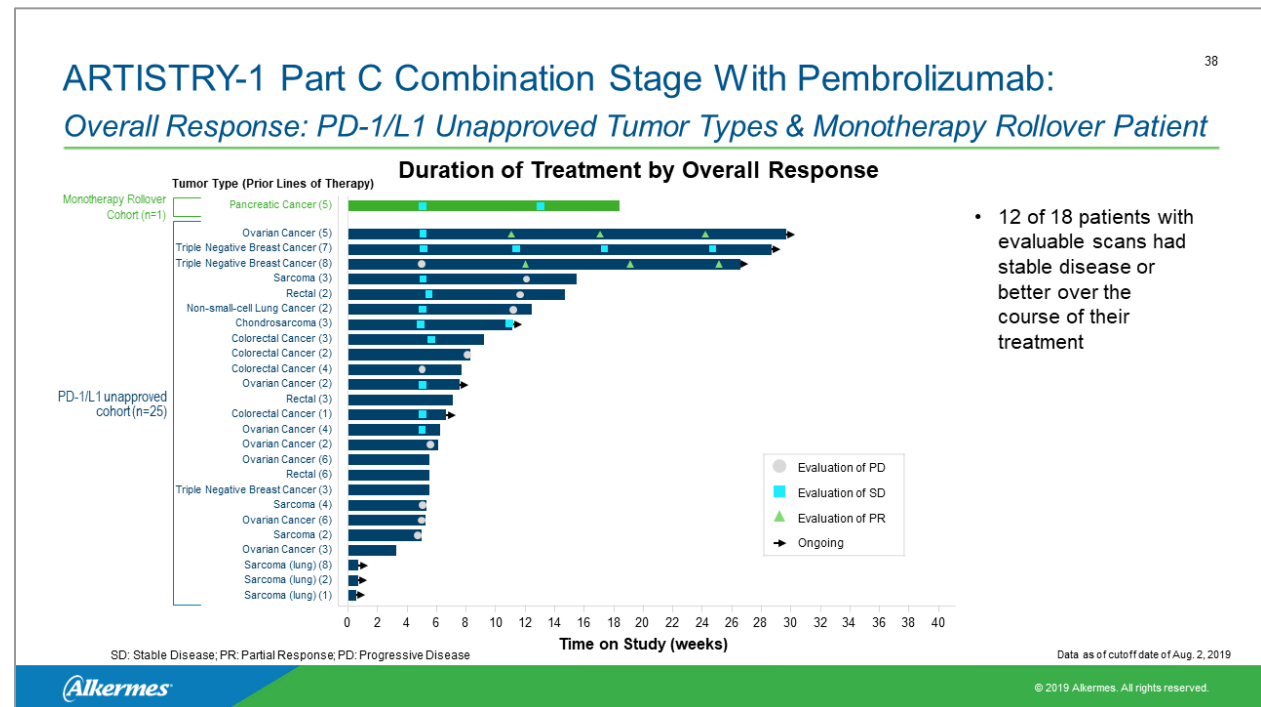
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Slide 37 outlines the summary of safety data from the PD-1 unapproved patients as well as the pancreatic cancer patient that rolled over from monotherapy dose escalation.

The side effects observed have been generally consistent with what one would expect to see with cytokine therapy, and there is no emerging evidence of additive or synergistic toxicities in combination with pembro. The most common adverse events were fever, chills and low-grade hypotension.

Consistent with the Part A monotherapy data, no Grade 4 or 5 treatment-related AEs were reported, and importantly, as of October 31st, 2019, we have not observed any evidence of vascular leak syndrome.

Slide 38



The swimmer's plot on slide 38 shows the overall response to ALKS 4230 and pembro combination therapy in the 25 patients who had PD-1 unapproved tumor types and the pancreatic carcinoma patient who rolled over from monotherapy.

As I mentioned previously, these are patients with limited treatment options, who have progressed on prior therapy.

Among the 26 patients included on this plot, 18 patients had evaluable scans. 12 of these 18 patients achieved stable disease or better.

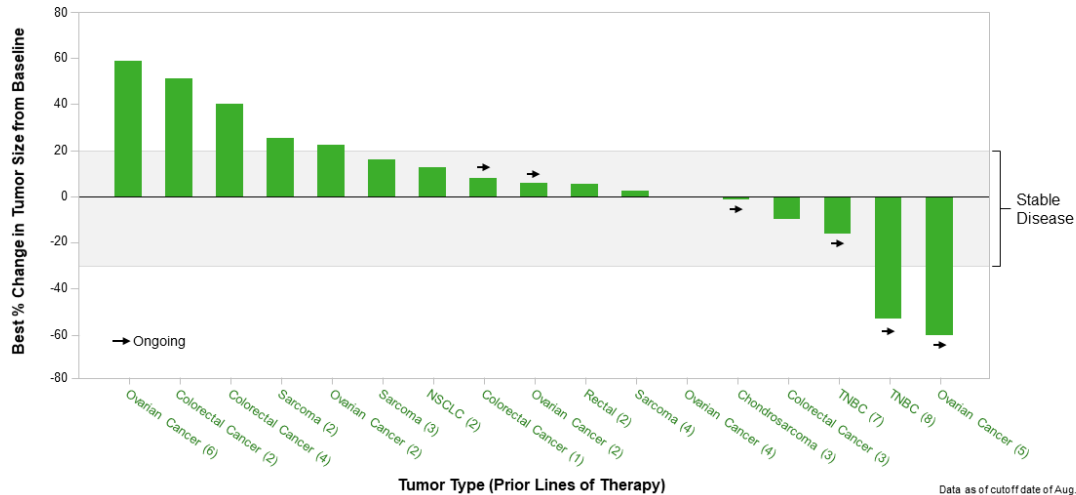
This includes one ovarian carcinoma patient who had a confirmed partial response, and one metastatic triple negative breast cancer patient who had an immune-partial response, with a 50% reduction in target lesion size.

We will review these cases in detail later.

Slide 39

ARTISTRY-1 Part C Combination Stage With Pembrolizumab: Best Response of Target Lesion in PD-1/L1 Unapproved Tumors

39

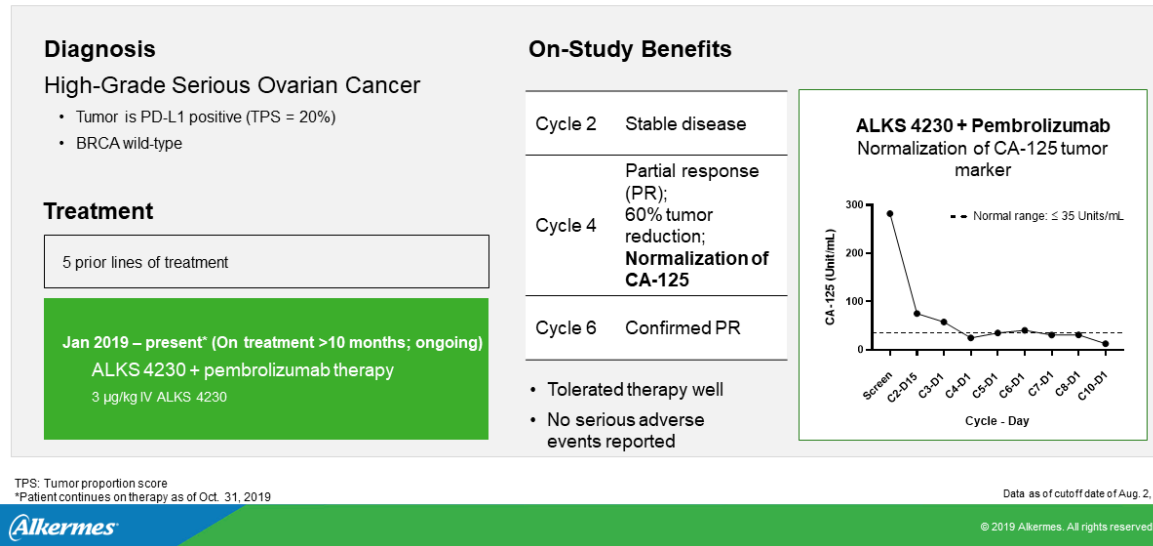


Here is a waterfall plot of the best response by target lesion for the 17 patients who had evaluable scans in the PD-1 unapproved tumor types cohort.

The area between the two gray horizontal lines indicate stable disease per RECIST criteria. Despite entering the study with rapidly progressing, refractory disease, the majority of patients in this cohort achieved stable disease.

The 2 partial responses are shown on the far right of the graph. I'll discuss these two patient cases next.

ARTISTRY-1 Part C Combination Stage With Pembrolizumab: Case Study: 48-Year-Old Female With High-Grade, Progressive Ovarian Cancer



The first case is a 48-year-old female patient who had high-grade serous ovarian carcinoma, which was PD-L1 positive and BRCA wild-type.

She had received 5 prior lines of therapy and had progressive disease prior to starting on combination therapy with ALKS 4230 and pembro in January 2019.

At Cycle 2, she had achieved stable disease. At Cycle 4, she had a 60% decrease in her target lesion, and at Cycle 6, she achieved a confirmed partial response.

Additionally, the patient demonstrated a complete normalization of her CA-125 tumor marker at Cycle 4, with a reduction from 282 Units / ml upon screening to 12.6 Units/ml at Cycle 10. CA 125 is an established prognostic indicator of ovarian carcinoma.

This patient tolerated therapy well, with no serious adverse events reported. As of October 31st, she remains on therapy and has been on ALKS 4230 for more than 10 months.

ARTISTRY-1 Part C Combination Stage With Pembrolizumab: Case Study: 47-Year-Old With Progressive Triple Negative Breast Cancer

41

Diagnosis Triple Negative Breast Cancer	On-Study Benefits <table> <tr> <td>Cycle 2</td><td>32% decrease in target lesions (2 lesions) - Patient developed small new lesions*</td></tr> <tr> <td>Cycle 4</td><td>45% decrease in target lesions from baseline along with reduction of the new lesions consistent with overall iPR*</td></tr> <tr> <td>Cycle 8</td><td>53% decrease in target lesions</td></tr> </table>	Cycle 2	32% decrease in target lesions (2 lesions) - Patient developed small new lesions*	Cycle 4	45% decrease in target lesions from baseline along with reduction of the new lesions consistent with overall iPR*	Cycle 8	53% decrease in target lesions
Cycle 2	32% decrease in target lesions (2 lesions) - Patient developed small new lesions*						
Cycle 4	45% decrease in target lesions from baseline along with reduction of the new lesions consistent with overall iPR*						
Cycle 8	53% decrease in target lesions						
Treatment <div>8 prior lines of treatment</div> <div>Jan 2019 – present* (On treatment >10 months; ongoing) ALKS 4230 + pembrolizumab therapy 3 µg/kg IV ALKS 4230</div>	<small>*Not uncommon with checkpoint inhibitor treatment *iPR (immune partial response) is based on iRECIST. iRECIST is immune-RECIST which accounts for new lesions that subsequently shrink</small> <ul style="list-style-type: none"> • Tolerated therapy well; primarily Grade 1 AEs • Intermittent Grade 2 tachycardia early on • No serious adverse events reported 						

*Patient continues on therapy as of Oct. 31, 2019

Data as of cutoff date of Aug. 2, 2019.

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The second case is a 47-year-old female patient who enrolled in the study with a diagnosis of progressive metastatic triple negative breast cancer. She had received 8 prior lines of therapy, and her best response to therapy had been progressive disease.

She initiated on ALKS 4230 combination treatment with pembro in January 2019. At initiation she had 2 target lesions.

At Cycle 2 of treatment the patient demonstrated a 32% decrease in target lesions. At that time, small new lesions were identified – which is not uncommon with checkpoint inhibitor treatment.

At Cycle 4, she had a 45% reduction of her target lesions from baseline along with reduction of her new lesions. At cycle 8, her target lesions had decreased by 53%.

Due to the emergence of the new lesions, iRECIST criteria were applied. As I mentioned earlier, iRECIST allows for inclusion of the measurements of new target lesions, that subsequently decrease in size.

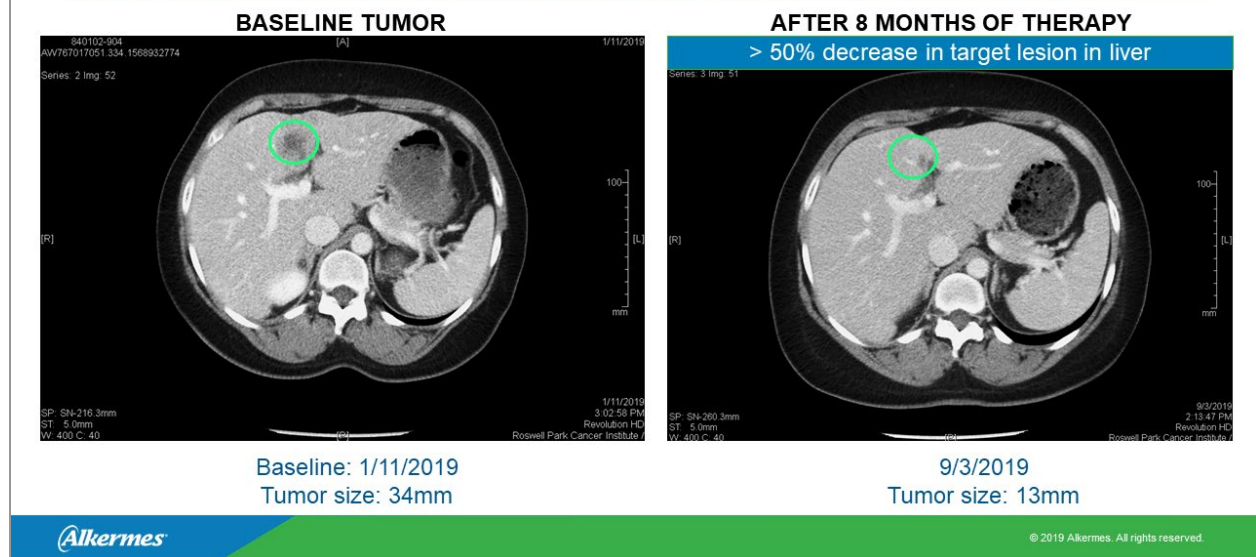
At Cycle 4, based on the reduction of both the target lesions and the new lesions, the patient qualified for immune-partial response based on iRECIST.

As of the August 2nd data cutoff, the patient had tolerated therapy well, having experienced primarily Grade 1 adverse events and intermittent Grade 2 tachycardia early on. She had not experienced any serious adverse events and, as of October 31st, she remains on study.

Slide 42

ARTISTRY-1 Part C Combination Stage With Pembrolizumab: Case Study: 47-Year-Old With Progressive Triple Negative Breast Cancer

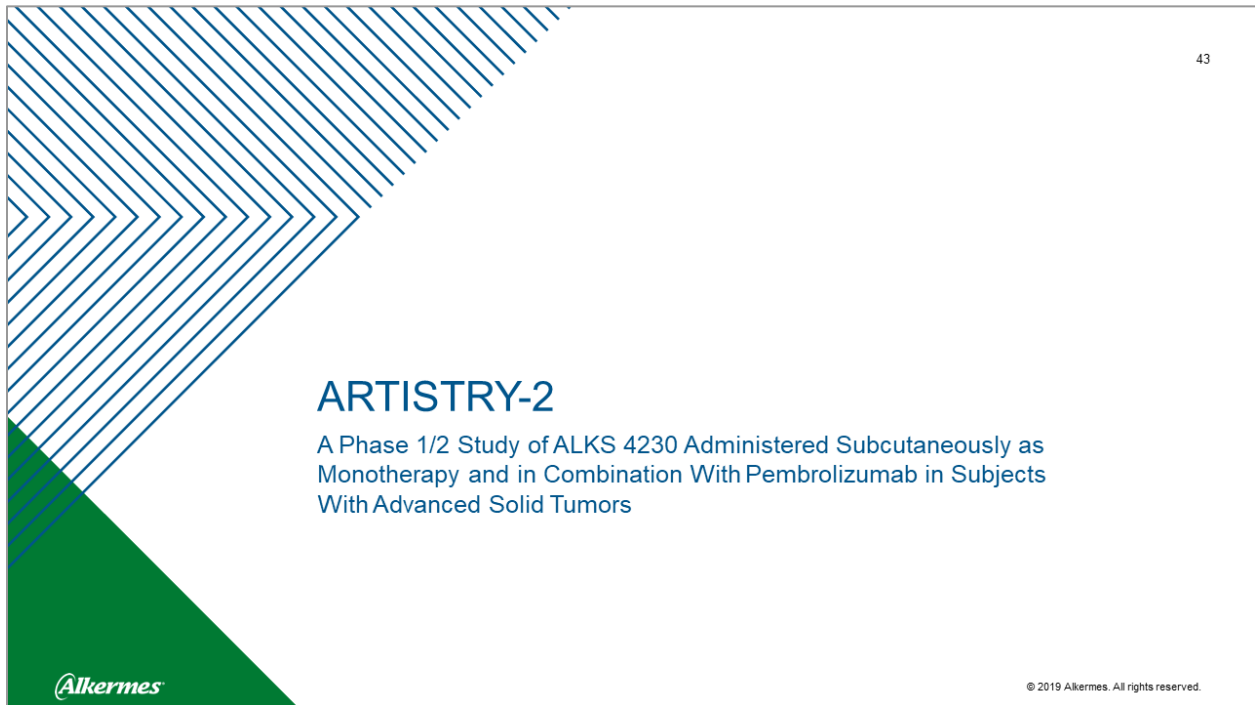
42



Here is an abdominal scan of the patient, depicting one of the target lesions in her liver.

As you can see, the target lesion decreased from 34 mm to 13 mm over 8 months of therapy, which is greater than 50% reduction from baseline.

Slide 43

The slide features a decorative graphic on the left side consisting of a series of blue chevron-like lines pointing right, transitioning into a solid green triangle at the bottom left. The Alkermes logo is positioned within the green area.

43

ARTISTRY-2

A Phase 1/2 Study of ALKS 4230 Administered Subcutaneously as Monotherapy and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors

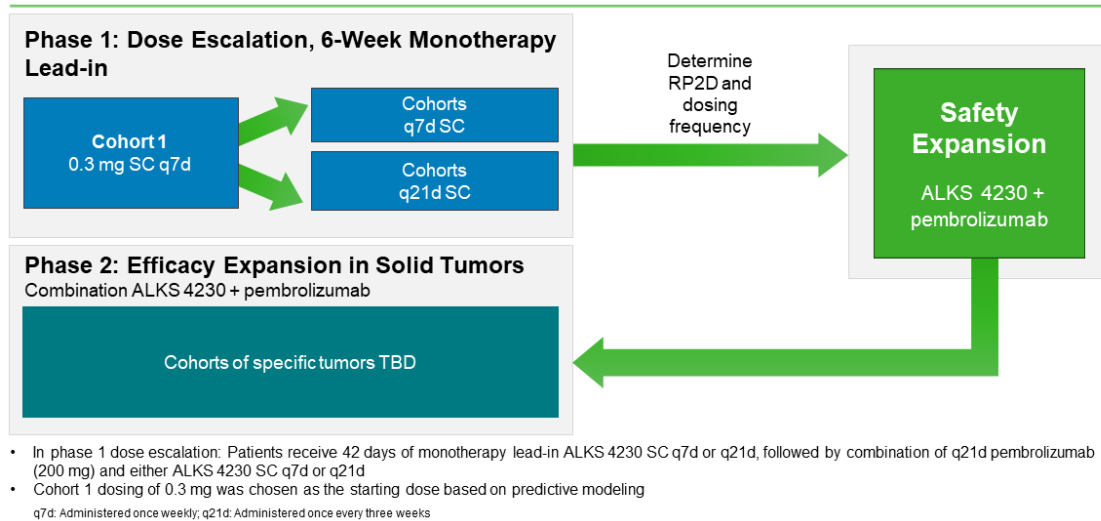
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The second poster we presented at SITC is a trials-in-progress poster on ARTISTRY-2. Status updates referenced here are from the cut-off date of August 2, 2019, unless otherwise noted.

Earlier this year, we initiated ARTISTRY-2 to evaluate the potential of subQ administration. As I mentioned previously, the IV dosing regimen used in ARTISTRY-1 was chosen to mimic the administration route and schedule used for high-dose IL-2. Data we presented last year at SITC demonstrated that, in non-clinical models, subQ administration of ALKS 4230 with less frequent dosing led to similar expansion of immunostimulatory cell populations compared to IV administration of ALKS 4230.

ALKS 4230: ARTISTRY-2 Phase 1/2 Study Design



ARTISTRY-2 is a Phase 1/2 study designed to explore the safety, tolerability and efficacy of ALKS 4230 administered subcutaneously once weekly and once every 3 weeks. In the dose-escalation stage of ARTISTRY-2, patients receive an initial six-week lead-in of ALKS 4230 monotherapy prior to moving into combination with pembro. The six-week lead-in serves three purposes: the first is to assess the safety and tolerability of escalating subQ doses in order to identify the recommended phase 2 dose, the second is to study the pharmacodynamics of subQ administration of ALKS 4230, and the third is to provide potentially useful additional data points related to monotherapy efficacy.

Once the recommended phase 2 subQ dose and dosing schedule are selected, the dose expansion phase of ARTISTRY- 2 is expected to evaluate multiple refractory solid tumor types in combination with pembro.

ALKS 4230: ARTISTRY-2 Phase 1/2 Study

45

Status Update

- ARTISTRY-2 is an ongoing study and clinical sites are actively recruiting
 - Fully enrolled cohort 1 at the once-weekly 0.3 mg dose (N=7)
 - 6 of 7 patients in this cohort remain on therapy as of October 31, 2019
- Initial safety findings
 - The most common adverse events (AEs) (regardless of relationship to study drugs) were fatigue (n = 4), chills (n = 3), injection site erythema (n = 3), injection site pruritus (n = 3), nausea (n = 3), and pyrexia (n = 3)
 - 1 patient had grade ≥ 3 AE: lymphopenia (transient; likely related to ALKS 4230 mechanism of action)
 - No discontinuations due to AEs
- As of October 31, 2019, dosing at next dose-escalation cohorts (0.6 mg once-weekly and 1.0 mg once-every-three-weeks) is ongoing

Data as of cutoff date of Aug. 2, 2019

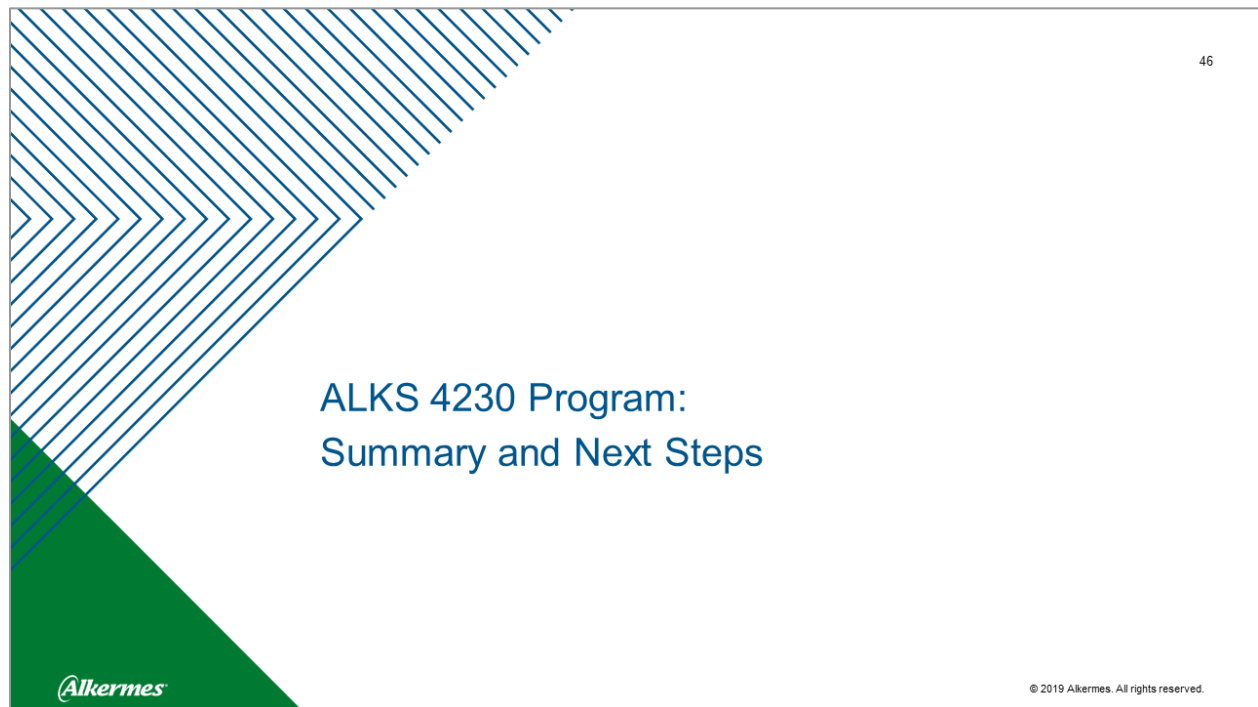
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ARTISTRY-2 is off to a solid start and we have completed the first cohort of 7 patients at the 0.3 mg once-weekly subQ dose.

6 of these 7 patients remain on treatment as of October 31st, and pharmacodynamic data from these patients have demonstrated NK and CD8+ T cell expansion consistent with our expectations, and with minimal activation of Tregs.

Overall, the safety signals we have seen so far have been encouraging, and the most common adverse events were manageable. Following a safety review of this initial cohort, we initiated the next two cohorts which are running in parallel: 0.6 mg once weekly and 1.0 mg once every three weeks.



Looking across the entire ARTISTRY clinical development program, while the sample set is still small, the preliminary data we have collected to date are consistent with the profile that we would have anticipated at this stage, and we are encouraged by the initial signals of efficacy that we have seen with ALKS 4230, both as monotherapy and in combination with pembro.

Looking ahead, we will continue enrollment in ARTISTRY-1, including the monotherapy dose expansion in renal cell carcinoma and melanoma and in combination with pembro in PD-1 approved tumor types, in patients that are treatment naïve as well as PD-1 refractory patients.

In addition, based on interest from advisors and investigators, we recently expanded the combination therapy portion of ARTISTRY-1 to include three additional cohorts evaluating patients with first-line melanoma, second-line non-small cell lung cancer and second-line head and neck squamous cell carcinoma. Patients in these newly initiating cohorts will receive the 6 micrograms/kg dose of ALKS 4230 in combination with pembro.

In ARTISTRY-2, we expect to complete enrollment and conduct the safety review of these next cohorts in the coming weeks.

ALKS 4230 represents our first clinical asset in immuno-oncology and we look forward to sharing additional details in the future about other cytokines we have in our labs. We have taken important steps to build our internal capabilities, including strengthening our internal expertise in oncology, establishing a greater presence at major medical meetings, working

with clinical investigators, and enhancing our worldwide clinical operations capabilities to execute larger-scale cancer studies.

I have spent a significant portion of my career focused in oncology, both in clinical development and Medical Affairs and I look forward to continuing that work at Alkermes as we work to advance ALKS 4230.

Slide 47



Sandy Coombs

Thank you, Craig. This concludes our remarks, but we are happy to make ourselves available for follow-up should you have questions. Thank you for your interest in the ALKS 4230 program.