Centurion BioPharma Corp

LADR™ (linker activated drug release)
- Mechanism
- Pre-clinical data (AACR Posters)
- Broad tumor potential
- Patient identifying companion diagnostic
- Advantages over ADC’s
- Clinical and regulatory considerations
- Areas unmet need / positioning
- Milestones
- Leading drug conjugates for IND enabling studies
- Platform

Business development objectives

Summary and next steps
Centurion BioPharma Corp

- Private oncology pre-clinical stage company
- Discovered and owns full rights to LADR™ platform
- Laboratory facility and discovery team located in Freiburg, Germany
- Subsidiary of CytRx Corporation (CYTR)
- Administrative location in Los Angeles, CA
LADR™ Platform Overview

Goal: accumulate drug in the tumor and minimize systemic toxicity

1. Ultra High Potency Drug Payload
   • Payloads are 10-1,000 times more potent than standard anti-cancer agents
   • Similar to those used for ADCs (auristatins, maytansinoids)

2. Cleavable Linker
   • Novel linker keeps the highly potent drug payload inactive until the conjugate reaches the tumor
   • The linker is then cleaved which activates the payload

3. Targeting
   • Anchor group ensures rapid and selective binding to circulating serum albumin
   • Serum albumin transports the LADR™ drug to the tumor
**LADR™ Mechanism of Action**

1. **Drug-linker conjugate is infused**
2. **Rapid and specific binding to circulating albumin**
3. **Albumin transports drug to the tumor and surrounding microenvironment**
4. **Linker dissolves in the acidic (low pH) environment and releases the drug payload**
Albumin as a Drug Delivery Vehicle

- **Albumin**
  - Most abundant protein in human blood plasma
  - Transport molecule
  - Long half-life (20 days)
  - Major source of essential amino acids ("fuel") for cancer cells
  - Localizes at tumor through the Enhanced Permeability and Retention Effect (EPR) effect and macropinocytosis
Superior Efficacy of Novel Albumin-binding Auristatin E-based Drugs Compared to Auristatin E in a Panel of Human Xenograft Models in Mice


CytRx Corporation, Drug Discovery Branch, Engesserstr. 4, 79108 Freiburg, Germany

INTRODUCTION & RATIONALE:

Albumin-based Drug Delivery Concept

Rapid binding to Cys34 residue of serum albumin

Acid-sensitive breaking point

In the bloodstream, drug circulates as an albumin drug conjugate

Preferential, acid-promoted drug release in the target tissue

Albumin-binding group

Linker

Drug

AE-Keto-Sulf07 (LADR-7) and AE-Ester-Sulf07 (LADR-8) albumin-binding are rationally designed to release highly potent auristatin E derivatives at the tumor site in a pH-dependent manner. Our design of albumin-binding drugs is based on:

- Auristatin E (AE) cannot be used as a free drug due to toxicity.
- AE derivatives bind to endogenous albumin after i.v. administration with subsequent accumulation in tumor tissue.
- The novel LADR® (albumin-activated drug release) cleavable linker Sulfo7 confines aqueous solubility to the hydrophobic drug.
- The acid-sensitive hydrazone moiety promotes the release of the active drug at the tumor site.

RESULTS:

<table>
<thead>
<tr>
<th>pH and plasma-stability of the two albumin drug conjugates</th>
<th>AE-Keto-Sulf07</th>
<th>AE-Ester-Sulf07</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.4</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>pH 4.1</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Murine Plasma (CD1)</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Human Plasma (normal)</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

pH-stability: AE-Keto-Sulf07 releases AE-Keto; AE-Ester-Sulf07 releases AE-Ester. At acidic pH, the release of AE-Keto is significantly lower than that of AE-Ester.

Pretreatment stability: AE-Keto-Sulf07 as well as its release product, AE-Keto, are stable in both murine and human plasma. For AE-Ester-Sulf07, a higher release is observed. In murine plasma, the released AE-Ester is rapidly converted to Auristatin E, while in human plasma the conversion to AE is significantly slower.

Evaluation of the albumin-binding drugs vs. auristatin E in four human tumor xenograft models in nude mice

The antitumor efficacy of AE-Keto-Sulf07 and AE-Ester-Sulf07 was statistically significant compared to the control group and to auristatin E at its MTD (p < 0.05) in all four xenograft models. All doses are stated as AE equivalents.

CONCLUSIONS:

- Both AE-Keto-Sulf07 and AE-Ester-Sulf07 demonstrated excellent antitumor activity in all selected human tumor xenograft models.
- The albumin-binding drugs induced long-term partial and complete tumor regressions, even in models with large starting tumor volumes (270-380 mm³).
- The albumin-binding drugs showed statistically significant superior activity compared to the parent drug auristatin E in 8 of the 9 models tested.

Toxicity:

- AE-Keto-Sulf07 induced average body weight change of +8% at the end of the studies.
- AE-Ester-Sulf07 induced body weight loss only in the NSCLC models (> 15%). However, nude mice related skin lesions due to scratching and biting were consistently observed.
The antitumor efficacy of AE-Keto-Sulf07 and AE-Ester-Sulf07 was statistically significant compared to the control group and to auristatin E at its MTD ($p < 0.05$) in all four xenograft models. All doses are stated as AE equivalents.

Charles River Discovery Research Services Germany GmbH used adult female NMRI nu/nu mice (Charles River Laboratories) for RXF 631 and LXFA 737 xenograft studies. $p$-values were calculated with Kruskal-Wallis test followed by Dunn's method. Epo GmbH, Germany, used adult female NMRI nu/nu mice (Janvier, France) for A 375 and A 2780 xenograft studies. $p$-values were calculated with Mann-Whitney U-test. $\dagger$ = mouse died/sacrificed; $\dagger$ = injection day; $\ddagger$ = dose change. 2-Hydroxypropyl-β-cycloextrin = 2-HP:CD.
LADR-7, LADR-8 efficacy

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>79%</td>
<td>14%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>36%</td>
<td>50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>53%</td>
<td>13%</td>
</tr>
</tbody>
</table>

• Durable responses averaged 60-90 days

• Demonstrated statistically significant superiority over the control group and parent compound

• Highly effective, even in large tumors with starting volumes of 270-380 mm³
LADR-7, LADR-8 toxicity

Toxicity findings

LADR 7
- Average body weight increase of >6%

LADR 8
- Body weight loss of >15% only in the NSCLC models. Skin lesions due to scratching and biting were observed with LADR-8
Novel albumin-binding maytansinoids inducing long-term partial and complete tumor regressions in several human cancer xenograft models in nude mice

CytRx Corporation, Drug Discovery Branch, Engessterstr. 4, 79108 Freiburg, Germany

INTRODUCTION & RATIONALE

Maytansine and its analogs (e.g. DM1 and DM4) are potent microtubule-targeting compounds with a narrow therapeutic window. So far, only TDM1, an antibody-maytansinoid conjugate targeting the HER2 receptor, has been approved for the treatment of Herceptin®-resistant breast cancer.

Our design of two novel albumin-binding maytansinoids (LADR-9 and LADR-10) is based on:
- Identification of two novel maytansine-based highly potent payloads (ANSA-05, ANSA-13), selected from screening a library of maytansinoids in vitro (Poster #1657)
- Derivatization with a new water-solubilizing linker (SULF-07) resulting in LADR-9 and LADR-10 which bind in situ to the Cys-34 position of endogenous albumin
- Accumulation of the drug-albumin conjugate in tumor tissue
- Acid mediated drug release at the tumor site

IN VITRO EVALUATION

pH-Dependent stability of both drug-albumin conjugates

<table>
<thead>
<tr>
<th>Compound</th>
<th>pH-Dependent Release of Albumin Component after 4 h (24 h) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-LADR-9</td>
<td>pH 4.0: 49.6 (48.7), pH 7.4: 65.3 (53.7)</td>
</tr>
<tr>
<td>SA-LADR-10</td>
<td>pH 4.0: 22.5 (25.4), pH 7.4: 1.1 (3.9)</td>
</tr>
</tbody>
</table>

The serum albumin (SA) conjugates of LADR-9 and LADR-10 are cleaved under acidic conditions and release the active component.

Plasma stability of both free drugs and drug-albumin conjugates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Remaining in Plasma after 4 h (24 h) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANSA-05</td>
<td>Mouse: 68 (68), Rat: 98 (78), Human: 96 (80)</td>
</tr>
<tr>
<td>ANSA-13</td>
<td>Mouse: 98 (95), Rat: 99 (58), Human: 98 (80)</td>
</tr>
<tr>
<td>SULF-07</td>
<td>Mouse: 98 (67), Rat: 98 (27), Human: 98 (46)</td>
</tr>
</tbody>
</table>

The in situ binding to endogenous albumin significantly stabilizes the drug against degradation in plasma (also see Poster #1657).

ANTITUMOR ACTIVITY IN VIVO

Overview of the antitumor activity of maytansine and both albumin-binding drugs in various human FXD and CDX xenograft tumor models in nude mice

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative Tumor Volume on Day 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>LADR-9</td>
<td>96 (51)</td>
</tr>
<tr>
<td>LADR-10</td>
<td>105 (70)</td>
</tr>
</tbody>
</table>

Performance of nude mice bearing PDX (PDX-200, PDX-3020, PDX-300) xenografts and orthotopic tumors. Circulating LADR-9 and LADR-10 were statistically significant compared to the controls (p < 0.05). All data were calculated with the Mann-Whitney U test on day 26.

CONCLUSION

Both albumin-binding maytansinoids LADR-9 and LADR-10 were evaluated in six human tumor xenograft models and showed excellent antitumor activity inducing long-term partial and complete remission in all rodent models. In addition, both albumin-binding drugs were consistently superior over maytansine which was essentially inactive (statistically significant results). Importantly, even the treatment of large tumors with starting volumes up to 350 mm³ was highly effective.

In a few cases (namely, LXFE 937, MDA-MB 468 and HN 10913), which depended on the tumor type, significant body weight loss (~20%) with maytansine as well as with the albumin binding drugs was observed in the animals.
Perform at Charles River Freiburg, Germany using adult female NMRI nu/nu mice (CRL). Fragments of the tumor were transplanted subcutaneously.

The antitumor efficacy of LADR-9 and LADR-10 was statistically significant compared to the control (p < 0.01). p-Values were calculated with the Kruskal-Wallis test followed by Dunn’s method on day 50.

Perform at Epo GmbH, Germany using adult female NMRI nu/nu mice (Janvier, France). 1x10^7 cells were transplanted subcutaneously.

The antitumor efficacy of LADR-9 and LADR-10 was statistically significant compared to both control and maytansine (p < 0.01). p-Values were calculated with the Mann-Whitney U-test on day 22.
LADR-9 and LADR-10 efficacy

- Statistically significant anti-tumor activity of in:
  - Lung, breast, ovarian, renal cell, head & neck

- Long-term partial and complete reductions in relative tumor volume in all cancer models studied

- Durable responses averaged 60-90 days

- Demonstrated statistically significant superiority over the control group and parent compound

- Highly effective, even in large tumors with starting volumes of 350 mm³
LADR-9 and LADR-10 toxicity

Toxicity findings

Treatment was generally well tolerated. Toxic effects were strongly dependent on the tumor model, and body weight loss was observed in three of the six xenograft models.
Proof of concept for **LADR™** mechanism - aldoxorubicin

- First generation LADR product
- Doxorubicin with an albumin binding linker activated release
- Studied in over 600 patients
- Completed phase 2 and 3 in STS
- NantCell owns license and holds the IND
- ASCO 2018 poster shows no cardiotoxicity with patients treated with doses beyond doxorubicin equivalent of 1,000mg/m²
- NantCell studying in combination with immunotherapies and cell based therapies
LADR™ has broad targeting potential with serum albumin

- Binds to cysteine-34 on serum albumin
- No antibody or narrow target needed
- Broad potential use

ADC’s
Target selection is complex and limited to the gene expression

>30 different targets being pursued for solid tumors

LADR™ companion diagnostic

- Our discovery lab is developing a **patient identification companion diagnostic** which works in conjunction with LADR to:

  1. Identify optimal patients for treatment
  2. Improve outcomes for those patients treated
  3. Serve as rationale for payer reimbursement
  4. Justify premium pricing

- Potential to be a separate product revenue stream
- We will begin sharing information by CDA on the companion diagnostic beginning in July 2018
## LADR™ Competitive Advantages

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LADR™ Conjugates</th>
<th>Antibody-Drug Conjugates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad Therapeutic Utility and Patient Populations</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>No Narrow Antibody Receptor Required</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Low Risk of Immune Response</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Probability of clinical and regulatory success</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Low Cost of Goods</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Manufacturing process simplicity</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
**LADR™: high probability of clinical success**

<table>
<thead>
<tr>
<th>Drug Payload</th>
<th>LADR™ 7, 8</th>
<th>LADR™ 9, 10</th>
<th>Adcetris</th>
<th>Kadcyla</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auristatin</strong></td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Maytansanoid</strong></td>
<td></td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

There are 2 products approved with a related drug payload to LADR™.
**LADR™: high probability of regulatory success:**

- Known safety profile of auristatin and maytansinoid treatment
- No antibody associated risks with **LADR™**
  - PML
  - Cardiomyopathy
  - Pulmonary toxicity
  - Anaphylaxis
  - Angiodema
- No unknown risks due to new antibody
Important Safety Information

BOXED WARNING

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

Peripheral neuropathy (PN): ADCETRIS causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.

Anaphylaxis and infusion reactions: Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

Hematologic toxicities: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS. Administer G-CSF primary prophylaxis starting with Cycle 1 for previously untreated patients who receive ADCETRIS in combination with chemotherapy for Stage III/IV cHL. Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses.

Serious infections and opportunistic infections: Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections. Monitor complete blood counts prior to each ADCETRIS dose. Monitor more frequently for patients with Grade 3 or 4 neutropenia or severe thrombocytopenia. Promptly evaluate patients for fever and fever plus neutropenia.

Serious dermatologic reactions: Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

Hepatotoxicity: Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

PML: Fatal cases of JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider PML diagnosis in patients with new, onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.

Pulmonary toxicity: Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

Serious dermatologic reactions: Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

Gastrointestinal (GI) complications: Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious GI complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

Embryo-fetal toxicity: Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.
Important Safety Information

Warnings and Precautions
Do not substitute KADCYLA for or with trastuzumab (Boxed WARNING)

Hepatotoxicity (Boxed WARNING)

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases, has been observed in clinical trials with KADCYLA. Serious hepatobiliary disorders, including at least 2 fatal cases of severe drug-induced liver injury and associated hepatic encephalopathy, have been reported in clinical trials with KADCYLA. Some of the observed cases may have been confounded by comorbidities and concomitant medications with known hepatotoxic potential.

Monitor serum transaminases and bilirubin prior to initiation of KADCYLA treatment and prior to each KADCYLA dose. Patients with known active hepatitis B virus or hepatitis C virus were excluded from EMILIA. Reduce dose or discontinue KADCYLA as appropriate in cases of increased serum transaminases and/or total bilirubin. Permanently discontinue KADCYLA treatment in patients with serum transaminases >3xULN and concomitant total bilirubin >2xULN.

In clinical trials of KADCYLA, cases of nodular regenerative hyperplasia (NRH) of the liver have been identified from liver biopsies (3 cases out of 584 treated patients, 1 of which was fatal). NRH should be considered in all patients with clinical symptoms of portal hypertension and/or cirrhosis-like pattern seen on the computed tomography scan of the liver but with normal transaminases and no manifestations of cirrhosis. Diagnosis can be confirmed only by histopathology. Upon diagnosis, KADCYLA treatment must be permanently discontinued.

Left Ventricular Dysfunction (Boxed WARNING)

Patients treated with KADCYLA are at increased risk of developing left ventricular dysfunction. A decrease of LVEF to <40% has been observed in patients treated with KADCYLA. In EMILIA, left ventricular dysfunction occurred in 1.8% of patients in the KADCYLA-treated group and 3.3% of patients in the comparator group.

Assess LVEF prior to initiation of KADCYLA and at regular intervals (eg every 3 months) during treatment. Treatment with KADCYLA has not been studied in patients with LVEF <50% prior to treatment. If, at routine monitoring, LVEF is <40%, or is 40% to 45% with a 10% or greater absolute decrease below the pretreatment value, withhold KADCYLA and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue KADCYLA if the LVEF has not improved or has declined further.

Embryo-Fetal Toxicity (Boxed WARNING)

Pregnancy Category D: KADCYLA can cause fetal harm or death when administered to a pregnant woman. There are no adequate and well-controlled studies of KADCYLA in pregnant women and no reproductive and developmental toxicology studies have been conducted with ado-trastuzumab emtansine. Nevertheless, treatment with trastuzumab, the antibody component of KADCYLA, during pregnancy in the postmarketing setting has resulted in oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. DM1, the cytotoxic component, can be expected to cause embryo-fetal toxicity. If KADCYLA is used during pregnancy, or if the patient becomes pregnant while receiving KADCYLA or within 7 months of the last dose of KADCYLA, apprise the patient of the potential hazard to the fetus.

Verify pregnancy status prior to the initiation of KADCYLA. advise patients of the risks of embryo-fetal death and birth defects and the need for contraception during and for 7 months following treatment. Advise patients to contact their healthcare provider immediately if they suspect they may be pregnant.

If KADCYLA is administered during pregnancy, or if a pregnant patient becomes pregnant while receiving KADCYLA or within 7 months of the last dose of KADCYLA, immediately report exposure to the Genentech Adverse Event Line at 1-888-335-2555. Encourage women who may be exposed during pregnancy or within 7 months prior to conception, to enroll in the MoHER Pregnancy Registry by contacting 1-800-690-6720.

Pulmonary Toxicity

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome, have been reported in clinical trials with KADCYLA. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. In EMILIA, the overall frequency of pneumonitis was 1.2%.

Treatment with KADCYLA should be permanently discontinued in patients diagnosed with ILD or pneumonitis.

Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events.

Infusion-Related Reactions, Hypersensitivity Reactions

Treatment with KADCYLA has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions (IRR) and/or hypersensitivity; treatment with KADCYLA is not recommended for these patients.

Infusion-related reactions, characterized by one or more of the following symptoms—flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials of KADCYLA. In the randomized trial, the overall frequency of IRRs in patients treated with KADCYLA was 1.4%. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated.

KADCYLA treatment should be interrupted in patients with severe IRRs and permanently discontinued in the event of a life-threatening IRR. Patients should be observed closely for IRRs especially during the first infusion.

One case of a serious allergic/anaphylactoid-like infusion reaction has been observed in clinical trials of single-agent KADCYLA. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.
Kadcyla important safety information (continued)

Hemorrhage
Cases of hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in clinical trials with KADCYLA. Some of these bleeding events resulted in fatal outcomes. In EMILIA the incidence of ≥ Grade 3 hemorrhage was 1.8% in the KADCYLA-treated group and 0.8% in the comparator group. Although in some of the observed cases the patients were also receiving anticoagulation therapy or antiplatelet therapy, or had thrombocytopenia, in others there were no known additional risk factors. Anticoagulation therapy and antiplatelet agents may increase the risk of bleeding. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary.

Thrombocytopenia
Thrombocytopenia was reported in clinical trials of KADCYLA. The majority of these patients had Grade 1 or 2 events (< LLN to ≥50,000/mm3) with the nadir occurring by day 8 and generally improving to Grade 0 or 1 (≥75,000/mm3) by the next scheduled dose. In clinical trials of KADCYLA, the incidence and severity of thrombocytopenia were higher in Asian patients. In EMILIA, the incidence of ≥ Grade 3 thrombocytopenia was 14.5% in the KADCYLA-treated group and 0.4% in the comparator group. In Asian patients, the incidence of ≥ Grade 3 thrombocytopenia was 45.1% in the KADCYLA group and 1.3% in the comparator group. Monitor platelet counts prior to initiation of KADCYLA and prior to each KADCYLA dose. KADCYLA has not been studied in patients with platelet counts ≤100,000/mm3 prior to initiation of treatment. In the event of decreased platelet count to Grade 3 or greater (<50,000/mm3), do not administer KADCYLA until platelet counts recover to Grade 1 (≥75,000/mm3). Patients with thrombocytopenia (≤100,000/mm3) prior to initiation of KADCYLA and patients on anticoagulant treatment should be closely monitored during treatment with KADCYLA.

Neurotoxicity
Peripheral neuropathy, mainly as Grade 1 and predominantly sensory, was reported in clinical trials of KADCYLA. In EMILIA, the incidence of ≥ Grade 3 peripheral neuropathy was 2.2% in the KADCYLA-treated group and 0.2% in the comparator group. KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral neuropathy until resolution to ≤ Grade 2. Patients should be clinically monitored on an ongoing basis for signs/symptoms of neurotoxicity.

HER2 Testing
Detection of HER2 protein overexpression or gene amplification is necessary for selection of patients appropriate for KADCYLA therapy because these are the only patients studied for whom benefit has been shown. Assessment of HER2 status should be done using an FDA-approved test performed by laboratories with demonstrated proficiency. In the randomized study, patients with breast cancer were required to have evidence of HER2 overexpression defined as 3+ IHC and/or FISH amplification ratio ≥2.0 assessed by a validated test.

Extravasation
In KADCYLA clinical studies, reactions secondary to extravasation have been observed. These reactions, observed more frequently within 24 hours of infusion, were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration. Specific treatment for KADCYLA extravasation is unknown.
LADR™ manufacturing / cost of goods

Manufacturing simplicity vs. antibodies
- Small molecule manufacturing
- Less risk
- Lower costs
- Potential for less batch failures
- No problems with cell lines

Low cost of goods vs. antibodies
- Potential better profit margin
- Pricing flexibility
Where can LADR™ outperform ADCs?

- Safety
- Broad tumor potential in common tumor types
- Manufacturing simplicity
- Cost of goods
LADR™ potential areas of study and utilization

- Early lines of therapy in combination with immuno-therapies or cell based therapies
- After progression with immuno-therapy or cell based therapies
- In tumor types with no genetic mutation
- Head to head vs. an ADC indicated in a solid tumor(s)
Centurion BioPharma Corp

- Four albumin binding ultra high potency LADR™ candidates ready for IND enabling studies
- Pharma strategic collaboration will determine next steps with IND pre-meeting, studies and IND filing

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<tbody>
<tr>
<td>Auristatin Program</td>
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<td>LADR7: AE-Keto-Sulf07</td>
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<td>LADR8: AE-Ester-Sulf07</td>
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<td>Maytansinoid Program</td>
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<td>LADR9: PP072</td>
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<td>LADR10: FN296</td>
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FIGHTING CANCER WITH CUTTING EDGE SCIENCE
## LADR™ Milestones

<table>
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<tr>
<th>Event</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>File one or more patent applications</td>
<td>Q4 2017</td>
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<tr>
<td>Initiate activities for GMP manufacturing of LADR™ linkers</td>
<td>Q4 2017</td>
</tr>
<tr>
<td>Nominate one or more candidates for advancement into IND enabling studies</td>
<td>Q1 2018</td>
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<tr>
<td>Present preclinical data on LADR™ candidates at AACR ‘18</td>
<td>1H 2018</td>
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<tr>
<td>Begin LADR™ partnering discussions</td>
<td>1H 2018</td>
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<tr>
<td>Signed term sheet for major strategic alliance</td>
<td>By Sept 30, 2018</td>
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<tr>
<td>Deal completion date in 2H and close</td>
<td>By Dec 31, 2018</td>
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<tr>
<td>Partnership will determine next steps on pre-IND mtg, studies and filing</td>
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✓ Represents a completed milestone
LADR™ platform could be expanded beyond oncology: value creation

- Expansion to other disease states
- Study in highly efficacious drugs with high toxicity
- Targeted LADR™ delivery minimizes high toxicity
LADR™ Summary

▪ MOA designed to maximize tumor cell kill while minimizing toxicity
▪ Patient identifying companion diagnostic
▪ Proof of concept in aldoxorubicin
▪ High probability of clinical and regulatory success
▪ Broad solid tumor type potential
▪ Many advantages vs. ADCs
▪ Four LADR candidates ready for IND enabling studies
▪ H.C. Wainwright & Co valued the LADR pipeline of candidates at $60M (May 2018)
Business Development Objectives

▪ Centurion BioPharma Corp has a goal to facilitate a strategic transaction(s) with a potential partner(s) having the capability to:
  ▪ Develop all or select LADR™ candidates
  ▪ Fully develop the LADR™ platform

▪ Given the broad potential of the LADR™ platform, as well as its ability to address areas of significant unmet medical need, Centurion BioPharma Corp is open to the following transaction structures:
  ▪ Global or regional out-license
  ▪ R&D Collaboration

▪ The ideal partner will have the following key characteristics
  ▪ Track record of successfully advancing preclinical programs through to regulatory approval
  ▪ Access to the capital required for all development, manufacturing and regulatory activities

For More Information Please Contact:

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