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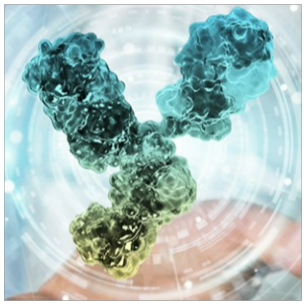


Enhanced Antibody Drug Conjugates (ADC)

Developer(s)

Ambrx (acquired by Johnson & Johnson, Inc.)

Originator

https://ambrx.com/

United States of America

Ambrx, founded in 2003 in San Diego, California, emerged from pioneering work in synthetic biology, specifically with the goal of expanding the genetic code to enable precise modifications of proteins. This idea was initiated by co-founders Peter Schultz and others from The Scripps Research Institute.

Sponsor(s)

Johnson & Johnson, Inc.

https://www.jnj.com/

Partnerships

Zhejiang Medicine Co., Ltd
https://www.zmc.top/en/

Novocodex Biopharmaceuticals Co., Ltd
http://www.novocodex.cn/

Sino Biopharmaceutical., Ltd
https://www.sinobiopharm.com/en/

Beigene
https://www.beigene.com

Technology information

Type of technology

Antibody conjugated drug molecule

Administration route

Intravenous, Oral, Subcutaneous, Topical (Rectal), Transdermal

Development state and regulatory approval

Active Pharmaceutical Ingredient (API)

ARX788

Development Stage

Phase III

Regulatory Approval

FDA granted orphan drug designation to ARX788 for the treatment of HER2-positive gastric cancer

Description

Antibody-drug conjugates (ADCs) employ site-specific antibodies incorporating non-natural amino acids, novel linker chemistries designed for both in vitro and in vivo stability, and a combination of existing and novel targeted receptor agonists as payloads. The primary mechanism of action for these ADCs involves the accumulation of free payload in the targeted tissues, which emerges as the predominant driver of biological activity. Due to this mechanism, the drug conjugate remains in the body for an extended period with increased plasma concentration peak stability compared to the parent drug.

Technology highlight

1) ADC contains a novel linker molecule that conjugates the drug molecule/ therapeutic protein with the human antibody. 2) Linker molecule is a synthetic amino acid (SAA) with site-specificity, homogenous, and undergoes stable conjugation. 3) These ADCs are based on AMBRX's proprietary genetic code technology i.e., noncanonical amino acids (ncAA) based protein engineering (amber codon (UAG) suppression) 4) These ADCs target human antigen-presenting immune cells, binding to them to subsequently activate specific cell signaling pathways. This leads to stimulation or inhibition of the targeted protein synthesis. Consequently leading to a sustained pharmacological action of the API payload at the target site.

Technology main components

1) Payload (API) (Drug that has a functional group that forms a covalent linkage with phosphate linker) 2) Targeting Ligand (eg: Chimeric, humanized, or human antibodies) 3) Linker Arm (Eg: Pyrophosphate ester; triphosphate ester; Tetraphosphate ester) 4) Phosphate Group All these ingredients combine to form a complex. This complex is stable extracellularly and labile intracellularly.

Information on the raw materials sourcing, availability and anticipated price

Not provided

Delivery device(s)

No delivery device

APIs compatibility profile

API desired features

Water-soluble molecules

Water-insoluble molecules

Small molecules

ADC has targeted enzyme inhibitors such as dihydrofolate reductase inhibitors and thymidylate synthase inhibitors, DNA intercalators, glucocorticoid receptor agonists, nuclear receptor agonists, anti-inflammatory agents, DNA cleavers, topoisomerase inhibitors, anthracycline family of drugs, vinca drugs, the mitomycins, bleomycin, the cytotoxic nucleosides, pteridine, diynenes, podophyllotoxins, differentiation inducers, and taxols. Cytotoxic drugs such as duocarmycins and CC-1065 and analogs of CBI, MCBI, doxorubicin, aolastatins, combretastatin, etc. Other drugs are glucocorticoid agonists.

Proteins

Biotherapeutics such as Monoclonal Antibodies (Eg: Brentuximab vedotin, Trastuzumab emtansine, Polatuzumab vedotin, Inotuzumab ozogamicin, Moxetumomab pasudotox) are targeted for the ADC formulation. Therapeutic proteins are also targeted as a payload for the ADC formulation.

Additional solubility data

Not provided

Additional stability data

Not provided

API loading: Maximum drug quantity to be loaded

75-90 wt%

API co-administration

2 different APIs : Not provided

LogP

Min: 3 Max: 6

Scale-up and manufacturing prospects

Scale-up prospects

Ambrx has a manufacturing capacity of 2000 liters for ADC formulations.

Tentative equipment list for manufacturing

Not provided

Manufacturing

1. Expression and purification of antibodies with non-natural amino acids 2. Synthesis of ADC payloads and linkers 3. Site-specific conjugation 4. Intact Mass determination 5. DAR determination and antibody preparation evaluation

Specific analytical instrument required for characterization of formulation

1. Mass Spectrometry (using Thermo Deconvolution 2.0 Software) 2. HPLC 3. Flow Cytometry 4. LCMS

Clinical trials

ARX788-1711

Identifier

NCT03255070

Link

https://clinicaltrials.gov/study/NCT03255070

Phase

Phase I

Status

Completed

Sponsor

Ambrx, Inc.

More details

This 2-part, Phase 1, open-label study will determine the recommended Phase 2 dose (RP2D) of ARX788 in subjects with advanced HER2 positive cancers and will assess the safety and anticancer activity in breast, gastric and other advanced HER2 positive solid tumors.

Purpose

A Dose-escalation, Expansion Study of ARX788, in Advanced Solid Tumors Subjects With HER2 Expression (ACE-Pan Tumor 01)

Interventions

Intervention 1

ARX788

Countries

United States of America

Australia

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2018-03-20

Anticipated Date of Last Follow-up

2024-01-31

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2023-09-13

Actual Completion Date

2023-10-18

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Inclusion Criteria * Age \>18 years * Life expectancy \>3 months. * Female or male subjects whose advanced HER2 expressing cancer has failed standard of care treatments, or for whom such therapy is not acceptable to the subject. Subjects with advanced breast, gastric cancer, or other solid tumor who test positive for HER2 by ASCO/CAP criteria (either IHC or FISH) must have received prior treatment with a trastuzumab containing therapy. Subjects who have been previously treated with pertuzumab, TDM-1, lapatinib, or other available and accessible HER2-directed therapies or investigational therapies are eligible. * Disease measurability: * Phase 1a: measurable or non-measurable disease per RECIST v 1.1. * Phase 1b

Health status

Not provided
Other health status: Breast cancer, gastric cancer / gastroesophageal adenocarcinoma, and other advanced HER2-positive solid tumors

Study type

Interventional (clinical trial)

Enrollment

106

Allocation

Not provided

Intervention model

Sequential assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Other : "Every 3 weeks/ Every 4 weeks "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

ARX517

Identifier

NCT04662580

Link

https://clinicaltrials.gov/study/NCT04662580

Phase

Phase I

Status

Recruiting

Sponsor

Ambrx, Inc.

More details

This is a phase 1 study to assess the safety and tolerability of ARX517 in adult subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC).

Purpose

ARX517 in Subjects With Metastatic Castration-Resistant Prostate Cancer

Interventions

Intervention 1

ARX517

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2021-07-27

Anticipated Date of Last Follow-up

2024-05-08

Estimated Primary Completion Date

2025-12-01

Estimated Completion Date

2027-03-01

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

- Male

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Key Inclusion Criteria: * Male subjects ≥ 18 years at the first time of providing written informed consent. * Histologically confirmed prostate adenocarcinoma. * Documented metastatic disease and evidence of disease progression * Castration-resistant prostate cancer defined as surgical or medical castration with serum testosterone levels of ≤ 50 ng/dL (1.73 nM) at Screening. For patients who have not undergone an orchiectomy, must be undergoing treatment with a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist and must agree to continue such therapy while on study treatment. * Prior receipt of the following for metastatic prostate cancer: * at least two lines of treatment * at least two Food and Drug Administration (FDA)-approved therapies

Health status

Not provided
Other health status: Metastatic Castration-Resistant Prostate Cancer

Study type

Interventional (clinical trial)

Enrollment

262

Allocation

Not provided

Intervention model

Single group assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Other : "once every 3 weeks, every 4 weeks "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

ACE-Breast-03

Identifier

NCT04829604

Link

https://clinicaltrials.gov/study/NCT04829604

Phase

Phase II

Status

Recruiting

Sponsor

Ambrx, Inc.

More details

A Global, Phase 2 Study of ARX788 in HER2-positive Metastatic Breast Cancer Patients who were previously treated with T-DXd

Purpose

ARX788 in HER2-positive, Metastatic Breast Cancer Subjects (ACE-Breast-03)

Interventions

Intervention 1

ARX788

Countries

United States of America

Australia

France

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2021-10-26

Anticipated Date of Last Follow-up

2024-06-10

Estimated Primary Completion Date

2025-06-01

Estimated Completion Date

2026-12-01

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Key Inclusion Criteria: * Age ≥ 18 years and older * Life expectancy ≥ 6 months * Unresectable or metastatic breast cancer subjects * Presence of at least one measurable lesion per RECIST v 1.1 * Subjects must have an adequate tumor sample available for confirmation of HER2 status * Subjects must have had prior treatment with no more than 5 prior regimens of systemic treatment in the metastatic setting. One of these prior treatments must have been treatment with T-DXd. * Subjects with stable brain metastases * Acute toxicities from any prior therapy, surgery, or radiotherapy must have resolved to Grade ≤1 as per the NCI-CTCAE v 5.0, except alopecia * Adequate organ functions * Willing and able to understand and sign an informed consent inform and to comply with all aspects of the protocol

Health status

Not provided
Other health status: HER2-positive, Metastatic Breast Cancer

Study type

Interventional (clinical trial)

Enrollment

71

Allocation

Not provided

Intervention model

Single group assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Other : "once every 3 weeks "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

ACE-Pan tumor-02

Identifier

NCT05041972

Link

https://clinicaltrials.gov/study/NCT05041972

Phase

Phase II

Status

Withdrawn

Sponsor

Ambrx, Inc.

More details

A Global Phase 2 Study to Evaluate the Efficacy and Safety of ARX788 for Selected HER2-mutated or HER2-amplified/overexpressed Solid Tumors (ACE-Pan tumor-02)

Purpose

ARX788 in Selected HER2-mutated or HER2-amplified/Overexpressed Solid Tumors (ACE-Pan Tumor-02)

Interventions

Intervention 1

ARX788

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2021-11-05

Anticipated Date of Last Follow-up

2022-09-09

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2022-04-20

Actual Completion Date

2022-04-20

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Inclusion Criteria: * Age ≥ 18 years and older * Life expectancy \> 3 months * Eastern Cooperative Oncology Performance Status ≤ 1 * HER2 status must be determined from a local Clinical Laboratory Improvement Amendments (CLIA) or equivalent-certified laboratory. * Cohort 1, Cohort 2, and Explanatory Cohort A: HER2 mutated subjects with pre-specified HER2 activating mutation. Subjects with HER2 mutations in NSCLC (Cohort 1), breast cancer (Cohort 2), and other solid tumors (Cohort A) who have not received prior HER2 antibody drug conjugate (ADC) treatment are eligible. * Cohort 3: Subjects with HER2 amplifications in biliary tract cancers (BTC) who have not received prior HER2 ADC treatment are eligible. * Cohort 4: Subjects with HER2 amplifications in colorectal cancer (CRC), ovarian.

Health status

Not provided
Other health status: HER2-amplified/Overexpressed Solid Tumors

Study type

Interventional (clinical trial)

Enrollment

Not provided

Allocation

Not provided

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Other : "once every 3 weeks "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

PRO-ARX201-701

Identifier

NCT00778518

Link

https://clinicaltrials.gov/study/NCT00778518

Phase

Phase II

Status

Completed

Sponsor

Ambrx, Inc.

More details

Study to find the optimal dose of Growth Hormone Replacement in young adult patients suffering from childhood onset growth hormone deficiency (GHD).

Purpose

Safety, Tolerability and PK/PD Study in Young Adult Patients With Childhood Onset Growth Hormone Deficiency (GHD).

Interventions

Intervention 1

ARX201

Intervention 2

ARX201

Intervention 3

ARX201

Countries

Hungary

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2008-07-01

Anticipated Date of Last Follow-up

2009-10-09

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2009-10-01

Actual Completion Date

2009-10-01

Studied populations

Age Cohort

Adults

Genders

- Male

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Inclusion Criteria: * 18-30 years old * GHD of childhood onset * completed growth * IGF-1 \<=2SDS * rhGH treatment naive * hGH levels below cut-off Exclusion Criteria: * History of malignancy or intracranial tumors * ECG abnormality * ICH * hepatic dysfunction * renal impairment * major medical conditions * inadequate T4 * positive for HBV, HCV, or HIV * alcohol or drug abuse

Health status

Not provided

Study type

Interventional (clinical trial)

Enrollment

36

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Single blind masking

Masking description

Not provided

Frequency of administration

Other : "Every 2 months "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

237527

Identifier

NCT06224673

Link

https://clinicaltrials.gov/study/NCT06224673

Phase

Phase II

Status

Not yet recruiting

Sponsor

Laura Huppert, MD, BA

More details

This phase II trial tests how well ARX788 works in treating patients diagnosed with HER2-low, locally advanced unresectable or metastatic breast cancer. ARX788 is an antibody-drug conjugate (ADC) that is given by infusion (diluted and injected slowly into veins). Antibodies are proteins which are naturally produced by the body's immune system to help fight infections. ARX788 consists of antibodies that have been attached to a toxin that has the potential to kill cancer cells. ARX788 sticks to a protein called human epidermal growth factor receptor (HER2), which is found on some breast cancer cells. Giving ARX788 may be safe and effective in treating patients with HER2-low locally advanced unresectable metastatic breast cancer.

Purpose

ARX788 for Treating Patients With HER2-low Locally Advanced Unresectable or

Metastatic Breast Cancer

Interventions

Intervention 1

ARX788

Intervention 2

Computed Tomography (CT)

Intervention 3

Biospecimen Collection

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

2024-10-15

Actual Start Date

Not provided

Anticipated Date of Last Follow-up

2024-09-10

Estimated Primary Completion Date

2028-02-29

Estimated Completion Date

2028-02-29

Actual Primary Completion Date

Not provided

Actual Completion Date

Not provided

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Inclusion Criteria: * Male or female participants age 18 years or greater with the ability to provide written informed consent for the study. * Eastern Cooperative Oncology Group (ECOG) score of 0-2. * Estimated life expectancy of at least at 6 months per investigator assessment. * Ability to understand and the willingness to sign a written informed consent document. * Pathologically documented HER2-low locally advanced unresectable or metastatic breast cancer. NOTE: human epidermal growth factor receptor 2 (HER2) low status determined by HER2 immunohistochemistry (IHC) 1+ or 2+ and no evidence of HER2 gene amplification by in situ hybridization (ISH)/fluorescence in situ hybridization (FISH), which can be documented from any tumor sample during the patient's cancer treatment history (earl

Health status

Not provided

Other health status: Advanced Unresectable or Metastatic Breast Cancer

Study type

Interventional (clinical trial)

Enrollment

36

Allocation

Not provided

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Other : "every 21 days "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

ZMC-ARX788-101

Identifier

NCT02512237

Link

https://clinicaltrials.gov/study/NCT02512237

Phase

Phase I

Status

Terminated

Sponsor

Zhejiang Medicine Co., Ltd.

More details

This is a 2-part, Phase 1 FIH study with Phase 1a designed to determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) in subjects with metastatic cancers with a human epidermal growth factor receptor 2 (HER2) test result that is in situ hybridization (ISH) positive (+) or immunohistochemistry (IHC) 3+ or 2+, and Phase 1b designed to assess anticancer activity and safety in three expansion cohorts: two different advanced breast cancer expansion cohorts (namely, for tumors that test as HER2 ISH positive or IHC3+ and for tumors that test as HER2 ISH negative with IHC 2+), and one advanced gastric cancer expansion cohort (for tumors that test as HER2 ISH positive or IHC3+).

Purpose

A Dose-escalation Study of ARX788, IV Administered in Subjects With Advanced

Cancers With HER2 Expression

Interventions

Intervention 1

ARX788

Countries

Australia

New Zealand

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2016-03-01

Anticipated Date of Last Follow-up

2020-06-03

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2017-01-01

Actual Completion Date

2017-01-01

Studied populations

Age Cohort

- Adults
- Older Adults

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

No

Comments about the studied populations

Inclusion Criteria: 1. Life expectancy \>12 weeks. 2. BMI is between 18 to 32 kg/m2 3. Subjects whose advanced cancer has failed treatment or whose cancer has progressed following available standard therapy or for whom such therapy is not acceptable to the subject. Subjects whose tumor tissue local laboratory results are HER2 ISH positive or IHC3+ must have been previously treated with a HER2 targeting therapy (e.g. trastuzumab, in the country or region where such therapies are available and part of standard of care), or have failed SOC therapy. Subjects who have been previously treated with a HER2 targeting therapy such as trastuzumab or ado-trastuzumab emtansine are eligible. 4. Disease measurability: Phase 1a: measureable or non-measureable disease; Phase 1b: disease must be measureabl

Health status

Not provided
Other health status: Advanced Cancers With HER2 Expression

Study type

Interventional (clinical trial)

Enrollment

9

Allocation

Not provided

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Other : "once every 3 weeks "

Studied LA-formulation(s)

Injectable

Studied route(s) of administration

Intravenous

Use case

Treatment

Key resources

Not provided

Excipients

Proprietary excipients used

No proprietary excipient used

Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration

No novel excipient or existing excipient used

Residual solvents used

No residual solvent used

Additional features

Other features of the technology

- Drug-eluting

Release properties

Preclinical studies of ARX788 show that the API released from the ADC increases with time.

Injectability

18-22 gauge needle is used for the ADC injection infusion

Safety

Phase 1 clinical trials of ARX788 revealed no dose-limiting toxicities or treatment-related serious adverse events (TEAE). 28/30 (93.3%) patients experienced at least one drug-related adverse event (AE) and 13.3% experienced grade 3 ARX788-related AEs. Preclinical studies in monkeys demonstrated a favorable safety profile for ARX788.

Stability

1. Structural stability - Preclinical studies show that ADCs have robust plasma stability coupled with rapid release of payload in a lysosomal environment. 2. Formulation stability - As a formulation, the stability data of ADC has not yet been disclosed.

Storage conditions and cold-chain related features

Not provided

Potential application(s)

Therapeutic area(s)

Other(s) : "inflammatory diseases"

Oncology

Use case(s)

Treatment

Use of technology

Ease of administration

- Administered by a community health worker
- Administered by a nurse
- Administered by a specialty health worker

Frequency of administration

Weekly, Monthly

User acceptance

Not provided

Targeted user groups

Age Cohort

- Adults
- Older Adults

Genders

- All

Pregnant individuals

Unspecified

Lactating individuals

Unspecified

Healthy individuals

No

Comment

Not provided

Potential associated API(s)

ARX788

Class(es)

anti-HER2 antibody drug conjugate

Development stage

Phase III

Clinical trial number(s)

NCT04829604

Foreseen/approved indication(s)

HER2-positive gastric cancer, advanced or metastatic HER2-positive breast cancer, and other solid tumors

Foreseen user group

Adults < 18 years of old having HER-2 positive gastric cancer

Foreseen duration between application(s)

Every 3 weeks

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

FDA granted orphan drug designation to ARX788 for the treatment of HER2-positive gastric cancer

ARX517

Class(es)

anti-PSMA antibody drug conjugate

Development stage

Phase I/II

Clinical trial number(s)

NCT04662580

Foreseen/approved indication(s)

Prostate cancer

Foreseen user group

Adults who are <18 years old with metastatic castration-resistant prostate cancer

Foreseen duration between application(s)

Every 3 weeks; Every 4 weeks

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

ARX305

Class(es)

anti-CD-70 antibody drug conjugate

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

Not provided

Foreseen user group

Not provided

Foreseen duration between application(s)

Not provided

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

ARX107

Class(es)

IL2 cytokine (PEGlated)

Development stage

Pre-clinical

Clinical trial number(s)

Not provided

Foreseen/approved indication(s)

Not provided

Foreseen user group

Not provided

Foreseen duration between application(s)

Not provided

Applications to Stringent Regulatory Authorities (SRA) / regulatory approvals

Not provided

Patent info

Description

Antibody drug conjugate for anti-inflammatory applications

Brief description

Antibody-drug conjugates (ADCs) comprising an antibody conjugated to an anti-inflammatory therapeutic agent via a phosphate-based linker with tunable extracellular and intracellular stability are described.

Representative patent

US11510993B2

Category

Not provided

Patent holder

Merck Sharp and Dohme LLC Ambrx Inc

Exclusivity

Not provided

Expiration date

November 15, 2038

Status

Active

Description

Phosphate based linkers for intracellular delivery of drug conjugates

Brief description

Phosphate-based linkers with tunable stability for intracellular delivery of drug conjugates are described. The phosphate-based linkers comprise a monophosphate, diphosphate, triphosphate, or tetraphosphate group (phosphate group) and a linker arm comprising a tuning element and optionally a spacer. A payload is covalently linked to the phosphate group at the distal end of the linker arm and the functional group at the proximal end of the linker arm is covalently linked to a cell-specific targeting ligand such as an antibody. These phosphate-based linkers have differentiated and tunable stability in blood vs. an intracellular environment (e.g. lysosomal compartment).

Representative patent

US10550190B2

Category

Not provided

Patent holder

Ambrx Inc; Merck Sharp and Dohme LLC

Exclusivity

Not provided

Expiration date

March 12, 2036

Status

Active

Description

Prostate-specific membrane antigen antibody drug conjugates

Brief description

This invention relates to prostate-specific membrane antigen (PSMA) antibodies and antibody drug conjugates comprising at least one non-naturally-encoded amino acid. Disclosed herein are αPSMA antibodies with one or more non-naturally encoded amino acids and further disclosed are antibody drug conjugates wherein the αPSMA antibodies of the invention are conjugated to one or more toxins. Also disclosed herein are non-natural amino acid dolastatin analogs that are further modified post-translationally, methods for effecting such modifications, and methods for purifying such dolastatin analogs. Typically, the modified dolastatin analogs include at least one oxime, carbonyl, dicarbonyl, and/or hydroxylamine group. Further disclosed are methods for using such non-natural amino acid antibody dru

Representative patent

US20220033518A1

Category

Formulation

Patent holder

Ambrx Inc

Exclusivity

Not provided

Expiration date

March 2, 2022

Status

Pending

Supporting material

Publications

** Lu, H., Wang, D., Kazane, S., Javahishvili, T., Tian, F., Song, F., Sellers, A., Barnett, B., & Schultz, P. G. (2013). Site-specific antibody-polymer conjugates for siRNA delivery. Journal of the American Chemical Society, 135(37), 13885–13891. https://doi.org/10.1021/ja4059525 **

We describe here the development of site-specific antibody-polymer conjugates (APCs) for the selective delivery of small interference RNAs (siRNAs) to target cells. APCs were synthesized in good yields by conjugating an aminooxy-derivatized cationic block copolymer to an anti-HER2 Fab or full length IgG by means of genetically encoded *para*-acetyl phenylalanine (*p*AcF). The APCs all showed comparable binding affinity to HER2 as their native counterparts and no significant cellular cytotoxicity. Mutant S202-*p*AcF Fab and Q389-*p*AcF IgG polymer conjugates specifically delivered siRNAs to HER2+ cells and mediated potent gene silencing at both the mRNA and protein levels. However, a mutant A121-*p*AcF IgG polymer conjugate, despite its high binding affinity to HER2 antigen, did not induce a significant RNA interference response in HER2+ cells, presumably due to steric interference with antigen binding and internalization. These results highlight the importance of conjugation site on the activity of antibody-polymer based therapeutics and suggest that such chemically-defined APCs may afford a useful targeted delivery platform for siRNAs or other nucleic acid based therapies.

** Jackson, D., Atkinson, J., Guevara, C. I., Zhang, C., Kery, V., Moon, S. J., Virata, C., Yang, P., Lowe, C., Pinkstaff, J., Cho, H., Knudsen, N., Manibusan, A., Tian, F., Sun, Y., Lu, Y., Sellers, A., Jia, X. C., Joseph, I., Anand, B., … Stover, D. (2014). In vitro and in vivo evaluation of**

**cysteine and site specific conjugated herceptin antibody-drug conjugates. PloS one, 9(1), e83865. https://doi.org/10.1371/journal.pone.0083865 **

We report the results from the first direct preclinical comparison of a site specific non-natural amino acid anti-Her2 ADC and a cysteine conjugated anti-Her2 ADC. We report that the site specific non-natural amino acid anti-Her2 ADCs have superior *in vitro* serum stability and preclinical toxicology profile in rats as compared to the cysteine conjugated anti-Her2 ADCs. We also demonstrate that the site specific non-natural amino acid anti-Her2 ADCs maintain their *in vitro* potency and *in vivo* efficacy against Her2 expressing human tumor cell lines. Our data suggests that site specific non-natural amino acid ADCs may have a superior therapeutic window than cysteine conjugated ADCs.

** Skidmore L, Sakamuri S, Knudsen NA, et al. ARX788, a site-specific anti-HER2 antibody-drug conjugate, demonstrates potent and selective activity in HER2-low and T-DM1–resistant breast and gastric cancer. Mol Cancer Ther. 2020;19(9):1833-1843. doi:10.1158/1535-7163.MCT-19-1004
 **

First-generation antibody-drug conjugates (ADC) are heterogeneous mixtures that have shown clinical benefit, but generally exhibited safety issues and a narrow therapeutic window due, in part, to off-target toxicity caused by ADC instability. ARX788 is a next-generation, site-specific anti-HER2 ADC that utilizes a unique nonnatural amino acid-enabled conjugation technology and a noncleavable Amberstatin (AS269) drug-linker to generate a homogeneous ADC with a drug-to-antibody ratio of 1.9. ARX788 exhibits high serum stability in mice and a relatively long ADC half-life of 12.5 days. When compared *in vitro* against T-DM1 across a panel of cancer cell lines, ARX788 showed superior activity in the lower HER2-expressing cell

lines and no activity in normal cardiomyocyte cells. Similarly, ARX788 significantly inhibited tumor growth, and generally outperformed T-DM1 in HER2-high and HER2-low expression xenograft models. Breast and gastric cancer patient-derived xenograft studies confirmed strong antitumor activity of ARX788 in HER2-positive and HER2-low expression tumors, as well as in a T-DM1-resistant model. The encouraging preclinical data support the further development of ARX788 for treatment of patients with HER2-positive breast and gastric cancer, including those who have developed T-DM1 resistance, and patients with HER2-low expression tumors who are currently ineligible to receive HER2-targeted therapy.

Additional documents

No documents were uploaded

Useful links

There are no additional links

Access principles

Collaborate for development

Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

Share technical information for match-making assessment

Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

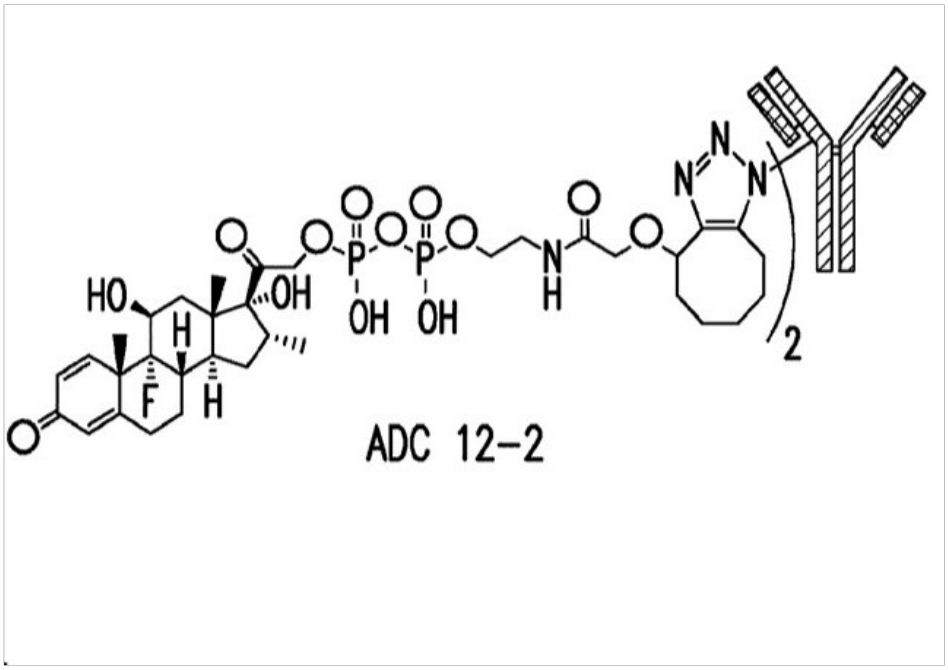
Work with MPP to expand access in LMICs

In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

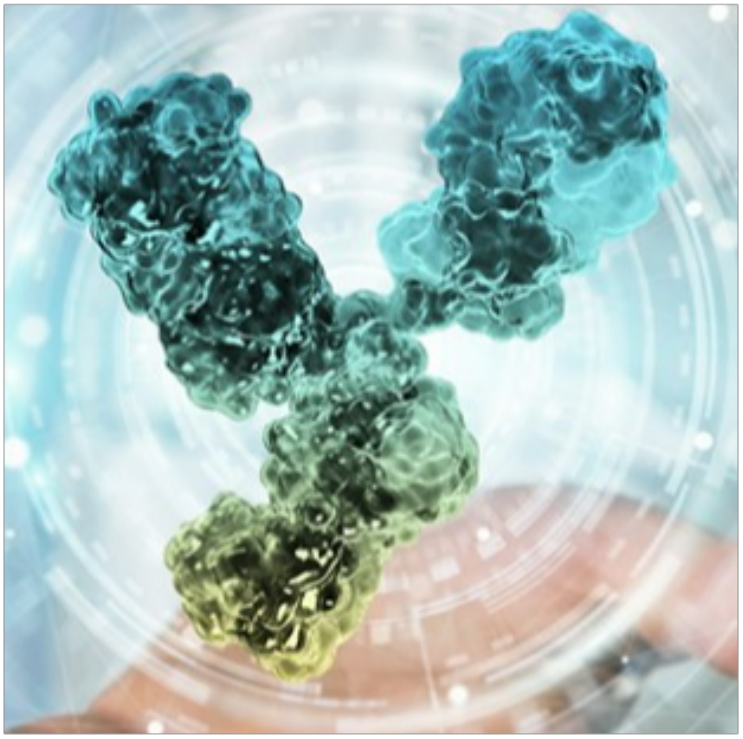
Comment & Information

Illustrations



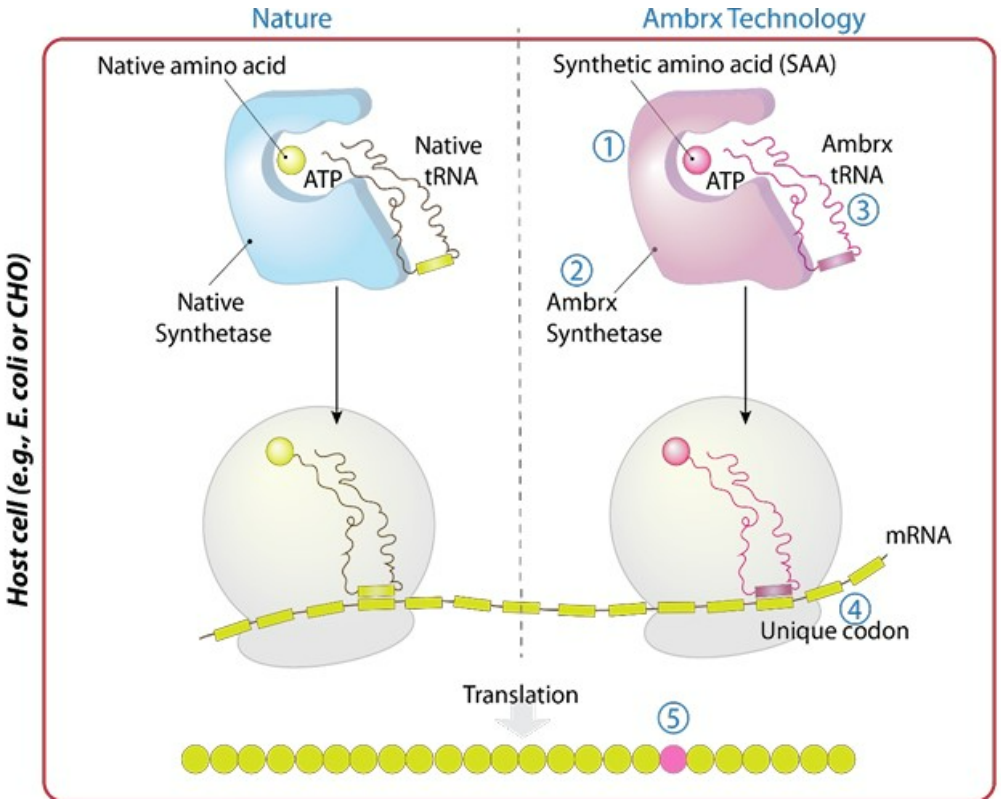
Antibody-drug conjugate (ADC)

Ambrx, Inc. (2020). Antibody-drug conjugates and methods of use (U.S. Patent No. 10,550,190). U.S. Patent and Trademark Office. https://patents.google.com/patent/US10550190B2/en



3D illlustration of ADC

Ambrx. (n.d.). Enhanced technology. Retrieved November 7, 2024, from https://ambrx.com/technology/#enhanced



Intracellular Mechanism of Action of ADC Technology

Ambrx. (n.d.). Enhanced technology. Retrieved November 7, 2024, from https://ambrx.com/technology/#enhanced