# Research and Development

## Research and Development

**Astellas aims to create a continuous stream of innovative medicines. We will focus on steady progress of six key post-POC pipeline projects that are expected to contribute to midterm growth, and will pursue cutting-edge science with efficient drug discovery approaches.**

### Core Strategy of Research and Development

Astellas sets targets of research and development (R&D) from multiple perspectives through the Focus Area approach and works to create innovative medicines to fulfill high unmet medical needs based on the concepts of Best Science, Best Talent (optimal personnel), and Best Place (optimum environment).

We determine the priorities of development candidates at the early stages and optimize resource allocation according to priorities. These efforts have achieved results in reduction of the time for R&D and improvement of cost efficiency.

In late-stage development, we allocate management resources extensively to six key post-POC* projects. We aim to characterize the therapeutic potential of these projects in development. In Strategic Plan 2018, the potential annual sales expected for these projects are described in the table below.

* POC ("Proof of Concept"): Verification of clinical efficacy

**Potential Size of Key Post-POC Pipeline**

| Potential size*1 (at peak, billion yen) | Key post-POC pipeline*2 |
|---|---|
| 400 – 500 | • XTANDI (enzalutamide) |
| 200 – 300 | • fezolinetant |
| 100 – 200 | • zolbetuximab |
| 50 – 100 | • enfortumab vedotin<br>• gilteritinib |

* Not disclosed for roxadustat
*1 Sales amount in the case of successful development in the patient segments currently being evaluated. Some patient segments under evaluation may not be included in the potential size because development is still in an early stage.
*2 Target diseases listed in the current pipeline list (P45) are included in the projection. XTANDI also includes sales for indications that have already been approved.

### Key Post-POC Pipeline Projects

**XTANDI (generic name: enzalutamide)**

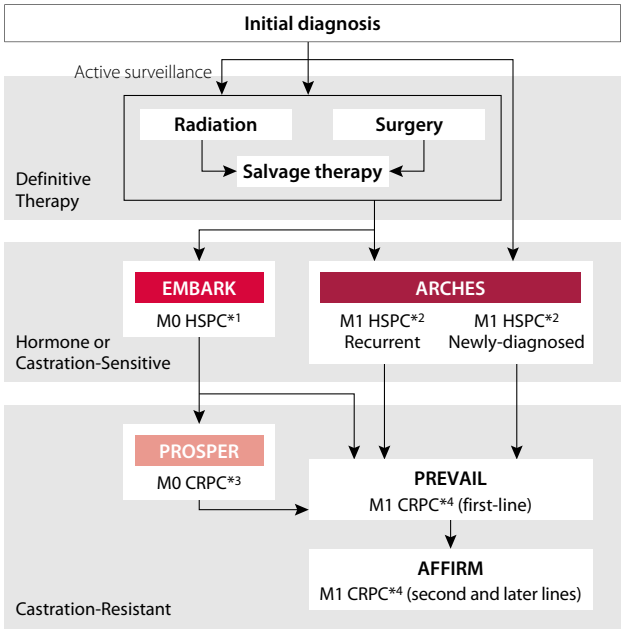
XTANDI is marketed worldwide for the treatment of metastatic castration-resistant prostate cancer (CRPC)*. Development is ongoing to expand the indication to earlier stages of prostate cancer.

In September 2017, Phase 3 PROSPER trial in patients with non-metastatic CRPC had achieved its primary endpoint. Astellas submitted regulatory applications based on these data in the U.S. and Europe. The U.S. Food and Drug Administration (FDA) granted approval for non-metastatic CRPC in July 2018.

Two Phase 3 trials (ARCHES and EMBARK) are also ongoing in patients with metastatic hormone-sensitive prostate cancer (HSPC) and non-metastatic HSPC.

* In Japan, XTANDI has been approved for CRPC.

**Maximizing the Value of Enzalutamide in Prostate Cancer**




*1 M0 HSPC: Non-metastatic hormone-sensitive prostate cancer
*2 M1 HSPC: Metastatic hormone-sensitive prostate cancer
*3 M0 CRPC: Non-metastatic castration-resistant prostate cancer
*4 M1 CRPC: Metastatic castration-resistant prostate cancer

## Gilteritinib

Gilteritinib is a FLT3/AXL inhibitor which is being developed for acute myeloid leukemia (AML). Gilteritinib inhibits both FLT3, a receptor-type tyrosine kinase known to be involved in cancer cell proliferation, and AXL, which is reported to be associated with resistance to some forms of chemotherapy.

AML is a cancer that is most commonly experienced in elderly people with the incidence rate increasing with age. In 2017, the numbers of newly diagnosed AML patients were around 17,500 in the U.S., 13,200 in western Europe, and 5,600 in Japan*. The prognosis of relapsed or refractory FLT3-mutation positive (FLT3mut+) AML is poor with low response rates to salvage therapy. Resistance to current AML treatment and ineligibility of high-intensity induction chemotherapy for elderly patients due to an excessive physical burden also make challenges in AML treatment. A promising new treatment has been awaited in AML treatment landscape.

**Development Progress of Gilteritinib in Each Region**

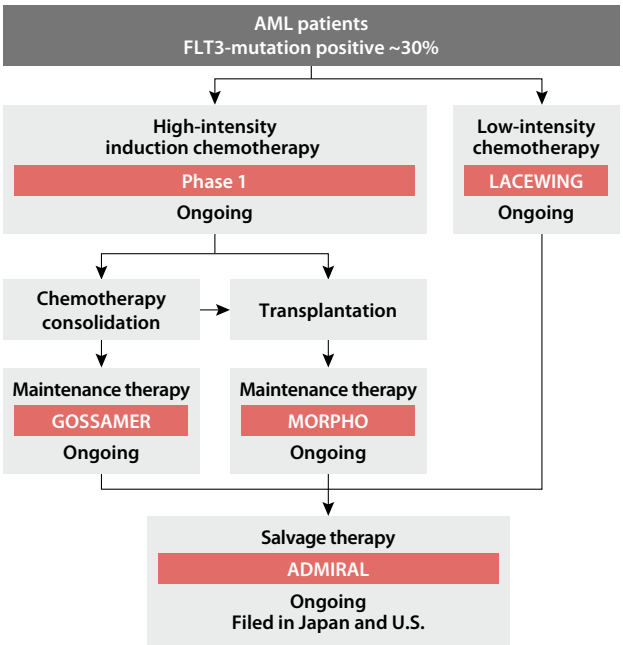
| | Development stage | Regulatory designation |
|---|---|---|
| **Japan** | Filed in Mar. 2018 | • SAKIGAKE designation<br>• Orphan Drug designation |
| **U.S.** | Filed in Mar. 2018<br>(PDUFA* date: Nov. 2018) | • Fast Track designation<br>• Orphan Drug designation |
| **Europe** | Phase 3 | • Orphan designation |

* PDUFA: Prescription Drug User Fee Act

Astellas is conducting the multiple Phase 3 trials to evaluate efficacy and safety of gilteritinib in AML patients at various therapeutic stages. In March 2018, a new drug application (NDA) for marketing approval of gilteritinib was submitted in Japan and the U.S. for the treatment of adult patients with FLT3mut+ relapsed and refractory AML based on the interim analysis data from the ongoing Phase 3 ADMIRAL trial. In this patient population, gilteritinib has been granted for SAKIGAKE designation in Japan and Fast Track designation in the U.S. Astellas has been working to accelerate development of gilteritinib by utilizing the various expedited regulatory pathways in each region. The status of filing and regulatory designation is shown in the table in this page.

* Annual Incidence in 2017 in U.S., EU5 and JP. CancerMPact (Synix Inc./Kantar Health)

**Gilteritinib in AML Treatment Landscape**



## Enfortumab Vedotin

Enfortumab vedotin is an antibody drug conjugate*1 (ADC) targeting Nectin-4, a cell adhesion molecule. While it is stable in blood, it is designed to kill only the targeted cancer cells after its internalization into cancer cells expressing Nectin-4.

Astellas is developing enfortumab vedotin as a treatment for urothelial cancer. In Japan, the U.S. and Europe, approximately 233,000*2 new patients are diagnosed with urothelial cancer annually. It is reported that some patients are confirmed for metastasis at the time of initial diagnosis of urothelial cancer and the five-year survival rate is low. A high recurrence rate is reported even if diagnosed and treated at an early stage. A promising new treatment is awaited.

Currently, aiming for earlier approval in each region, Phase 2 and Phase 3 trials in patients with locally advanced or metastatic urothelial cancer previously treated with a checkpoint inhibitor (CPI) are ongoing. Enfortumab vedotin is also being evaluated for the various usage in urothelial cancer including combination therapy with a CPI or monotherapy.

The U.S. FDA has granted Breakthrough Therapy designation to enfortumab vedotin for patients with locally advanced or metastatic urothelial cancer who were previously treated with CPIs.

*1 Antibody drug conjugate (ADC): ADCs are monoclonal antibodies that are designed to selectively deliver cytotoxic agents to cancer cells.
*2 Annual Incidence in 2017 in U.S., EU5 and JP. CancerMPact (Synix Inc./Kantar Health)

**Development Progress of Enfortumab Vedotin in Locally Advanced or Metastatic Urothelial Cancer**

| Clinical trial | Patient segment | Progress |
|---|---|---|
| **Phase 3** | Patients with prior CPI treatment (platinum-pretreated) | Started in Jul. 2018 |
| **Phase 2** | Patients with prior CPI treatment<br>Cohort 1: Platinum-pretreated<br>Cohort 2: Platinum naïve<br>Cisplatin ineligible | Started in Oct. 2017 |
| **Phase 1b** | Combination with CPI | Started in Nov. 2017 |
| **Phase 1** | Metastatic urothelial cancer patients<br>Patients with renal insufficiency<br>Patients with prior CPI treatment | Ongoing<br>Data presented at medical conferences |

## Zolbetuximab

Zolbetuximab is an antibody that targets Claudin 18.2, a transmembrane protein that forms a tight junction connecting and binding two adjoining cell membranes. Claudin 18.2 is expressed locally in stomach cells for normal cells. Claudin 18.2 is expressed in various cancer types including gastrointestinal adenocarcinomas and pancreatic, biliary duct, ovarian and lung cancers.

Gastric cancer is the fourth leading cause of cancer death worldwide*1. Moreover, the overall five-year survival rate for metastatic gastric and gastroesophageal junction (GEJ) cancer is under 20%*2. Gastric and GEJ cancer is one of the malignancies with the highest unmet medical needs. Chemotherapy and anti-HER2 antibodies are widely used for the treatment of metastatic or recurrent gastric and GEJ cancer. However, other therapeutic options are awaited especially in HER2-negative patients with a lack of effective targeted therapies.

Astellas is developing zolbetuximab as a treatment for gastric and GEJ cancer. Two Phase 3 trials are planned to evaluate zolbetuximab in combination with (1) mFOLFOX6*3, which is commonly used as the first-line therapy in Europe and the U.S, and with (2) CAPOX*4, the preferred regimen in Asia, including China. The former study was initiated first.

*1 World Health Organization Fact Sheet, 2018
*2 Pennathur et al, 2013; Sahin et al, 2008
*3 mFOLFOX6: Fluorouracil, leucovorin, oxaliplatin
*4 CAPOX: Capecitabine, oxaliplatin

**Development Progress of Zolbetuximab**

| Clinical trial | Trial overview | Progress |
|---|---|---|
| **Phase 3** | vs placebo<br>Combination with mFOLFOX6 | Started in Jun. 2018 |
| **Phase 3** | vs placebo<br>Combination with CAPOX | Under preparation |
| **Phase 2** | Monotherapy,<br>Combination with mFOLFOX6 | Started in Jun. 2018 |

## Roxadustat

Roxadustat is hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) inhibitor with oral administration. Roxadustat is thought to increase HIF involving in the production of red blood cells by inhibiting HIF-PH, thereby enhancing the production of red blood cells and improving anemia. Astellas is currently developing roxadustat for anemia associated with chronic kidney disease (CKD) in patients on dialysis and non-dialysis.

Anemia is one of the common complications of CKD. It is said that the progression of anemia in CKD leads to end-stage renal disease and increases the mortality rate. Therefore, managing the hemoglobin levels in patients with anemia in CKD is a crucial issue in the treatment of renal dysfunction.

Roxadustat has a different mechanism of action than the conventional treatments and can be administered orally. It is thus expected to become a new treatment option which could provide both effectiveness and convenience for patients.

For filing and reimbursement in Europe, a total of six Phase 3 trials are being conducted. In addition, six Phase 3 trials are being conducted in Japan. Four Japanese trials in patient with anemia in CKD on dialysis have all achieved their primary objectives. Astellas is planning to submit a NDA in Japan for anemia associated with CKD in patients on dialysis in 2018.

### Development Progress of Roxadustat

#### Global

| Treatment phase | Trial overview | Status |
|---|---|---|
| Dialysis | HIMALAYAS: Incident dialysis, vs epoetin alfa | Enrollment completed |
| | SIERRAS: Stable dialysis, vs epoetin alfa | Enrollment completed |
| | PYRENEES: Stable dialysis, vs epoetin alfa or darbepoetin | Enrollment completed |
| Non-dialysis | DOLOMITES: vs darbepoetin | Enrollment completed |
| | ALPS: vs placebo | Study completed |
| | ANDES: vs placebo | Enrollment completed |

#### Japan

| Treatment phase | Trial overview | Status |
|---|---|---|
| Dialysis | Hemodialysis: Conversion, vs darbepoetin | Study completed |
| | Hemodialysis: Conversion, long-term | Study completed |
| | Hemodialysis: Correction (ESA*-naïve) | Study completed |
| | Peritoneal dialysis | Study completed |
| Non-dialysis | Conversion, vs darbepoetin | Recruiting |
| | Correction (ESA*-naïve) | Enrollment completed |

* ESA: Erythropoiesis-stimulating agents

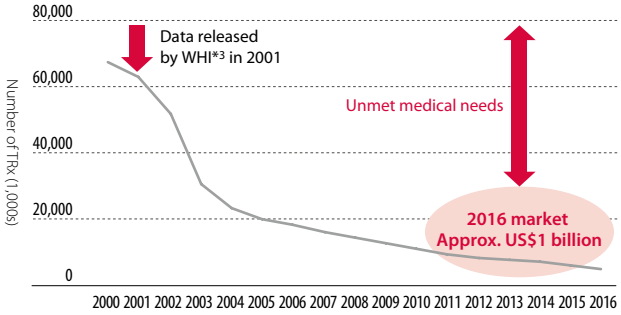
## Fezolinetant

Fezolinetant is an antagonist of the G protein-coupled receptor (GPCR) known as NK3 receptor. Fezolinetant is expected to act on specific neurons that control body temperature in menopausal women, and is being developed for menopause-related vasomotor symptoms (MR-VMS: hot flashes and night sweats). It is reported that MR-VMS is recognized in nearly 80%*1 of menopausal women. Given that existing hormone replacement treatments present safety concerns*2, a safe and effective non-hormone therapy is awaited as a new treatment option.

In Phase 2a (POC) trial, fezolinetant showed positive results in terms of the improvement in the frequency and severity of hot flashes. Based on these results, Astellas expects fezolinetant to become a safe, first-in-class, non-hormonal treatment for MR-VMS. Phase 2b trial is currently ongoing in the U.S. with an expected data readout in 2018.

*1 UpToDate – Clinical manifestations and diagnosis of menopause (Literature review current through: June 2017)
*2 JAMA 2013 Oct 2; 310(13): 1353-1368

### U.S. Annual Branded TRx*1 Trends for MR-VMS*2




*1 TRx: Total prescriptions
*2 IQVIA NPA (2000-2016)/IQVIA NSP (2000-2016) (3HTs and SSRI), NAMS 2015 Position Statement
*3 WHI: Women's Health Initiative