ICD-10-PCS Presentation for XOSPATA® (gilteritinib)

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Overview: New ICD-10-PCS Code Is Needed for Administration of XOSPATA® (gilteritinib)

- **Issue:** There is not a unique ICD-10-PCS code to describe the oral administration of XOSPATA® (gilteritinib) to treat patients with relapsed/refractory (R/R) FLT3mut+ acute myeloid leukemia (AML). Astellas requests to establish new ICD-10-PCS codes to better identify XOSPATA® administration for the treatment of R/R FLT3mut+ AML.

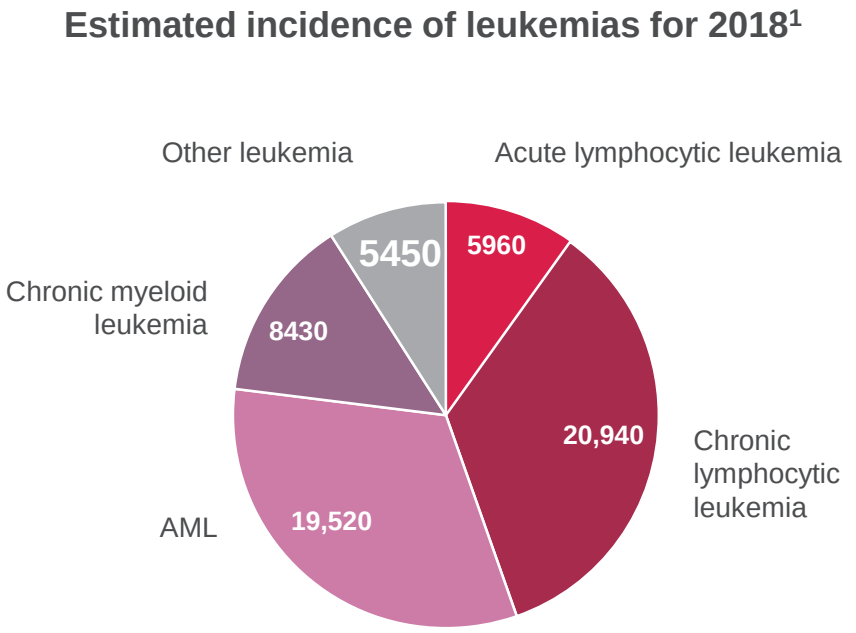
- **New Technology Application?** Yes, Astellas submitted a New Technology Add-On Payment (NTAP) application for XOSPATA® (gilteritinib) for fiscal year (FY) 2020.

- **FDA Approval:** The New Drug Application (NDA) for XOSPATA® (gilteritinib) was approved on November 28, 2018.

- **Background:** XOSPATA ® (gilteritinib) is FDA approved for the treatment of adult patients who have relapsed or refractory Acute Myeloid Leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test. XOSPATA is the first FLT3-targeting agent approved for the treatment of relapsed or refractory FLT3 mutation-positive (FLT3mut+) AML.

AML is a Rare Malignancy that Accounts for a Small Number of Cancer Patients[1]

- AML is a heterogeneous, hematologic disease that arises from the rapid expansion of myeloid blasts in the bone marrow and peripheral blood of adult patients[2]
- AML represents 1.1% of all new cases of cancer in the United States[1]
- In 2018, there will be an estimated 19,520 new cases of AML[1]*
- In the United States, the 5-year survival rate for AML is 26.9%[3]
- FLT3 is one of the most commonly identified mutations in AML[4]



*Estimated new cases are based on 2000-2014 incidence data reported by the North American Association of Central Cancer Registries (NAACCR). References: 1. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed 01-05-2018. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia Version 1.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed 02-19-2018. To view the most recent and complete version of the guideline, go online to NCCN.org. 3. National Cancer Institute. https://seer.cancer.gov/csr/1975_2014/results_merged/topic_survival.pdf. Accessed 03-02-2018. 4. Patel JP et al. N Engl J Med 2012;366(12):1079-89.

Key AML Epidemiological Statistics, 2018

Epidemiological estimates in the United States, 2018:

AML Characteristic	U.S. Statistic
Incidence	19,520, mostly adults
Deaths	10,670, nearly all in adults
Average age	Approximately 68 years
Average lifetime risk	<0.5%

Reference: American Cancer Society. https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html. Accessed 03-12-2018.

Patients with AML Often Relapse or are Refractory

Approximately 57% of newly diagnosed patients will become relapsed or refractory (R/R)[1]

- Suggests more than 10,000 newly diagnosed US patients are expected to progress to R/R AML each year[2*]
- More than 70% of patients die within 12 months following relapse[3]

R/R AML has limited treatment options**

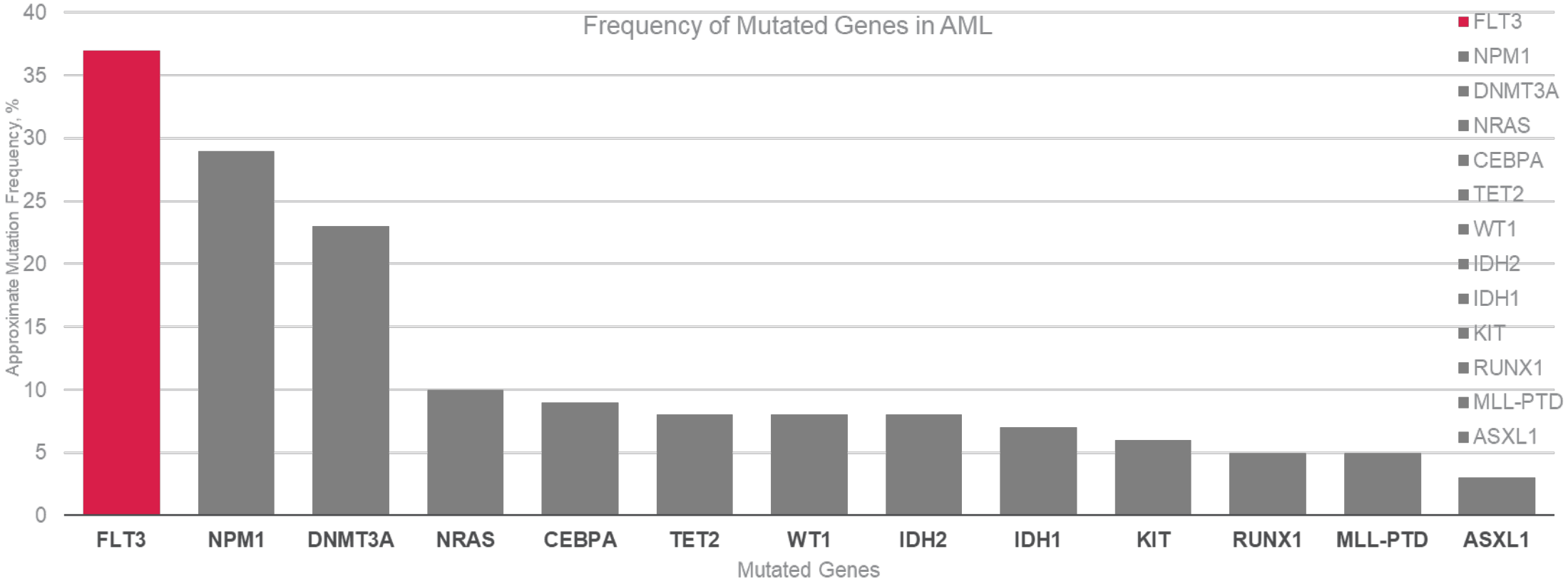
- Salvage chemotherapy has marginal efficacy, with limited survival benefit[3]
- Salvage chemotherapy is poorly tolerated in general, with up to 28% rate of treatment-related mortality/30-day mortality reported[3]

NCCN recommends clinical trials for patients with R/R disease[4]

- Safety and efficacy of agents in clinical trials is not established for investigational therapies

*Based on SEER 2018 estimates of 19,520 new cases of AML in the US.
** Targeted therapies for R/R AML have also recently become available to treat R/R AML with select mutations.4,5
References: 1. Walter RB et al. Leukemia. 2015;29(2):312-320. 2. Surveillance Epidemiology and End Results Program. https://seer.cancer.gov/statfacts/html/amyl.html.Accessed 09-08-2018. 3. Ramos NR et al. J Clin Med. 2015;4(4):665-695. 4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia, Version 2.2018. 5 . Döhner H et al. Blood. 2016;129(4):424-447.

FLT3 Mutations are One of the Most Commonly Occurring Mutations in AML



Patients with FLT3 Mutations are Challenging to Treat[1,2]

There are primarily 2 types of FLT3 mutations, ITD and TKD. The ITD mutation affects risk of relapsed or refractory disease.

- FLT3-ITD[3-5] Occurs in ~30% of AML patients
  - *FLT3-ITD* mutations are associated with a significantly decreased response rate and reduced overall survival

- FLT3-TKD[3,5,6] Occurs in ~7% of AML patients
  - *FLT3-TKD* mutations have a less clear impact on prognosis, with some studies not reporting any significant correlation and others demonstrating that prognosis may depend on other genetic aberrations

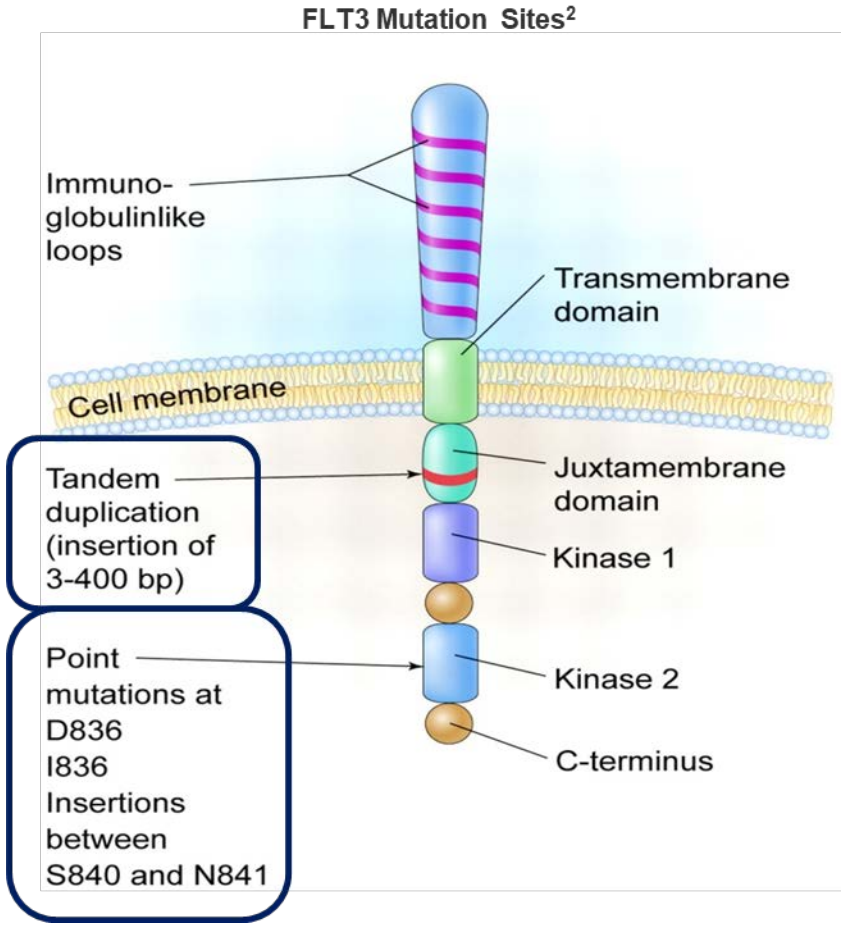
FLT3-ITD mutations adversely impact patient outcomes in AML[7-9]

- FLT3-ITD mutations are a risk factor for relapsed disease and negatively impact survival after first relapse[2,9]
- According to one study, 64% of patients who have an *FLT3-ITD* mutation relapsed within 5 years[4]

References: 1. Fey MF, Buske C. Ann Oncol 2013;24(Suppl 6):vi138-43. 2. Wagner K et al. Haematologica 2011;96(5):681-6. 3. Patel JP, et al. NEJM 2012;366(12):1079-1089. 4. Kottaridis PD et al. Blood 2001;98(6):1752-9. 5. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed 01-05-2018. 6. Bacher U et al. Blood 2008;111(5):2527-37. 7. Whitman SP et al. Blood 2010;116(18):3622-6. 8. Whitman SP et al. Cancer Res 2001;61(19):7233-9. 9. Brunet S et al. J Clin Oncol 2012;30(7):735-41.

Gilteritinib Inhibits FLT3 Receptor Signaling

- Gilteritinib is the first FDA-approved kinase inhibitor for relapsed or refractory FLT3m+ AML to target FLT3-ITD and FLT3-TKD mutations[1]
  - Gilteritinib is a small-molecule FLT3 tyrosine kinase inhibitor[1]
- Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 mutations, including[2]:
  - FLT3-ITD
  - FLT3-TKD (FLT3-D835Y)
  - FLT3-ITD and FLT3-TKD (FLT3-ITD-D835Y)



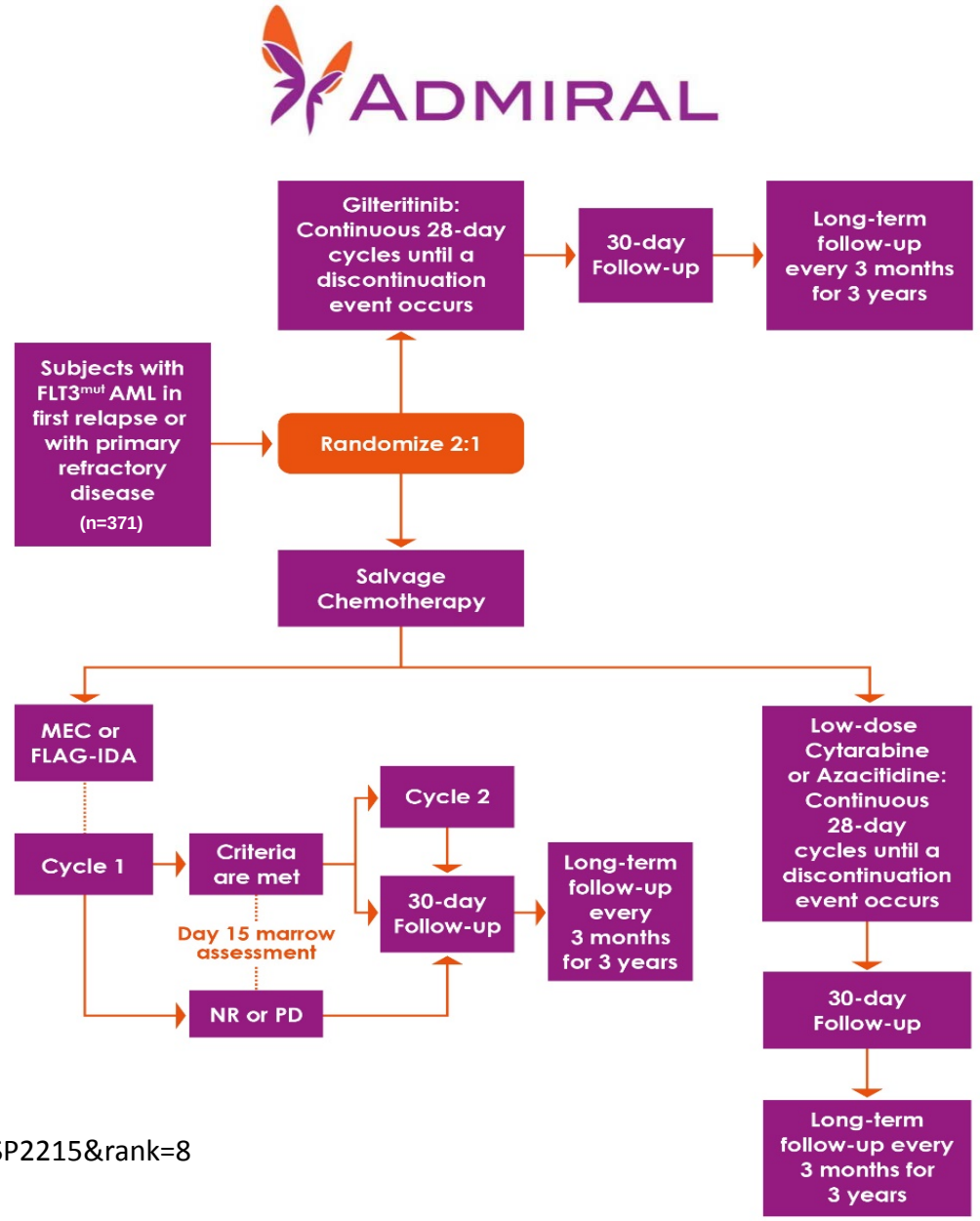
References: 1. Prescribing information for XOSPATA (gilteritinib). Astellas Pharma. Nov. 2018 2. Litzow MR. Blood. 2005;106(10):3331-2

XOSPATA (gilteritinib) Prescribing Information

- XOSPATA is kinase inhibitor indicated for the treatment of adult patients who have relapsed or are refractory acute myeloid leukemia with a FLT-3 mutation as detected by an FDA-approved test
- XOSPATA is dosed at 120 mg orally once-daily as three 40 mg tablets
- XOSPATA may be taken with or without food
- Warnings and Precautions for XOSPATA include:
  - Posterior reversible encephalopathy (1%)
  - Prolonged QT interval (7% increase in baseline >60msec)
  - Pancreatitis (rare)
  - Embryo-Fetal Toxicity
- The safety of XOSPATA is based on 292 patients with relapsed/refractory AML treated with 120 mg gilteritinib daily
- Median duration of exposure to XOSPATA at the interim analysis was 3 months (range 0.1-42.8 months)

Prescribing information for XOSPATA (gilteritinib). Astellas Pharma. Nov. 2018

Study Design



MEC = Mitoxantrone, Etoposide, Cytarabine
FLAG-IDA = Fludarabine, Cytarabine, G-CSF, Idarubicin

http://www.astellasamltrials.com/Admiral.html
https://clinicaltrials.gov/ct2/show/NCT02421939?term=ASP2215&rank=8

Study Objectives

COPRIMARY OBJECTIVES

Measure	Definition
CR/CRh*	Percent of patients who achieve either complete response or complete response with incomplete hematologic recovery while on treatment
OS	Time from randomization to death any cause

KEY SECONDARY OBJECTIVES

Measure	Definition
EFS	Time from randomization to relapse (except after PR), treatment failure, or death
CR	Percent of patients who achieve complete response

* =CR was defined as morphologic leukemia-free state and must have an ANC ≥ 1 x 10^9/L and platelet count ≥ 100 x 10^9/L and normal marrow differential with < 5% blasts, and they will be RBC and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia. CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.
Other secondary objectives were leukemia-free survival, duration of response, composite complete remission, transplantation rate, patient reported fatigue, adverse events (AEs), safety labs, vital signs, ophthalmologic exams, electrocardiograms (ECGs), and Eastern Cooperative Oncology Group (ECOG) performance scores. Multiple exploratory objectives were included.

Patient Population

- Diagnosis
  - FLT3m AML (included FLT3-ITD, FLT3TKD/D835, FLT3-TKD/I836)
  - Relapsed (1st relapse only) or Refractory
  - Prior therapy with midostaurin or sorafenib in 1st line therapy was allowed
  - Excluded certain types of AML (APL and BCR-ABL+ AML, therapy related AML)
- Medical Conditions
  - Performance status (≤ 2)
  - Organ function (liver, kidney, cardiac)
  - QTcF ≤ 450 mSec
  - No active infection
  - No active clinically significant GVHD
- Other
  - Adults (>18yo)
  - No other active cancer
  - Non-pregnant
  - Concomitant drugs (CYP3A inducers prohibited, PgP inhibitors or inducers OR 5HT1R or 5HT2BR blockers excluded unless essential)

https://clinicaltrials.gov/ct2/show/NCT02421939?term=ASP2215&rank=8, November 2018

Admiral Interim Analysis Data: Gilteritinib Only Arm

Admiral Interim Analysis

- A pre-planned interim analysis was performed to evaluate efficacy in the gilteritinib arm
  - Planned when approximately 141 patients randomized to the gilteritinib arm and ≥112 days (4 treatment cycles) past the 1st dose of gilteritinib
- 142 patients evaluated
  - 138 patients with FLT3 status confirmed by central lab
- Efficacy endpoint of CR/CRh evaluated
- Data cutoff date August 4, 2017
  - As of the data cutoff date, 83 sites in a total of 14 countries, including North America, Europe, Asia and rest of the world, have participated in ADMIRAL

Admiral Interim Analysis: Patient Demographics and Disease Characteristics

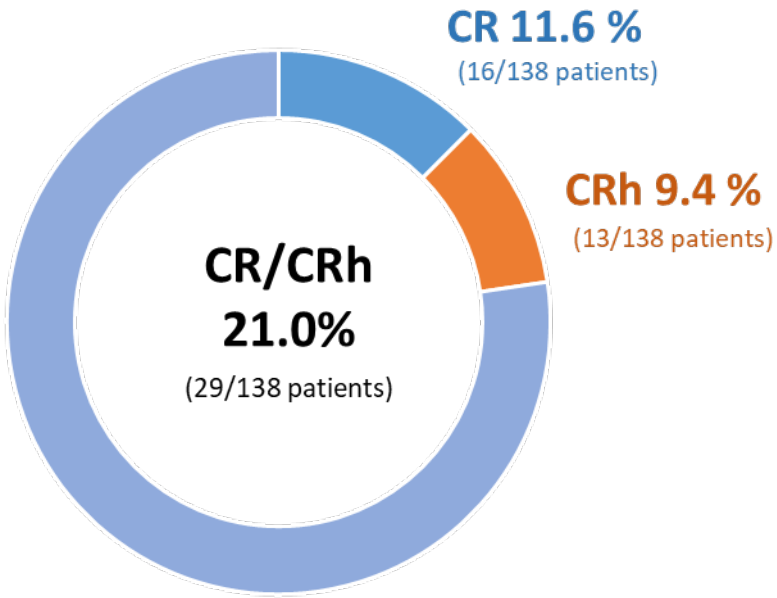
Characteristic	Gilteritinib Monotherapy Arm (n = 138)
Median age in years, n (range)	60 (20 – 84)
Male, n (%)	64 (46.0)
Race (%) White Asian Black or African American	 60.7 26.4 7.9
ECOG status 0-1, n (%)	113 (82.0)
FLT3 mutation status*, n (%) ITD alone TKD alone ITD and TKD	 121 (88.0) 12 (9.0) 5 (4.0)
Disease characteristics Primary refractory AML, n (%) Untreated relapse AML, n (%)	 56 (41.0) 82 (59.0)
Cytogenetics (%) Intermediate Unfavorable	 66.2 12
Prior stem cell transplant, n (%)	27 (20.0)
Transfusion-dependent, n (%)	106 (77.0)

*4 patients were enrolled based on local FLT3 results and were negative by the companion diagnostic assay.

Gilteritinib Prescribing Information, Astellas Pharma. Nov. 2018.

Admiral Interim Analysis: CR/CRh Rate

- Data shown for pre-planned interim analysis of 138 patients in the gilteritinib monotherapy arm with FLT3 status confirmed by central lab
- Patients censored at time of HSCT
- Median follow-up: 4.6 months (95% CI: 2.8, 15.8)
- Median time to first response (CR/CRh): 3.6 months (range, 0.9 – 9.6 months)



CR: complete remission; CRh: complete remission with partial hematologic recovery; CR/CRh: composite CR plus CRh.

CR was defined as absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.

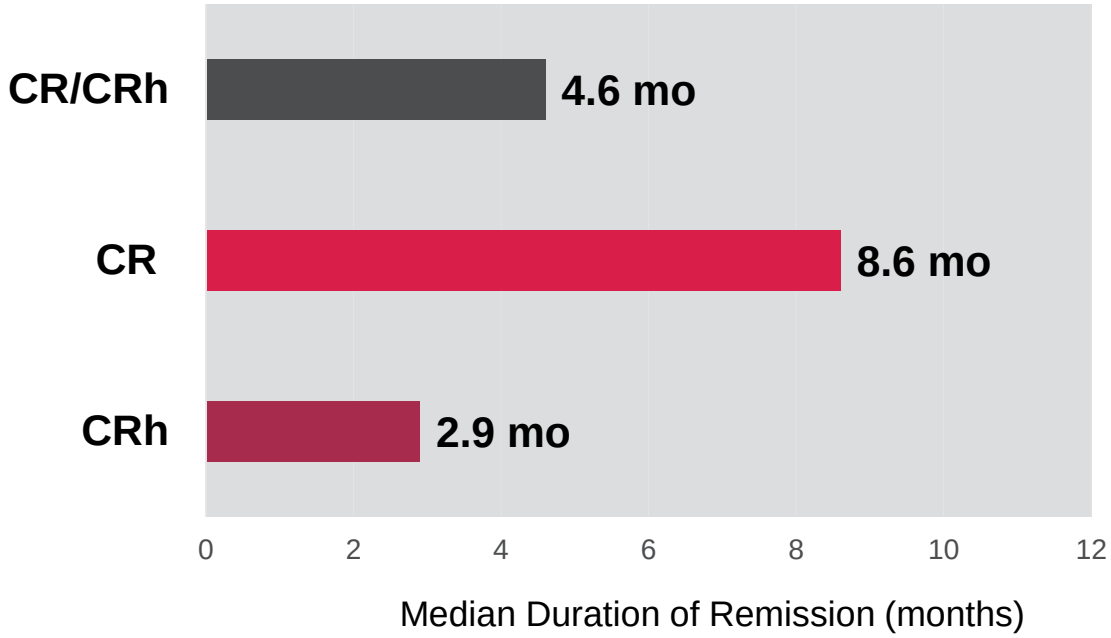
CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.

HSCT: hematopoietic stem cell transplant

Gilteritinib Prescribing Information. Astellas Pharma. Nov. 2018.

Admiral Interim Analysis: Duration of Remission

- Data shown for pre-planned interim analysis of 138 patients in the gilteritinib monotherapy arm with FLT3 status confirmed by central lab
- Duration of Remission (DOR) was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type. Deaths were counted as events.



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CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.

Gilteritinib Prescribing Information. Astellas Pharma. Nov. 2018.

Admiral Interim Analysis: Transfusion Independence

- Transfusion dependence was also evaluated in the gilteritinib-treated patients. In some hematologic disorders, becoming transfusion independent or receiving fewer transfusions over a specified interval is defined as improvement or response depending on whether therapy is given.

- In Study 2215-CL-0301, at baseline, 106 patients in the gilteritinib arm were classified as transfusion dependent prior to therapy initiation, with 32 patients classified as transfusion independent.

- Of the 106 patients who were transfusion dependent at baseline, 33 of these patients (31.1%) became transfusion independent during gilteritinib treatment.

- Of the 32 patients who were classified as transfusion independent at baseline, 17 of these patients (53.1%) maintained transfusion independence during gilteritinib treatment.

Patients were classified as transfusion independent at baseline if there were no RBC or platelet transfusions within the baseline period (defined as 28 days prior to the first dose to 28 days after the first dose).
Patients were classified as transfusion independent post-baseline if the patient had 1 consecutive period of 56 day without any RBC or platelet transfusion from 29 days after the first dose until the last dose date.
Gilteritinib Prescribing Information. Astellas Pharma. Nov. 2018.

Questions?