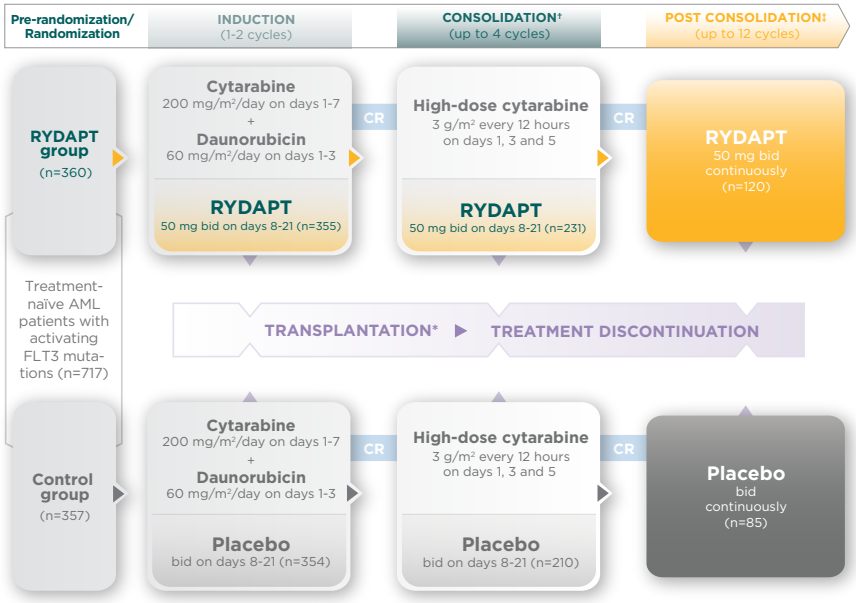
The RATIFY Clinical Trial

- The RATIFY (CALGB 10603 [Alliance]) clinical trial was conducted to evaluate the potential use of Rydapt® (midostaurin) in adults with newly diagnosed acute myeloid leukemia (AML) and a FLT3 mutation.[1]
- Rydapt was evaluated in the international Phase III placebo-controlled, randomized, double-blind clinical trial RATIFY (**R**andomized **A**ML **T**rial **I**n **F**LT3 in patients less than 60 **Y**ears old, NCT00651261).[1]
- RATIFY compared Rydapt to placebo when administered with standard induction "7+3" chemotherapy (daunorubicin/cytarabine) and consolidation chemotheraphy (high-dose cytarabine), followed by either Rydapt or placebo as a single agent for up to 12 cycles in patients who continued in complete remission after consolidation chemotherapy.[1]
- The RATIFY study was sponsored by the Alliance for Clinical Trials in Oncology in North America and by Novartis Oncology outside of North America. The study drug, Rydapt, was provided by Novartis Oncology.
- RATIFY is the largest worldwide clinical trial in FLT3-mutated AML to date. A total of 225 sites from 17 countries participated in this study, spanning North America, Europe and Australia.[2]
- A total of 717 patients with a FLT3 mutation aged 18 to less than 60 were enrolled.[3]

The RATIFY clinical trial protocol



CR, complete remission.
*Transplantation was allowed but not specifically mandated per study protocol. Patients who proceeded to haematopoietic stem cell transplant (SCT) stopped receiving study treatment prior to initiation of transplant conditioning regimen, but all patients were followed for survival.
†There was no re-randomization at the start of post consolidation therapy.
‡For the post consolidation phase, patients were not re-randomized between the Rydapt arm and placebo arm. Rydapt is not indicated for maintenance treatment.

Trial Endpoints

- The primary endpoint of the study was overall survival (OS).[1]
- Secondary endpoints included:[1]
  - Event-free survival (EFS, key secondary endpoint)
  - OS censored at the time of stem cell transplant (SCT)
  - Complete remission (CR) rate within 60 days of start of treatment
  - Disease-free survival (DFS)
  - DFS rate one year after completing the planned continuation phase
  - SCT rate

See safety information on reverse side.

NOVARTIS

Novartis Pharma AG
CH-4002 Basel Switzerland

4/17
G-PKC-1153661
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

The RATIFY Clinical Trial

Approved Indications for Rydapt[3]

- Rydapt is approved for the treatment of adult patients with newly diagnosed AML who are FMS-like tyrosine kinase 3 mutation-positive (FLT3+), as detected by an FDA-approved test,[§] in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy. Rydapt is not indicated as a single-agent induction therapy for the treatment of patients with AML.
- Rydapt is also approved for aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia.

Important Safety Information for Rydapt® (midostaurin) Capsules

Patients who are allergic to midostaurin or any of the ingredients in Rydapt should not take Rydapt. If a patient taking Rydapt develops signs of an allergic reaction, they should seek medical help immediately. Signs of an allergic reaction include trouble breathing, flushing, chest pain, throat tightness, and swelling of lips, mouth or throat.

Rydapt should be not be used during pregnancy since Rydapt may harm an unborn baby. Pregnancy testing should be conducted for women who might become pregnant. Effective birth control should be used during treatment and for at least four months after stopping Rydapt. If a patient becomes pregnant or thinks she may be, the patient should tell their doctor right away. Women should not breastfeed during treatment with Rydapt and for at least four months after the final dose. Men taking Rydapt who have female partners that are able to become pregnant should use effective birth control during his treatment with Rydapt and for at least four months after the last Rydapt dose. Rydapt may cause fertility problems in women and men, which may affect their ability to have children.

Rydapt may cause lung problems that may lead to death. Patients on Rydapt who develop a new or worsening cough, shortness of breath, or chest discomfort should get medical help right away. These may be signs of serious lung problems.

Common sides effects reported during Rydapt treatment for AML included low level of white blood cells with fever (febrile neutropenia); nausea; redness, pain or ulcers inside the mouth (mucositis); vomiting; headache; bruising; muscle or bone pain; nose bleeds; device-related infection; high blood sugar levels (hyperglycemia) and upper respiratory infections.

Common side effects reported during treatment for ASM, SM-AHN or mast cell leukemia included nausea; vomiting; diarrhea; swelling of the hands, feet or ankles; muscle or bone pain; stomach-area pain; tiredness; upper respiratory infection; constipation; fever; headache and trouble breathing.

If side effects including nausea, vomiting, and diarrhea occur, get worse or do not go away during treatment with Rydapt, patients should contact their doctor. Depending on the side effect and/or severity of the side effect that occur, their doctor may decrease their dose, temporarily stop, or completely stop treatment with Rydapt.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Rydapt may affect how these medicines work or these other medicines may affect how Rydapt works.

The full prescribing information for Rydapt can be found at:
https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/rydapt.pdf.

[§]In order to identify FLT3+ AML patients, Novartis collaborated with Invivoscribe Technologies, Inc. on the development of LeukoStrat® CDx FLT3 Mutation Assay, a companion molecular diagnostic test. LeukoStrat® CDx FLT3 Mutation Assay is the first molecular companion diagnostic in AML and identifies both FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations and is performed by The Laboratory for Personalized Molecular Medicine, a subsidiary of Invivoscribe Technologies, Inc.

References

1. ClinicalTrials.gov. www.clinicaltrials.gov/ct2/show/NCT00651261. Accessed April 17, 2017.
2. Stone RM, Mandreekar S, Sanford BL, et al. ASH Abstract Presentation. *Blood*. 2015;126(23):6.
3. Rydapt [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp, 2017.

NOVARTIS

Novartis Pharma AG
CH-4002 Basel Switzerland

4/17 G-PKC-1153661

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080