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If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Prescribing Information can be found at the end of this presentation.

RYD18-C034 September 2018

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Rydapt® ▼ (midostaurin) is indicated in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive.

Prescribing Information can be found at the end of this presentation.

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CLINICAL UTILITY OF *FLT3*-ITD AND *FLT3*-TKD IN THE RYDAPT® ERA

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Acute Myeloid Leukemia (AML) has one of the lowest survival rates among Leukaemias[1]

It is thought that approximately 30% of AML patients are FLT3+[2]

½ of patients diagnosed with AML are older than 65 years of age[3]

1. Deschler, B., Lubbert, M. Acute Myeloid Leukaemia:epidemiology and etiology. Cancer. 2006; 107 (9): 2099-2107.
2. Ferrara F, Schiffer CA. Lancet. 2013;381(9865):484-495.
3. Chen Y, Kantarjian H, Wang H, et al. *Cancer.* 2012;118(23):5811-5818.

FLT3 is the most common mutation in AML patients[1-3]

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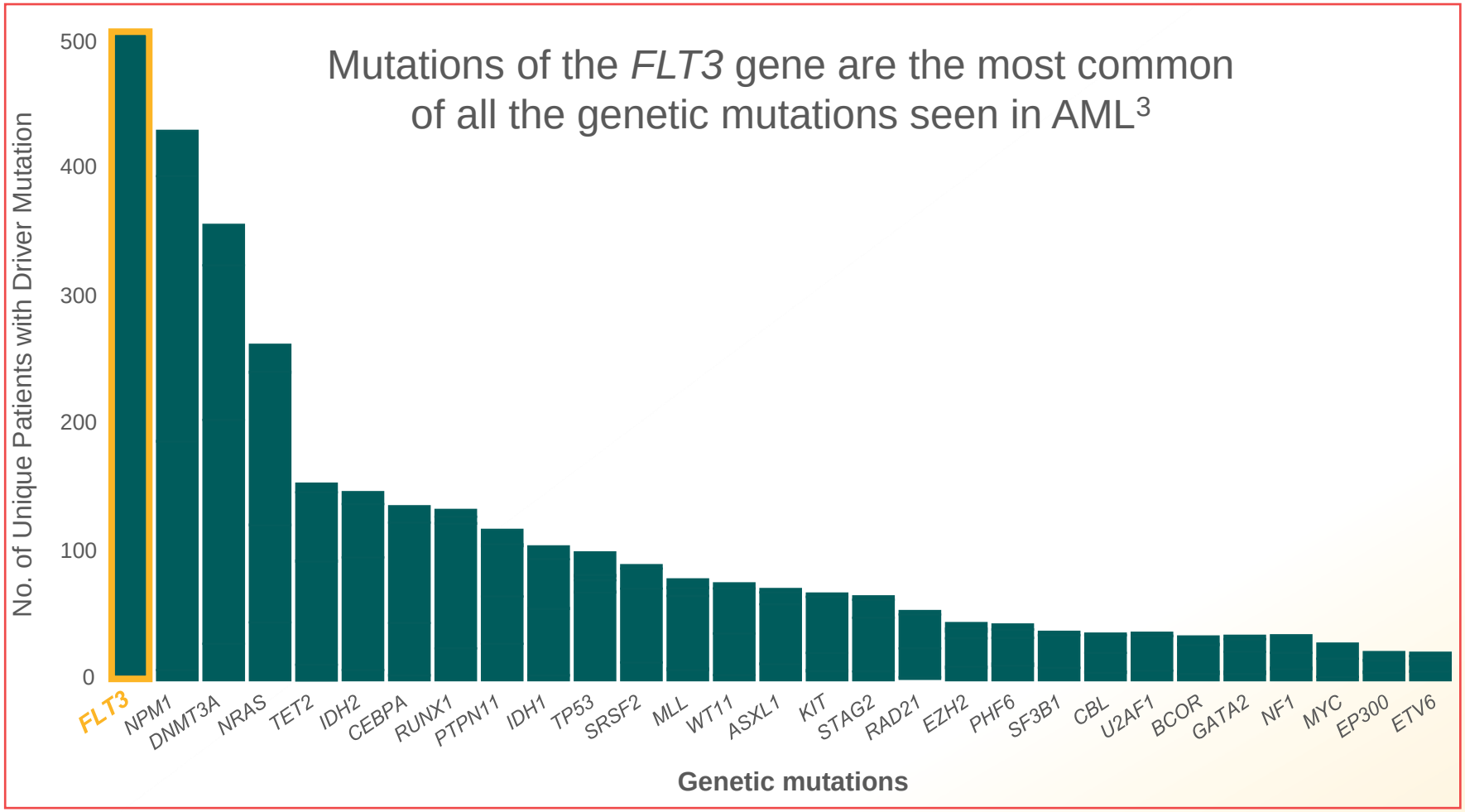


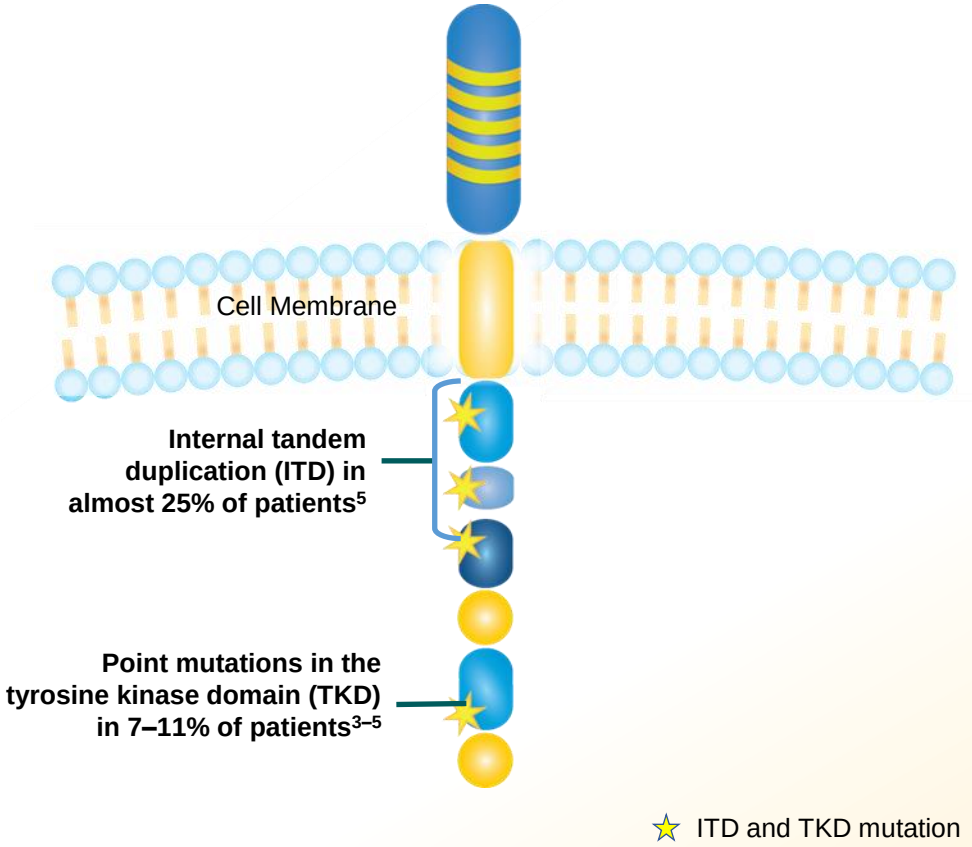
FLT3 READY

Image adapted from Papaemmanuil E, Gerstung M, Bullinger L, et al. *N Engl J Med*. 2016:374(23):2209-2221.

1. Döhner H, Weisdorf DJ, Bloomfield CD. *N Engl J Med*. 2015;373(12):1136-1152;
2. Döhner H, Estey E, Grimwade D, et al. *Blood*. 2017;129(4):424-447;
3. Papaemmanuil E, Gerstung M, Bullinger L, et al. *N Engl J Med*. 2016:374(23):2209-2221

FLT3 is an important hematopoietic receptor tyrosine kinase class III[1]

- Approximately 1/3 AML patients have *FLT3* ITD or TKD mutations[2–5]
- Both types of *FLT3* mutation lead to constitutive activation of downstream signaling pathways such as STAT[1]



1. Choudhary C, Schwäble J, Brandts C, et al. *Blood*. 2005;106(1):265-273;
2. Fröhling S, Schlenk RF, Breitruck J, et al. *Blood*. 2002;100(13):4372-4380;
3. Patel JP, Gönen M, Figueroa ME, et al. *N Engl J Med*. 2012;366(12):1079-1089;
4. Schlenk RF, Döhner K, Krauter J, et al. *N Engl J Med*. 2008;358(18):1909-1918;
5. Schlenk RF, Kayser S, Bullinger L, et al. *Blood*. 2014;124(23):3441-3449.

FLT3-ITD mutations predict relapse and worse overall survival[1,2]

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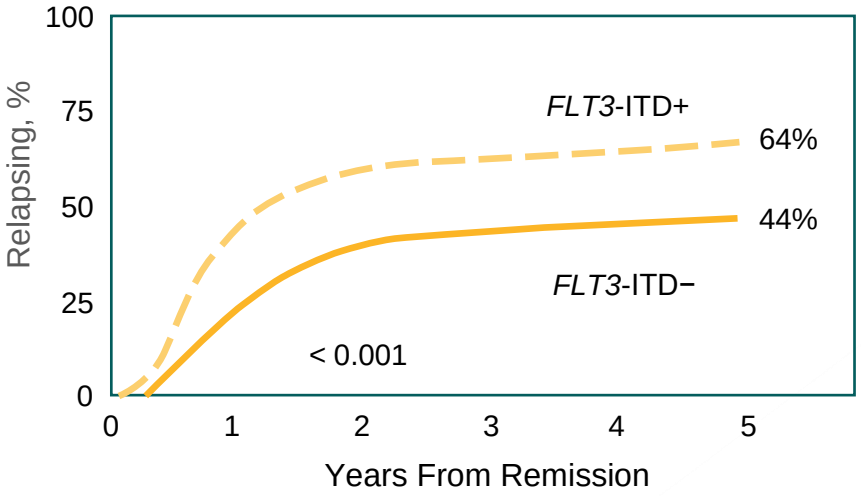
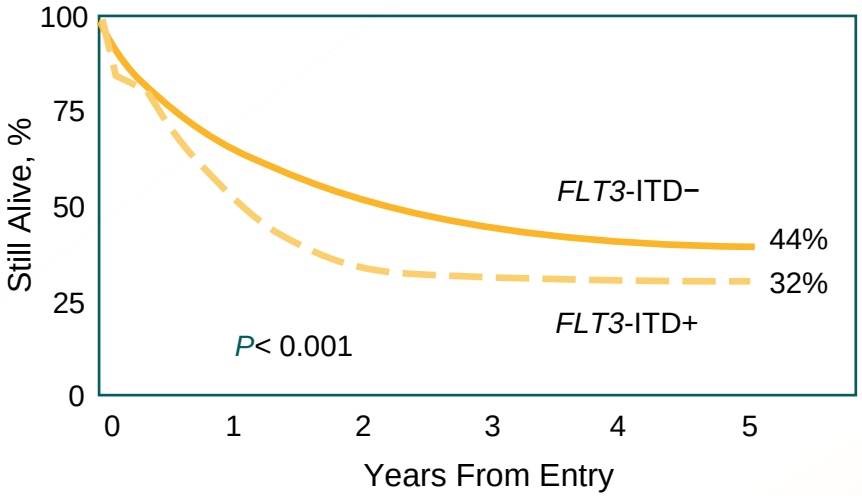
Earlier Relapse in *FLT3*-ITD AML[1]



Worse Overall Survival *FLT3*-ITD AML[1]



The effects of *FLT3*-ITD mutations on relapse and overall survival were determined in the context of standard of care (SoC) chemotherapy[1]

FLT3 READY

Images reused with permission from Kottaridis PD, Gale RE, Frew ME, et al. *Blood*. 2001;98(6):1752-1759.

1. Kottaridis PD, Gale RE, Frew ME, et al. *Blood*. 2001;98(6):1752-1759;
2. Thiede C, Steudel C, Mohr B, et al. *Blood*. 2002;99(12):4326-4335.

The prognostic impact of *FLT3*-TKD mutations is not well understood

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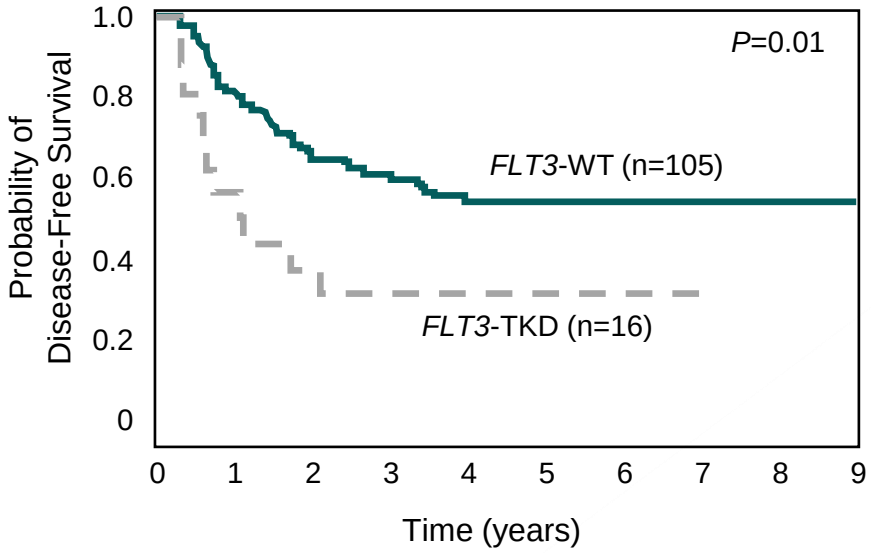
Negative: Relapse in newly diagnosed *FLT3*-TKD, normal karyotype AML patients achieving a CR after chemotherapy[1]



Positive: Lower cumulative incidence of relapse (CIR), higher recurrence-free survival (RFS) and OS in patients with *FLT3*-TKD mutations[2]

	% *FLT3*-TKD-	% *FLT3*-TKD+	Odds Ratio	*P*
5-year CIR	48	39	0.75 (0.57–0.98)	0.03
5-year RFS	35	48	0.74 (0.59–0.93)	0.008
5-year OS	37	53	0.72 (0.58–0.89)	0.002

Key Message

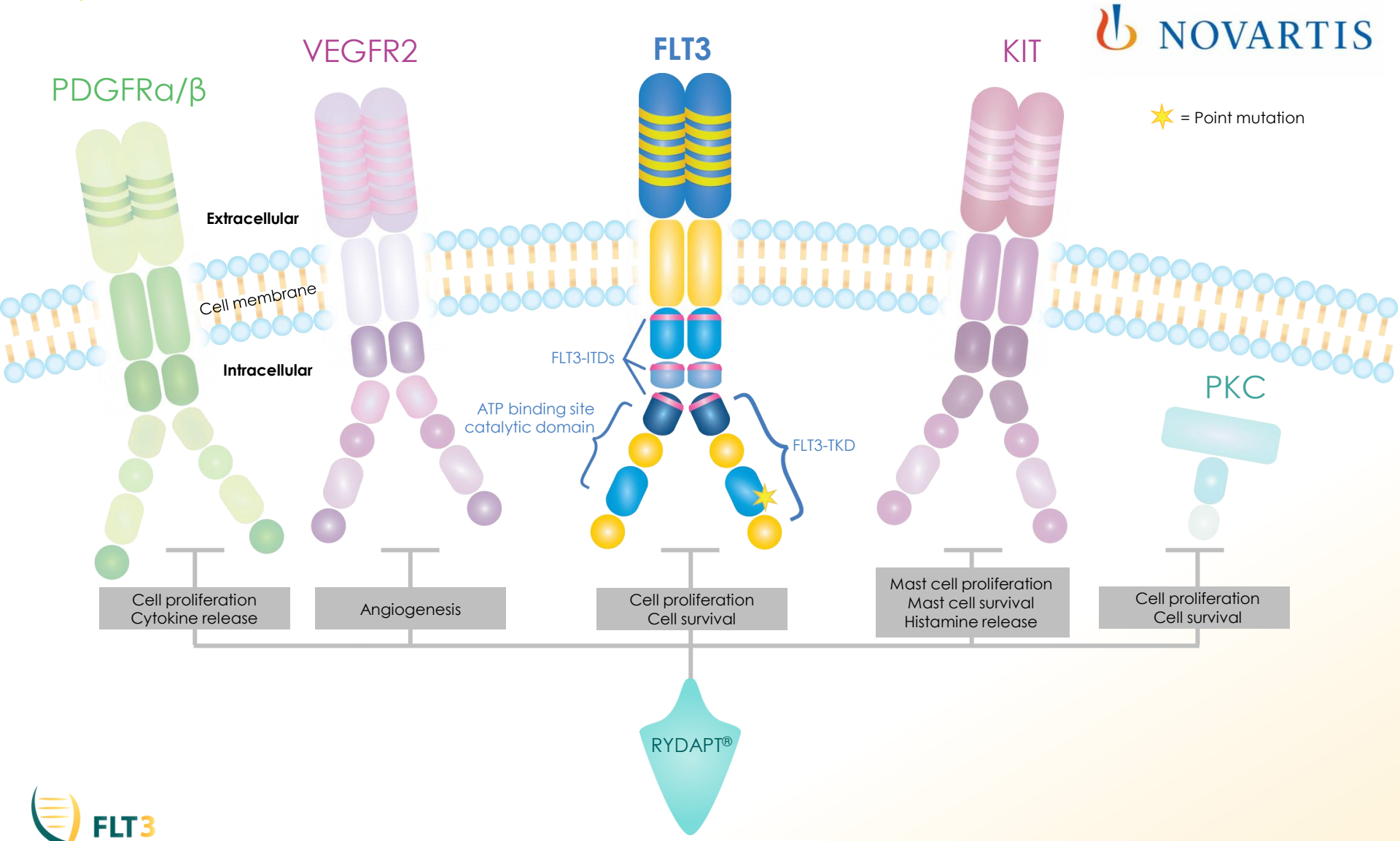
The prognostic impact of *FLT3*-TKD mutations whilst not well understood, is useful and used as an entry criteria for the RATIFY trial

FLT3 READY

Image reused with permission from Whitman SP, Ruppert AS, Radmacher MD, et al. Blood. 2008;111(3);1552-1559.

1. Whitman SP, Ruppert AS, Radmacher MD, et al. *Blood*. 2008;111(3);1552-1559;
2. Mead AJ, Linch DC, Hills RK, et al. *Blood*. 2007;110(4):1262-1270.

RYDAPT® directly inhibits signalling of *FLT3* and other kinases by binding the active domains[1]

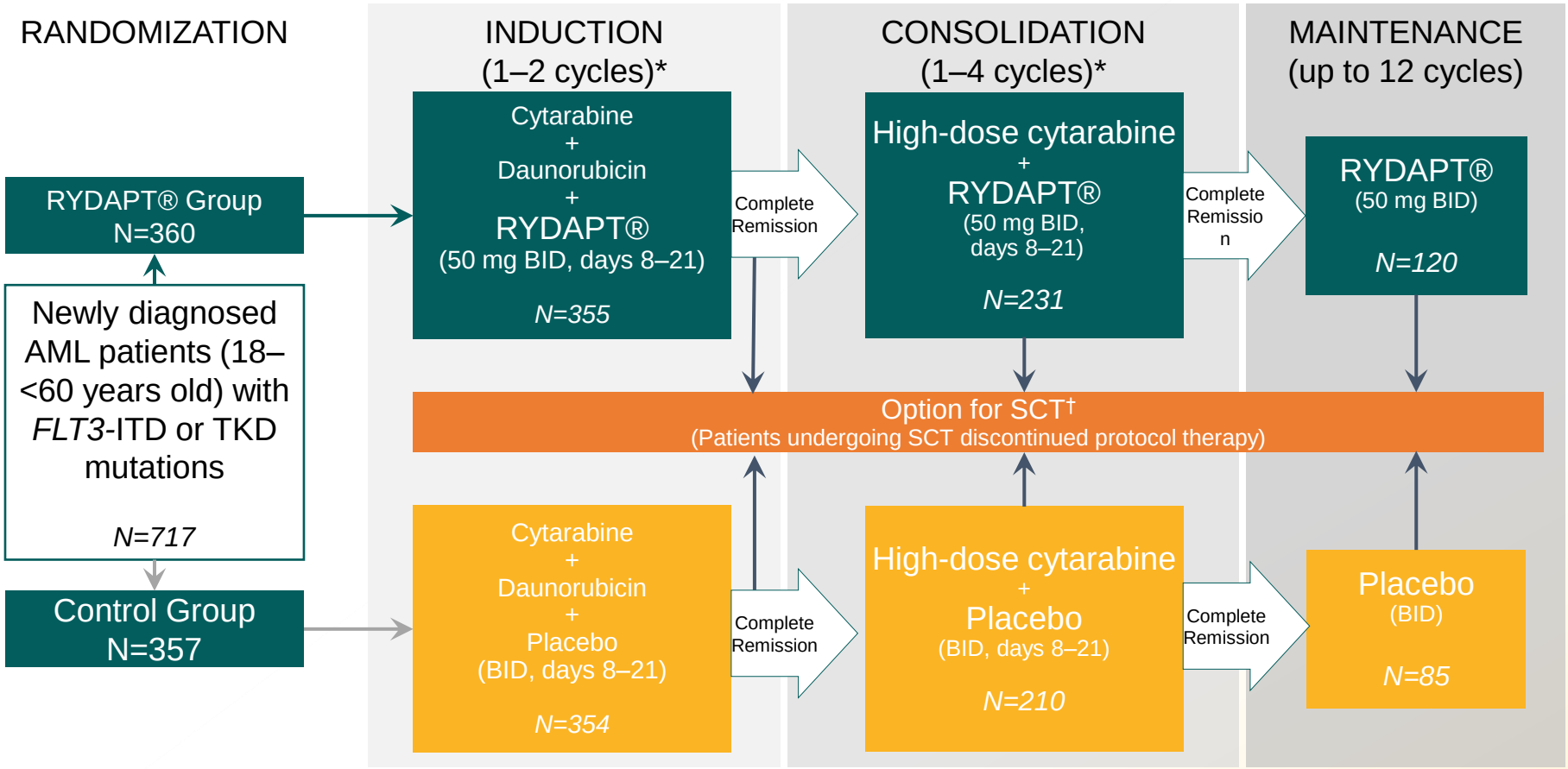


FLT3 READY

1. RYDAPT (Summary of Product Characteristics). Novartis Pharma AG

RATIFY: An evaluation of RYDAPT® added to the standard of care for newly diagnosed *FLT3*+ AML adults[1,2]

RATIFY: an international multicenter Phase III randomized study with RYDAPT® versus placebo, with overall survival as primary endpoint
RYDAPT® at a dose of 50 mg orally twice daily



FLT3 READY

* A cycle was 28 days. Chemotherapy dosing during induction was cytarabine IV, 200 mg/m2/d on days 1–7, and daunorubicin IV, 60 mg/m2/d on days 1–3. During consolidation, high-dose cytarabine was given at a dose of 3 g/m2/d IV q12h on days 1, 3, and 5.
†Transplantation was allowed but not specifically mandated per study protocol

1. RYDAPT (Summary of Product Characteristics). Novartis Pharma AG; 2. Data on file. Study no. CPKC412A2301. Novartis Pharmaceuticals Corp; 2016.

RATIFY: An evaluation of RYDAPT® added to the SoC for newly diagnosed *FLT3*+ AML adults[1,2]

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INDUCTION
(1–2 cycles)*

Cytarabine
+
Daunorubicin
+
RYDAPT®

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	Day 2	Day 3				

Standard 7+3
chemotherapy regimen

Day 8	Day 9	Day 10	Day 11	…	Day 21

RYDAPT® started here

FLT3 result must be available

FLT3 READY

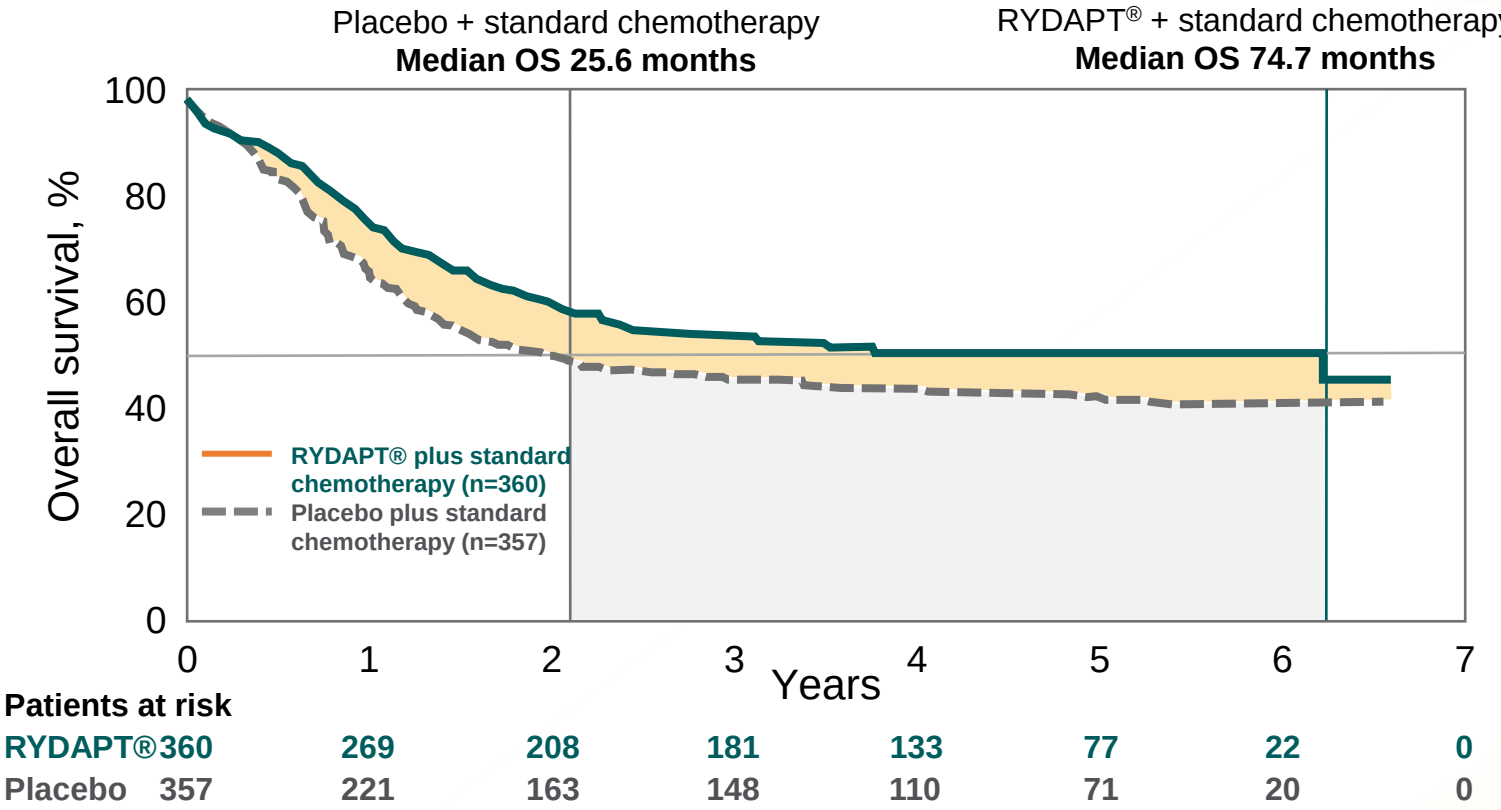
A cycle was 28 days. Chemotherapy dosing during induction was cytarabine IV, 200 mg/m2/d on days 1–7, and daunorubicin IV, 60 mg/m2/d on days 1–3. Transplantation was allowed but not specifically mandated per study protocol.

RYDAPT® at a dose of 50 mg orally twice daily.

1. RYDAPT (Summary of Product Characteristics). Novartis Pharma AG

2. Data on file. Study no. CPKC412A2301. Novartis Pharmaceuticals Corp; 2016.

Administration of RYDAPT® resulted in significant improvement in overall survival (non-censored for SCT)



22% reduction in the risk of death[2]

HR=0.78
(95% CI, 0.63–0.95)
P=0.0078

Newly diagnosed *FLT3*+ patients who received RYDAPT® plus chemotherapy experienced significant improvement in overall survival (25.6 months in Placebo arm vs. 74.7 months in RYDAPT® arm) with a 22% reduction in the risk of death compared with chemotherapy alone (hazard ratio [HR] = 0.78, 95% confidence interval [CI], 0.63, 0.95; 2 sided p=0.016).[1]

1. Stone RM, Mandrekar SJ, Laumann SK, et al. *NEJM*. 2017;377:454-64.
2. RYDAPT (Summary of Product Characteristics). Novartis Pharma AG

Median Event Free Survival (EFS) in patients with a *FLT3* mutation is increased with the use of RYDAPT® (non-censored for SCT)

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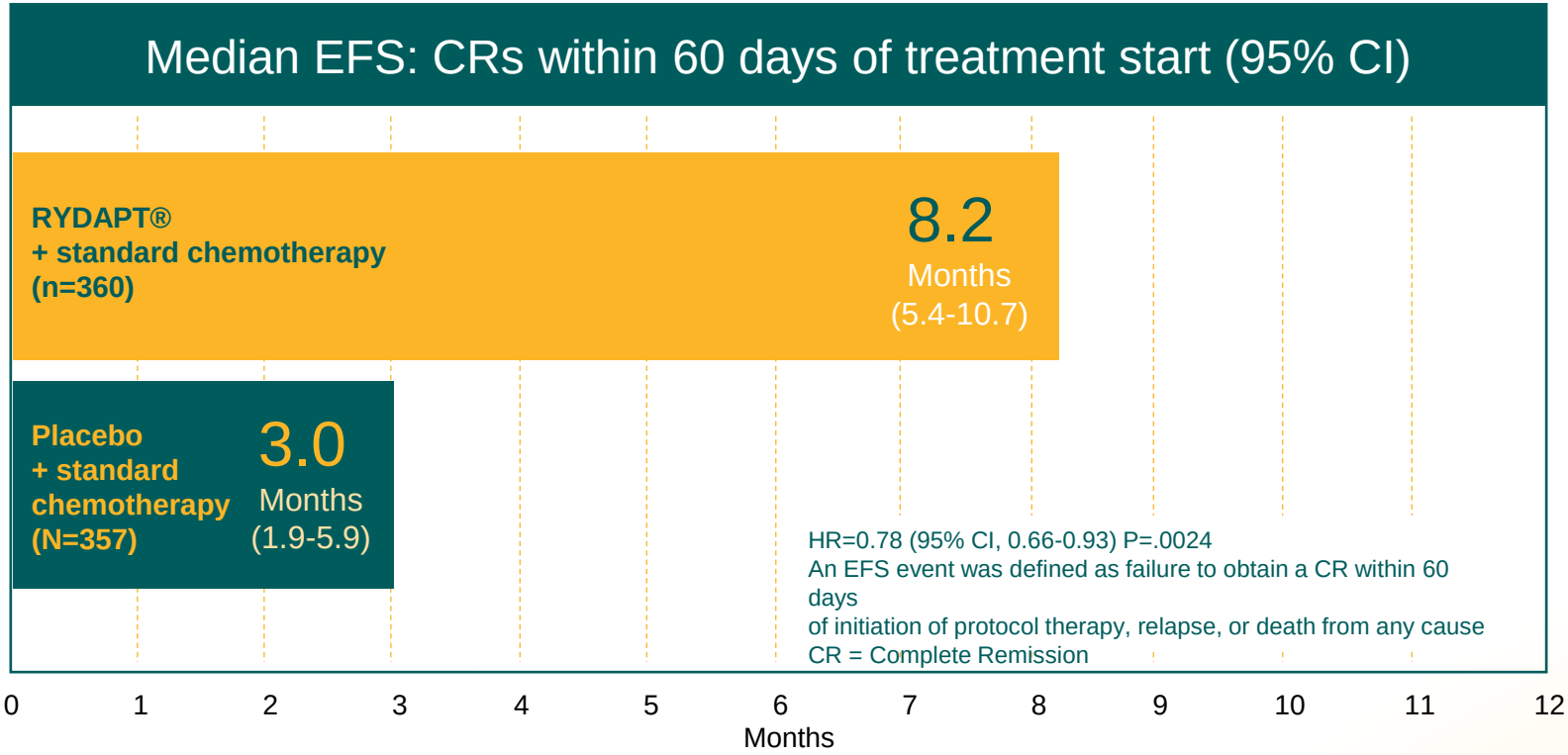


Key Message

Newly diagnosed *FLT3*+ patients who received RYDAPT® plus chemotherapy experienced a 22% reduction in the risk of an event[1] with a median 8.2 month increase of EFS in the trial

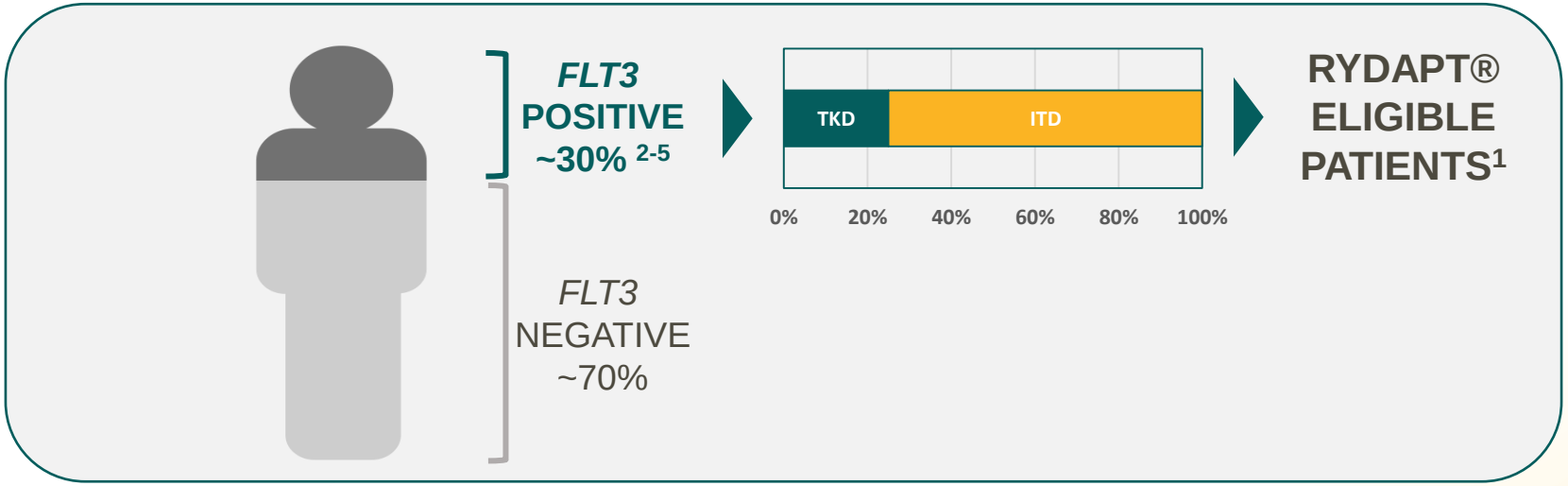
FLT3 READY

1. Stone RM, Mandrekar SJ, Laumann SK, et al. *NEJM*. 2017;377:454-64.

Both *FLT3*-ITD and TKD mutations are applicable for identifying patients eligible for RYDAPT®

Patients characteristics in the RATIFY trial by *FLT3* mutation type[1]

FLT3 mutation type	All patients	RYDAPT® group	Placebo group
ITD (high; FLT3 signal ratio >0.7)	214 (29.8%)	108 (30%)	106 (29.7%)
ITD (low; FLT3 signal ration 0.05 – 0.7)	341 (47.6%)	171 (47.5%)	170 (47.6%)
TKD	162 (22.6%)	81 (22.5%)	81 (22.7%)



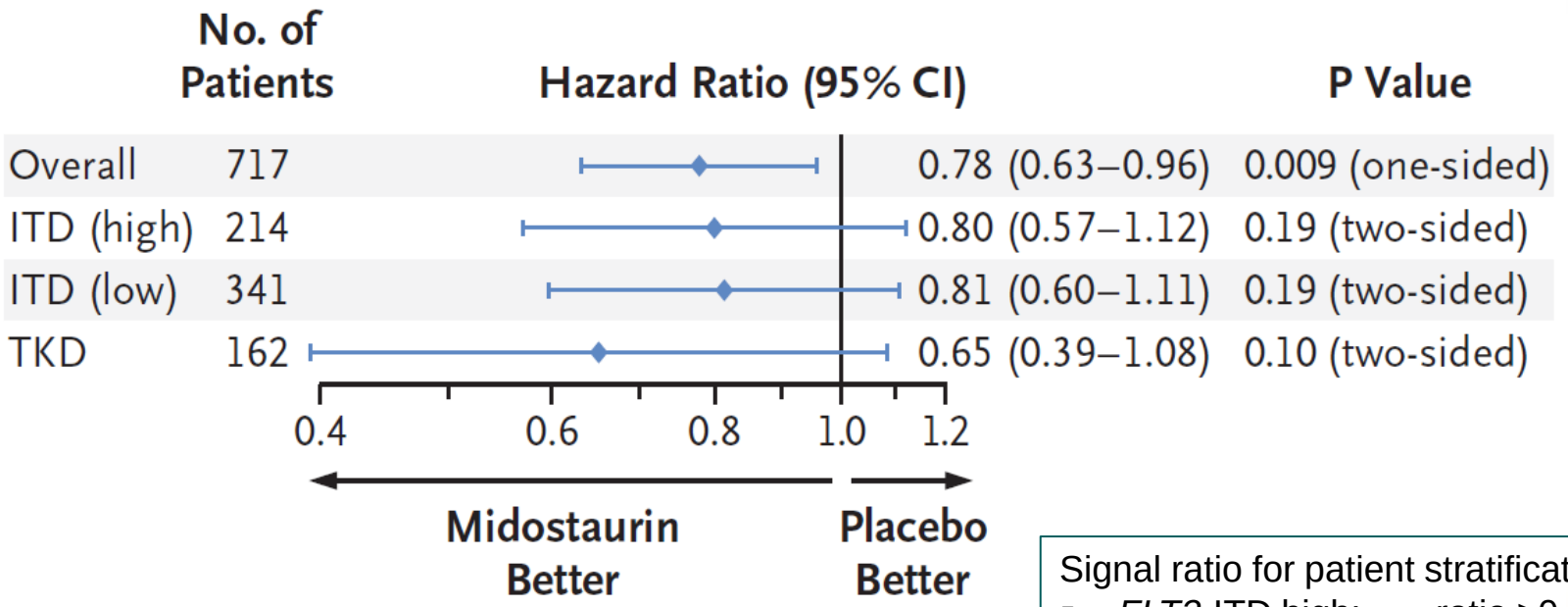
Key Message

All patients with AML should be tested for *FLT3*-ITD an TKD mutation in order to be eligible to start RYDAPT® therapy[1]

1. Stone RM, Mandrekar SJ, Laumann SK, et al. *NEJM*. 2017;377:454-64;
2. Fröhling S, Schlenk RF, Breitruck J, et al. *Blood*. 2002;100(13):4372-4380;
3. Patel JP, Gönen M, Figueroa ME, et al. *N Engl J Med*. 2012;366(12):1079-1089;
4. Schlenk RF, Döhner K, Krauter J, et al. *N Engl J Med*. 2008;358(18):1909-1918;
5. Schlenk RF, Kayser S, Bullinger L, et al. *Blood*. 2014;124(23):3441-3449.

All patient groups benefited from RYDAPT® treatment in the RATIFY trial[1]

Overall Survival



Signal ratio for patient stratification:

- *FLT3*-ITD high: ratio >0.07
- *FLT3*-ITD low: ratio 0.05 – 0.7
- *FLT3*-TKD: ratio ≥ 0.05

Key Message

All *FLT3* mutated patients did benefit from RYDAPT® Therapy irrespective of the *FLT3* mutation type or signal ratio

1. Stone RM, Mandrekar SJ, Laumann SK, et al. *NEJM*. 2017;377:454-64.

Serious adverse drug reactions occurred at similar rates in patients in the RYDAPT® arm versus the placebo[1]

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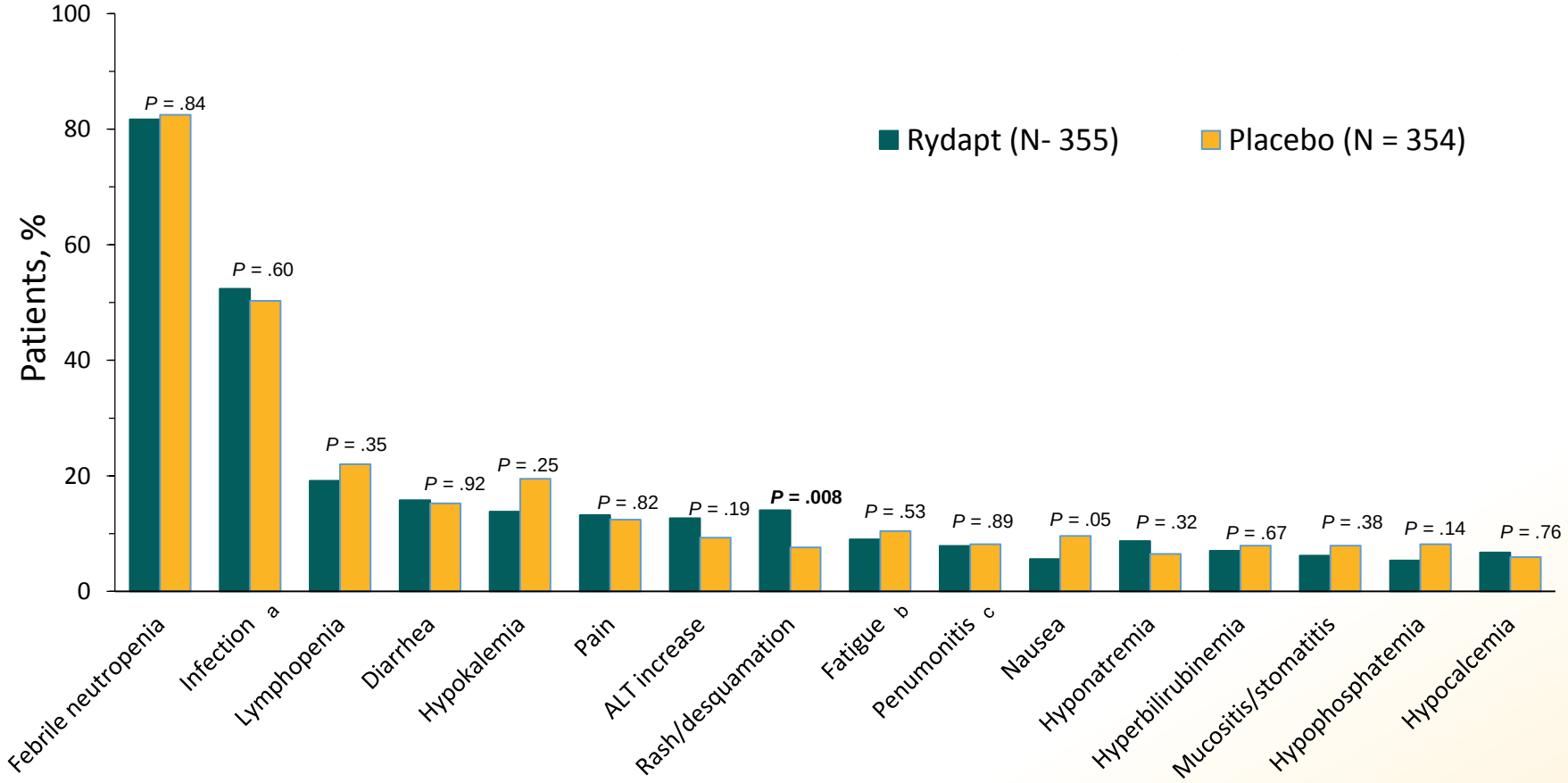
Twenty most frequent non-hematologic adverse events (AE) regardless of attribution



FLT3 READY

[a] Infection includes the following terms: infection with grade 3/4 neutrophils (ANC < 1.0 × 10^3/μL), infections with normal ANC or grade 1/2 neutrophils, infection with unknown ANC, opportunistic infection associated with grade ≥ 2 lymphopenia, and other infections.
[b] Fatigue includes asthenia, lethargy, and malaise.
[c] Includes pneumonitis and pulmonary infiltrates.

1. Stone RM et al., N Engl J Med. 2017; 377:354-64

Anemia was the only significant grade 3 or 4 adverse hematological event in the RYDAPT® arm versus placebo[1]

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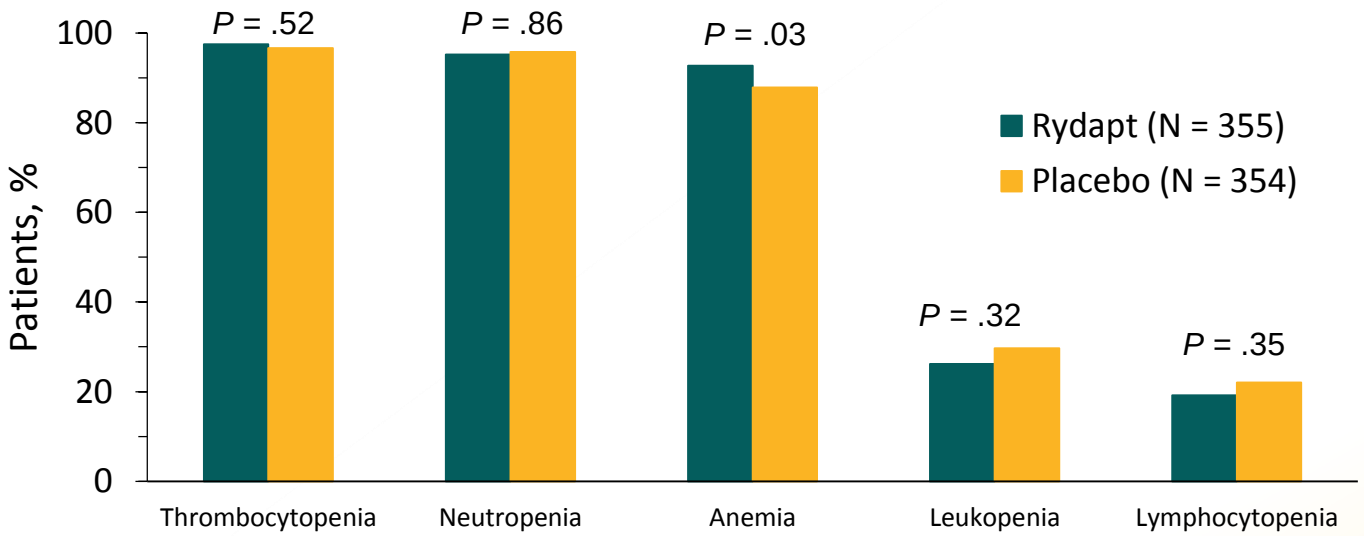
Grade ≥ 3 AEs occurring in ≥ 20% of patients regardless of attribution



FLT3 READY

1. Stone RM et al., N Engl J Med. 2017; 377:354-64

Summary

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Clinical utility of FLT3-ITD and FLT3-TKD in the RYDAPT® era
Patients with both FLT3-ITD- and TKD mutations were enrolled in the RATIFY Trial irrespective of karyotype
RYDAPT® was added to the SoC for newly diagnosed FLT3+ AML at day 8
Administration of RYDAPT® resulted in significant improvement in overall survival and event free survival
Patients with both FLT3-ITD and TKD mutations benefited from RYDAPT® therapy
FLT3 mutations in AML have changed from prognostic to selective for treatment using RYDAPT®

FLT3 READY

1. Oliver S, Samy F, Lawton S, et al; National Cancer Intelligence Network. Trends in incidence and outcome for haematological cancers in England: 2001-2010. London, UK: Public Health England; 2014. http://www.ncin.org.uk/view?rid=2818. Published November 2014. Accessed August 2018.
2.Gale RE, Green C, Allen C, et al; Blood. 2008;111(5):2776-2784. 3. Ferrara F, Schiffer CA. Lancet. 2013;381(9865):484-495. 4. RYDAPT® (Summary of Product Characteristics). Novartis Pharma AG.

Prescribing Information. Rydapt® ▼(midostaurin) Important note: Before prescribing, consult Summary of Product Characteristics (SmPC). **Presentation:** Soft capsule containing 25 mg midostaurin. **Indication:** In combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive. As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL). **Dosage:** Rydapt should be taken orally twice daily at approximately 12-hour intervals. The capsules should be taken with food. Prophylactic antiemetics should be administered as per patient tolerance. AML: Patients must have confirmation of FLT3 mutation using a validated test. The recommended dose is 50 mg orally twice daily. Rydapt is dosed on days 8 to 21 of induction and consolidation chemotherapy cycles, and then for patients in complete response every day as single agent maintenance therapy until relapse for up to 12 cycles of 28 days each. In patients receiving a haematopoietic stem cell transplant (SCT), Rydapt should be discontinued 48 hours prior to the conditioning regimen for SCT. ASM, SM AHN and MCL - The recommended starting dose of Rydapt is 100 mg orally twice daily. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.**Dose Modification:** AML *Grade 3/4 pulmonary infiltrates*: Interrupt Rydapt for the remainder of the cycle. Resume Rydapt at the same dose when infiltrate resolves to Grade ≤1. *Other Grade 3/4 non-haematological toxicities:* Interrupt Rydapt until toxicities considered at least possibly related to Rydapt have resolved to Grade ≤2, then resume. *QTc interval >470 msecs and ≤500 msecs:* Decrease Rydapt to 50 mg once daily for the remainder of the cycle. If QTc interval improves to ≤470 msecs, resume at the initial dose in the next cycle. Otherwise continue at 50 mg once daily. *QTc interval >500 msecs:* Withhold or interrupt Rydapt for the remainder of the cycle. If QTc improves to ≤470 msecs just prior to the next cycle, resume at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer Rydapt during that cycle. Rydapt may be held for as many cycles as necessary until QTc improves. *Grade 4 neutropenia (Absolute Neutrophil Count (ANC) <0.5 x 10^9/l) during maintenance therapy:* Interrupt Rydapt until ANC ≥1.0 x 10^9/l, then resume at 50 mg twice daily. If neutropenia persists >2 weeks and is suspected to be related to Rydapt, discontinue Rydapt. Persistent Grade 1 or 2 toxicity during maintenance therapy that patients deem unacceptable may prompt an interruption for as many as 28 days. ASM, SM-AHN and MCL: ANC <1.0 x 109/l attributed to Rydapt in patients without MCL, or ANC < 0.5 x 109/l attributed to Rydapt in patients with baseline ANC value of 0.5-1.5 x 109/l Interrupt Rydapt until ANC ≥1.0 x 109/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low ANC persists for >21 days and is suspected to be related to Rydapt. Platelet count < 50 x 109/l attributed to Rydapt in patients without MCL, or platelet count < 25 x 109/l attributed to Rydapt in patients with baseline platelet count of 25-75 x 109/l: Interrupt Rydapt until platelet count ≥ 50 x 109/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low platelet count persists for >21 days and is suspected to be related to Rydapt. *Haemoglobin < 8 dg/l attributed to Rydapt in patients without MCL, or life-threatening anaemia attributed to Rydapt in patients with baseline haemoglobin value of 8-10 dg/l:* Interrupt Rydapt until haemoglobin ≥ 8 dg/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low haemoglobin persists for >21 days and is suspected to be related to Rydapt. *Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy:* Interrupt Rydapt for 3 days (6 doses), then resume at 50 mg twice daily and, if tolerated, gradually increase to 100 mg twice daily. *Other Grade 3/4 non-haematological toxicities:* Interrupt Rydapt until event has resolved to Grade ≤2, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if toxicity is not resolved to Grade ≤2 within 21 days or severe toxicity recurs at a reduced dose of Rydapt. Elderly (≥65 years): No dose adjustment is required in patients aged over 65 years. In patients aged ≥60 years, Rydapt should be used only in patients eligible to receive intensive induction chemotherapy with adequate performance status and without significant comorbidities. **Contraindications:** Hypersensitivity to the active substance or to any other listed excipients. Concomitant administration of potent CYP3A4 inducers, e.g. rifampicin, St. John's Wort (Hypericum perforatum), carbamazepine, enzalutamide, phenytoin. **Special Warnings and Precautions:** White blood cell counts should be monitored regularly, especially at treatment initiation. Any active serious infection should be under control prior to starting treatment. Patients should be monitored for signs and symptoms of infection and if a diagnosis of infection is made appropriate treatment must be instituted promptly, including, as needed, the discontinuation of Rydapt. In patients at risk of cardiac dysfunction, Rydapt should be used with caution and the patient closely monitored by assessing LVEF when clinically indicated (at baseline and during treatment). An increased frequency of QTc prolongation was noted in midostaurin-treated patients, however, a mechanistic explanation for this observation was not found. Caution is warranted in patients at risk of QTc prolongation. Interval assessments of QT by ECG should be considered if Rydapt is taken concurrently with medicinal products that can prolong QT interval. Interstitial lung disease (ILD) and pneumonitis, in some cases fatal, have occurred in patients treated with Rydapt monotherapy or in combination with chemotherapy. Patients should be monitored for pulmonary symptoms indicative of ILD or pneumonitis and Rydapt discontinued in patients who experience pulmonary symptoms indicative of ILD or pneumonitis that are ≥Grade 3. **Interactions:** Midostaurin undergoes extensive hepatic metabolism mainly through CYP3A4 enzymes which are either induced or inhibited by a number of concomitant medicinal products. Strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites. Strong CYP3A4 inhibitors may increase midostaurin blood concentrations. Medicinal products with a narrow therapeutic range that are substrates of CYP1A2, CYP2D6, CYP2C8, CYP2C9, CYP2C19, CYP2E1, CYP3A4/5, CYP2B6, P-gp, BCRP or OATP1B1 should be used with caution when administered concomitantly with midostaurin and may need dose adjustment to maintain optimal exposure. **Pregnancy:** Rydapt is not recommended during pregnancy or in women of childbearing potential not using contraception. Sexually active women of childbearing potential are advised to have a pregnancy test within 7 days prior to starting treatment with Rydapt and should use effective contraception when using Rydapt and for at least 4 months after stopping treatment. It is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception. Breast-feeding should be discontinued during treatment with Rydapt and for at least 4 months after stopping treatment. **Undesirable Effects:** *Very common***:** Device-related infection, Urinary tract infection, Upper respiratory tract infection, Febrile neutropenia, Petechiae, Lymphopenia, Hypersensitivity, Insomnia, Headache, Dizziness, Hypotension, Epistaxis, Laryngeal pain, Dyspnoea, Cough, Pleural effusion, Nausea, Vomiting, Diarrhoea, Constipation, Stomatitis, Abdominal pain upper, Haemorrhoids, Dermatitis exfoliative, Hyperhidrosis, Back pain, Arthralgia, Pyrexia, Oedema peripheral, Fatigue, Absolute lymphocyte decree, Haemoglobin decreased, ANC decreased, Total bilirubin increased, Lipase increased, ALT increased, AST increased, Amylase increased, Hypokalaemia, Hyperglycaemia, Hypernatraemia, Activated partial thromboplastin time prolonged, *Common*: Pneumonia, Sepsis, Bronchitis, Oral herpes, Cystitis, Sinusitis, Erysipelas, Herpes zoster, Hyperuricaemia, Syncope, Tremor, Disturbance in attention, Tremor, Vertigo, Eyelid oedema, Sinus tachycardia, Hypertension, Pericardial effusion, Nasopharyngitis, Acute respiratory distress syndrome, Haematoma, Oropharyngeal pain, Dyspepsia, Gastrointestinal haemorrhage, Anorectal discomfort, Abdominal discomfort, Dry skin, Keratitis, Bone pain, Pain in extremity, Neck pain, Catheter-related thrombosis, Asthenia, Chills, Oedema, Hypercalcaemia, Weight increased, Contusion, Fall. *Uncommon:* Neutropenic sepsis, Anaphylactic shock **Basic NHS Cost:** Rydapt 25mg x 56 soft capsules, £5609.94 **Marketing Authorisation (MA) Holder:** Novartis Europharm Ltd **MA Number:** EU/1/17/1218/001-002 **Legal category:** POM Full prescribing information is available from Novartis Pharmaceuticals UK Limited, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Telephone: (01276) 698370 Fax: (01276) 692508. **Date of Revision**: May 2018

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If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com