INREBIC®
(fedratinib) capsules
100mg

ANOTHER PLAN OF ATTACK AGAINST MYELOFIBROSIS

for patients with intermediate-2 or high-risk primary or secondary MF

MF, myelofibrosis.

INDICATION

INREBIC® (fedratinib) is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF).

IMPORTANT SAFETY INFORMATION

WARNING: ENCEPHALOPATHY INCLUDING WERNICKE'S

Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with INREBIC. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue INREBIC and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

Please see additional Important Safety Information throughout. Click to see full Prescribing Information, including Boxed WARNING.

Cases of encephalopathy, including Wernicke's encephalopathy (WE), in the INREBIC® clinical development program[1]

- In the clinical development program of INREBIC®, which included 608 patients, serious and fatal cases of encephalopathy, including WE, occurred in INREBIC®-treated patients. Serious cases were reported in 1.3% (8/608) of patients treated with INREBIC® in clinical trials and 0.16% (1/608) of cases were fatal
- Encephalopathy, including WE, is a neurologic emergency that can be fatal
- WE is attributable to thiamine (vitamin B1) deficiency
- Signs and symptoms of WE may include ataxia, mental status changes, and ophthalmoplegia (eg, nystagmus, diplopia)
- Any change in mental status, confusion, or memory impairment should raise concern for potential encephalopathy, including WE, and prompt a full evaluation including a neurologic examination, assessment of thiamine levels, and imaging

Management of encephalopathy, including WE[1]

Assess at treatment initiation

- Assess thiamine levels prior to starting INREBIC®
- Do not start INREBIC® in patients with thiamine deficiency

Monitor during treatment

- Assess thiamine levels periodically during treatment and as clinically indicated
- Monitor for signs and symptoms of WE, which may include ataxia, mental status changes, and ophthalmoplegia (eg, nystagmus, diplopia)

Intervene immediately if thiamine deficient or if encephalopathy is suspected

- Do not start INREBIC® in patients with thiamine deficiency; replete thiamine prior to treatment initiation and during treatment if thiamine levels are low
- **If encephalopathy is suspected, immediately discontinue treatment with INREBIC® and initiate parenteral thiamine treatment**
- Monitor until symptoms resolve or improve and thiamine levels normalize

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Encephalopathy, including Wernicke's: Serious and fatal encephalopathy, including Wernicke's encephalopathy, has occurred in INREBIC-treated patients. Serious cases were reported in 1.3% (8/608) of patients treated with INREBIC in clinical trials and 0.16% (1/608) of cases were fatal.

Wernicke's encephalopathy is a neurologic emergency resulting from thiamine (Vitamin B1) deficiency. Signs and symptoms of Wernicke's encephalopathy may include ataxia, mental status changes, and ophthalmoplegia (e.g., nystagmus, diplopia). Any change in mental status, confusion, or memory impairment should raise concern for potential encephalopathy, including Wernicke's, and prompt a full evaluation including a neurologic examination, assessment of thiamine levels, and imaging. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated.

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INREBIC® is started at the full dose (400 mg) in patients with platelets ≥50 x 10^9/L and is given once daily[1]

- INREBIC® may be taken with or without food. Administration with a high-fat meal may reduce the incidence of nausea and vomiting
- Patients who are on treatment with ruxolitinib before the initiation of INREBIC® must taper and discontinue according to the ruxolitinib prescribing information

Reduction in starting dose

- Reduce the INREBIC® dose to 200 mg once daily in patients using concomitant strong CYP3A4 inhibitors
- Reduce the INREBIC® dose to 200 mg once daily in patients with severe renal impairment (creatinine clearance [CLcr] 15 mL/min to 29 mL/min)

Avoid use

- Avoid use of INREBIC® with strong and moderate CYP3A4 inducers
- Avoid use of INREBIC® with dual CYP3A4 and CYP2C19 inhibitors
- Avoid use of INREBIC® in patients with severe hepatic impairment

Obtain blood tests

- Obtain the following blood tests prior to starting treatment with INREBIC®, periodically during treatment, and as clinically indicated: thiamine (vitamin B1) level, complete blood count with platelets, creatinine and BUN, hepatic panel, and amylase and lipase

Dose modifications and treatment discontinuations with INREBIC® during the randomized period[1]

Dosage interruptions due to an AR occurred in 21% of patients

ARs requiring dosage interruption in >3% of patients who received INREBIC® included diarrhea and nausea.

Dosage reductions due to an AR occurred in 19% of patients

ARs requiring dosage reduction in >2% of patients who received INREBIC® included anemia (6%), diarrhea (3%), vomiting (3%), and thrombocytopenia (2%).

Permanent discontinuation due to an AR occurred in 14% of patients

Most frequent reasons for permanent discontinuation in ≥2% of patients included cardiac failure (3%), thrombocytopenia, myocardial ischemia, diarrhea, and increased blood creatinine (2% each).

AR, adverse reaction; BUN, blood urea nitrogen.

Please see WARNINGS AND PRECAUTIONS: PREGNANCY/LACTATION on page 12.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Encephalopathy, including Wernicke's (cont'd): Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue INREBIC and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.

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INREBIC® was studied in patients with similar characteristics to those seen in practice[1,2]

A robust phase-3 study (JAKARTA)

A double-blind, randomized, placebo-controlled, phase-3 study (N=289) in patients not previously treated with a JAK inhibitor with intermediate-2 or high-risk primary or secondary myelofibrosis (MF)

Randomized 1:1:1

INREBIC® 500 mg qd for at least 6 cycles (n=97)	INREBIC® 400 mg qd for at least 6 cycles (n=96)	Placebo qd for at least 6 cycles (n=96)

Primary endpoint
% of patients with ≥35% spleen volume reduction (SVR)

Baseline characteristics overview

	INREBIC® 400 mg n=96	Placebo n=96
Median age, years (range)	63 (39-86)	66 (27-85)
MF subtype		
Primary MF	65%	60%
Post-PV MF	25%	28%
Post-ET MF	10%	12%
Platelet count		
Median	221 x 10^9/L	187 x 10^9/L
50 to <100 x 10^9/L	14%	19%
≥100 x 10^9/L	85%	81%
IPSS risk status		
Intermediate-2	59%	48%
High risk	41%	52%

The recommended daily dose is 400 mg; therefore, only the 400-mg arm will be shown relative to placebo

Additional trial information[1,2]

Select inclusion criteria

A diagnosis of intermediate-2 or high-risk MF, post-polycythemia vera MF, or post-essential thrombocythemia MF with splenomegaly.

Study endpoints

Primary endpoint

The proportion of patients achieving greater than or equal to a 35% reduction from baseline in spleen volume at the end of cycle 6 as measured by magnetic resonance imaging (MRI) or computed tomography (CT) with a scan 4 weeks later.

Secondary endpoint

Secondary endpoints included the proportion of patients with a 50% or greater reduction in Total Symptom Score (TSS) from baseline to the end of cycle 6 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary. The modified MFSAF included 6 key MF-associated symptoms: night sweats, itching, abdominal discomfort, early satiety, pain under the ribs on the left side, and bone or muscle pain. The symptoms were measured on a scale from 0 (absent) to 10 (worst imaginable).

Treatment period

Patients continued to receive INREBIC® as long as they were benefiting (defined as having had a complete or partial remission, clinical improvement, or stable disease) and had not experienced progressive disease/relapse (as defined by the modified IWG-MRT criteria) or unacceptable toxicity requiring discontinuation of INREBIC®.

ET, essential thrombocythemia; IPSS, International Prognostic Scoring System; IWG-MRT, International Working Group–Myeloproliferative Neoplasms Research and Treatment; JAK, Janus-associated kinase; PV, polycythemia vera; qd, once daily.

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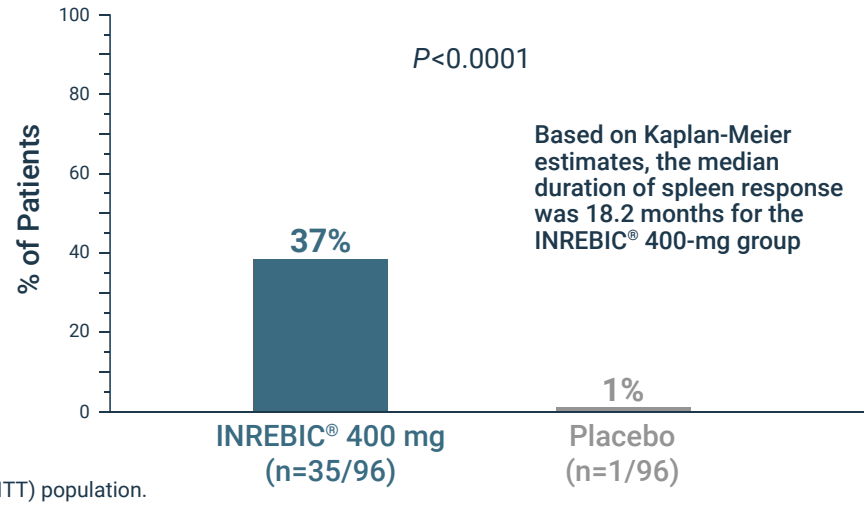
INREBIC® provided a powerful spleen response and a statistically significant reduction in TSS vs placebo[1]

Spleen reduction

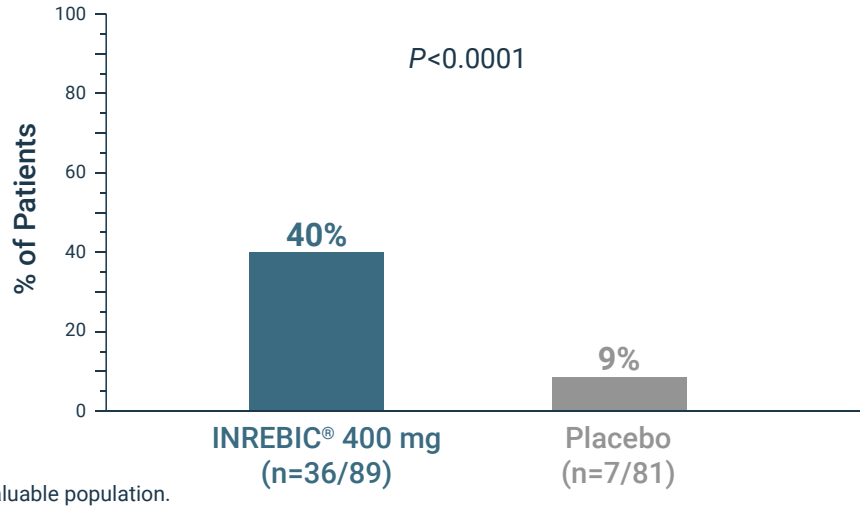
Proportion of patients with SVR ≥35% from baseline at the end of cycle 6 as measured by MRI or CT with a follow-up scan 4 weeks later[a]



[a]Intent-to-treat (ITT) population.

Symptom reduction

Proportion of patients with ≥50% reduction in TSS from baseline at the end of cycle 6 as measured by the MFSAF[a]



[a]In symptom-evaluable population.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Anemia: New or worsening Grade 3 anemia occurred in 34% of INREBIC-treated patients. The median time to onset of the first Grade 3 anemia was approximately 2 months, with 75% of cases occurring within 3 months. Mean hemoglobin levels reached nadir after 12 to 16 weeks with partial recovery and stabilization after 16 weeks. Red blood cell transfusions were received by 51% of INREBIC-treated patients and permanent discontinuation of INREBIC occurred due to anemia in 1% of patients. Consider dose reduction for patients who become red blood cell transfusion dependent.

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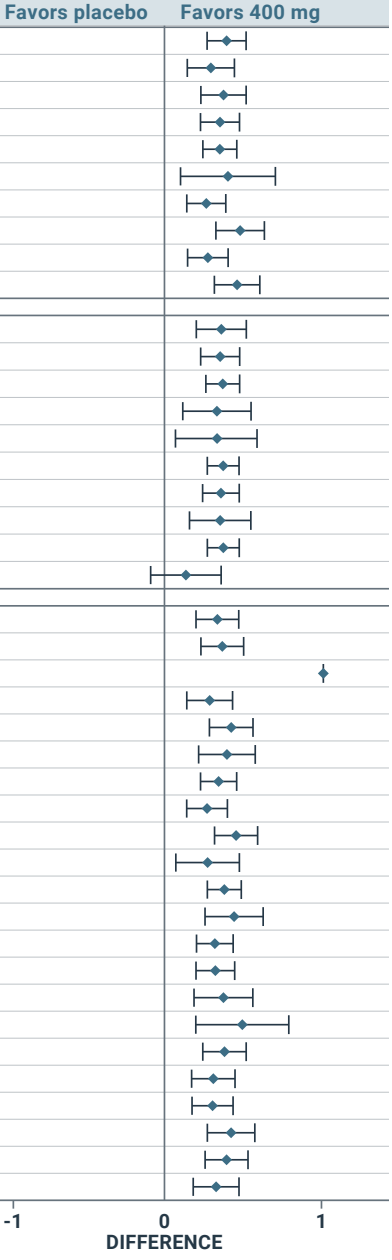
Primary endpoint subgroup analysis: treatment with INREBIC® across subgroups vs placebo for spleen response rate[2]

Analyses included a subgroup of patients with low platelet counts (50 to <100 x 10^9/L)

Subgroup analyses of spleen response rate (≥35% SVR) at the end of cycle 6 confirmed 4 weeks later—400 mg vs placebo (ITT population)

Subgroup	N
Age: ≤65 years old	105
Age: >65 years old	87
ECOG: 0	72
ECOG: ≥1	119
Race: White	176
Race: Non-white	16
Sex: Male	109
Sex: Female	83
Weight: >median	94
Weight: ≤median	91
HGB ≥10 g/dL: No	80
HGB ≥10 g/dL: Yes	111
LDH >5 ULN: No	157
LDH >5 ULN: Yes	31
Platelet: 50-100 x 10^9/L	31
Platelet: ≥100 × 10^9/L	159
WBC ≥25 × 10^9/L: No	138
WBC ≥25 × 10^9/L: Yes	53
RBC transfusion dependence: No	178
RBC transfusion dependence: Yes	14
Blasts ≥1%: No	85
Blasts ≥1%: Yes	102
Fibrosis grade: 0	4
Fibrosis grade: 1 or 2	85
Fibrosis grade: 3	96
Spleen size >10 cm: No	53
Spleen size >10 cm: Yes	139
Spleen volume: >median	97
Spleen volume: ≤median	88
Constitutional symptoms: No	49
Constitutional symptoms: Yes	143
Prior hydroxyurea therapies: No	69
Prior hydroxyurea therapies: Yes	123
Myelofibrosis type: Primary MF	120
Myelofibrosis type: Post-PV MF	51
Myelofibrosis type: Post-ET MF	21
Intermediate-2 risk	103
High-risk MF	89
1st diagnosis time[a]: >median	103
1st diagnosis time[a]: ≤median	89
Total Symptom Score: >median	85
Total Symptom Score: ≤median	91



Analysis Limitations: These data should not be interpreted to determine a treatment difference in these selected subgroups because of potential selection bias, insufficient sample size, and a higher probability of making a false-positive finding.

ECOG, Eastern Cooperative Oncology Group; HGB, hemoglobin; LDH, lactate dehydrogenase; RBC, red blood cell; ULN, upper limit of normal; WBC, white blood cell.

[a]First diagnosis time=time from first diagnosis of MF to randomization.

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INREBIC® hematologic safety profile[1]

Selected laboratory abnormalities that have worsened from baseline (≥20%) in patients receiving INREBIC®[a]				
Laboratory parameter	INREBIC® 400 mg n=96		Placebo n=95	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Anemia	74	34	32	10
Thrombocytopenia	47	12	26	10
Neutropenia	23	5	13	3.3

[a]With a difference between arms of >10% when compared to placebo in JAKARTA during randomized treatment.

Dose reductions and discontinuations due to hematologic ARs

- Thrombocytopenia-related dose reductions and discontinuations occurred in 2.1% of patients
- Anemia-related dose reductions (6%) and discontinuations (1%) occurred with INREBIC®

Median time to onset of lab abnormalities: The median time to the first onset of grade 3 anemia was approximately 2 months, with 75% of cases occurring within 3 months. The median time to the first onset of grade 3 thrombocytopenia was approximately 1 month, with 75% of cases occurring within 4 months.

Transfusions: 51% of patients treated with INREBIC® received red blood cell transfusions. 3.1% of patients treated with INREBIC® received platelet transfusions.

Serious ARs: Occurred in 21% of patients. Serious ARs that occurred in ≥2% of patients included cardiac failure (5%) and anemia (2%). Fatal ARs of cardiogenic shock occurred in 1% of patients receiving INREBIC®.

Permanent discontinuation due to an AR occurred in 14% of patients receiving INREBIC®

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Thrombocytopenia: New or worsening Grade ≥3 thrombocytopenia during the randomized treatment period occurred in 12% of INREBIC-treated patients. The median time to onset of the first Grade 3 thrombocytopenia was approximately 1 month; with 75% of cases occurring within 4 months. Platelet transfusions were received by 3.1% of INREBIC-treated patients. Permanent discontinuation of treatment due to thrombocytopenia and bleeding that required clinical intervention both occurred in 2.1% of INREBIC-treated patients. Obtain a complete blood count (CBC) at baseline, periodically during treatment, and as clinically indicated. For Grade 3 thrombocytopenia with active bleeding or Grade 4 thrombocytopenia, interrupt INREBIC until resolved to less than or equal to Grade 2 or baseline. Restart dose at 100 mg daily below the last given dose and monitor platelets as clinically indicated.

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Gastrointestinal (GI) and nonhematologic ARs with INREBIC®[1]

Selected ARs reported in patients on INREBIC®				
Adverse reaction[a]	INREBIC® 400 mg n=96		Placebo n=95	
	All Grades %	Grade ≥3[b] %	All Grades %	Grade ≥3 %
ARs in ≥5% of patients				
Diarrhea	66	5	16	0
Nausea	62	0	15	0
Vomiting	39	3.1	5	0
Anemia	40	30	14	7
Fatigue or asthenia	19	5	16	1.1
Muscle spasms	12	0	1.1	0
Blood creatinine increased	10	1	1.1	0
Pain in extremity	10	0	4.2	0
ALT increased	9	0	1.1	0
Headache	9	0	1.1	0
Weight increased	9	0	4.2	0
Dizziness	8	0	3.2	0
Bone pain	8	0	2.1	0
Urinary tract infection[c]	6	0	1.1	0
Dysuria	6	0	0	0
AST increased	5	0	1.1	0
Biochemistry[d]				
Creatinine increased	59	3.1	19	1.1
ALT increased	43	1	14	0
AST increased	40	0	16	1.1
Lipase increased	35	10	7	2.2
Hyponatremia	26	5	11	4.3
Amylase increased	24	2.1	5	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

[a]Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

[b]Only 1 grade 4 event (anemia).

[c]Includes cystitis.

[d]Selected laboratory abnormalities that have worsened from baseline (≥20%) in patients receiving INREBIC®, with a difference between arms of >10% when compared to placebo in JAKARTA during randomized treatment.

Median time to onset: The median time to onset of any grade nausea, vomiting, and diarrhea was 1 day, with 75% of cases occurring within 2 weeks of treatment. The median time to onset of any grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 3 months.

Management of GI ARs: Consider providing appropriate prophylactic antiemetic therapy (eg, 5-HT3 receptor antagonists) during INREBIC® treatment. Treat diarrhea with antidiarrheal medications promptly at the first onset of symptoms. INREBIC® may be taken with or without food. Administration with a high-fat meal may reduce the incidence of nausea and vomiting.

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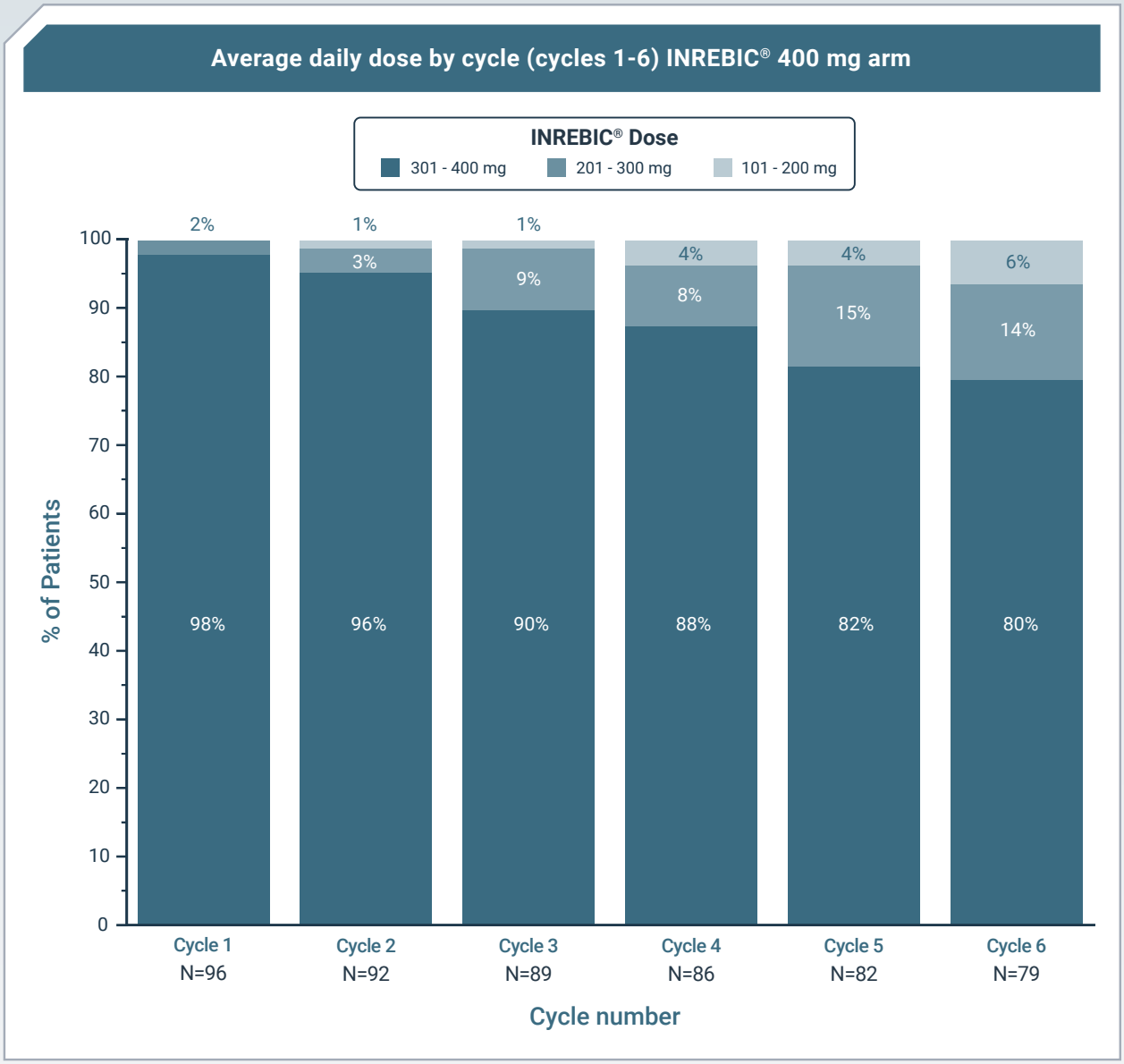
Average daily dose of INREBIC®[2]



Analysis Limitations: This is a post-hoc analysis without intention to make statistical inferences.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Gastrointestinal Toxicity: Gastrointestinal toxicities are the most frequent adverse reactions in INREBIC-treated patients. During the randomized treatment period, diarrhea occurred in 66% of patients, nausea in 62% of patients, and vomiting in 39% of patients. Grade 3 diarrhea 5% and vomiting 3.1% occurred. The median time to onset of any grade nausea, vomiting, and diarrhea was 1 day, with 75% of cases occurring within 2 weeks of treatment. Consider providing appropriate prophylactic anti-emetic therapy (e.g., 5-HT3 receptor antagonists) during INREBIC treatment. Treat diarrhea with anti-diarrheal medications promptly at the first onset of symptoms. Grade 3 or higher nausea, vomiting, or diarrhea not responsive to supportive measures within 48 hours, interrupt INREBIC until resolved to Grade 1 or less or baseline. Restart dose at 100 mg daily below the last given dose. Monitor thiamine levels and replete as needed.

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The NCCN Guidelines® include fedratinib[1,3]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)* recommend fedratinib as initial therapy (category 2B) for

- Patients with higher-risk MF (intermediate-2 or high risk)
- AND platelets ≥50 x 10^9/L
- AND who are transplant ineligible

NCCN, National Comprehensive Cancer Network.

*NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hepatic Toxicity: Elevations of ALT and AST (all grades) during the randomized treatment period occurred in 43% and 40%, respectively, with Grade 3 or 4 in 1% and 0%, respectively, of INREBIC-treated patients. The median time to onset of any grade transaminase elevation was approximately 1 month, with 75% of cases occurring within 3 months. Monitor hepatic function at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher ALT and/or AST elevations (greater than 5 × ULN), interrupt INREBIC dose until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose. If re-occurrence of a Grade 3 or higher elevation of ALT/AST, discontinue treatment with INREBIC.

Amylase and Lipase Elevation: Grade 3 or higher amylase 2% and/or lipase 10% elevations developed in INREBIC-treated patients. The median time to onset of any grade amylase or lipase elevation was 15 days, with 75% of cases occurring within 1 month of starting treatment. One patient developed pancreatitis in the fedratinib clinical development program (n=608) and pancreatitis resolved with treatment discontinuation. Monitor amylase and lipase at baseline, periodically during treatment, and as clinically indicated. For Grade 3 or higher amylase and/or lipase elevations, interrupt INREBIC until resolved to Grade 1 or less or to baseline. Restart dose at 100 mg daily below the last given dose.

ADVERSE REACTIONS:

The most common adverse reactions for INREBIC treated vs. placebo were diarrhea (66% vs. 16%), nausea (62% vs. 15%), anemia (40% vs. 14%), and vomiting (39% vs. 5%). Dosage interruptions due to an adverse reaction during the randomized treatment period occurred in 21% of patients who received INREBIC. Adverse reactions requiring dosage interruption in >3% of patients who received INREBIC included diarrhea and nausea. Dosage reductions due to an adverse reaction during the randomized treatment period occurred in 19% of patients who received INREBIC. Adverse reactions requiring dosage reduction in >2% of patients who received INREBIC included anemia (6%), diarrhea (3%), vomiting (3%), and thrombocytopenia (2%).

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INREBIC® in patients previously treated with ruxolitinib (JAKARTA2)[2]

Limitations

JAKARTA2, a phase-2, single-arm, open-label study, was prematurely terminated, which impacts the interpretability of the data. No conclusions regarding the benefits or risks of fedratinib in patients who are resistant or intolerant to ruxolitinib can be established based on this study. These data are not included in the Prescribing Information.

JAKARTA2 study design and select patient characteristics

- Single-arm, open-label, phase-2 study in 97 primary or secondary MF patients resistant or intolerant to ruxolitinib per investigator assessment
- The primary endpoint was the proportion of patients achieving ≥35% spleen volume reduction at the end of cycle 6 as measured by MRI or CT
- Median exposure to ruxolitinib prior to enrollment in study was 10.7 months
- Median exposure to INREBIC® during enrollment in study was 24 weeks (range 0.7-79.4 weeks)

Methodology for spleen and symptom assessment

- Post hoc analyses of spleen volume in the ITT population and Total Symptom Score
- Only patients who were confirmed responders at the end of cycle 6 were included; patients missing spleen volume assessments at the end of cycle 6 were considered nonresponders

Spleen response (ITT)

30.9% of patients (N=30/97) experienced ≥35% spleen volume reduction at the end of cycle 6

Symptom response

26.7% of patients (N=24/90)* experienced ≥50% reduction in Total Symptom Score at the end of cycle 6

*Includes patients with an evaluable baseline and ≥1 post-baseline assessment of Total Symptom Score.

Additional NCCN Guidelines® recommendations for fedratinib[1,3]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)† include fedratinib (category 2A) for

- Patients with higher-risk MF (intermediate-2 or high risk), previously treated with ruxolitinib with no response or loss of response
- AND platelets ≥50 x 10^9/L
- AND who are transplant ineligible

†NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

IMPORTANT SAFETY INFORMATION (cont'd)

DRUG INTERACTIONS:

Coadministration of INREBIC with a strong CYP3A4 inhibitor increases fedratinib exposure. Increased exposure may increase the risk of adverse reactions. Consider alternative therapies that do not strongly inhibit CYP3A4 activity. Alternatively, reduce the dose of INREBIC when administering with a strong CYP3A4 inhibitor. Avoid INREBIC with strong and moderate CYP3A4 inducers. Avoid INREBIC with dual CYP3A4 and CYP2C19 inhibitor. Coadministration of INREBIC with drugs that are CYP3A4 substrates, CYP2C19 substrates, or CYP2D6 substrates increases the concentrations of these drugs, which may increase the risk of adverse reactions of these drugs. Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates as necessary when coadministered with INREBIC.

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ARs with INREBIC® in patients previously treated with ruxolitinib[2]

Hematologic ARs (ITT)			
Laboratory parameter[a]	INREBIC® 400 mg N=97		
	All Grades %	Grade 3 %	Grade 4 %
Anemia	99.0	46.4	0
Thrombocytopenia	70.1	16.5	7.2
Neutropenia	24.0	5.2	2.1

[a]Presented values are worst-grade values regardless of baseline.

Nonhematologic ARs reported (ITT)			
Adverse reaction	INREBIC® 400 mg N=97		
	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal ARs in ≥10% of patients			
Diarrhea	61.9	4.1	0
Nausea	55.7	0	0
Vomiting	41.2	0	0
Constipation	20.6	1.0	0
Other nonhematologic ARs in ≥10% of patients			
Fatigue	15.5	2.1	0
Headache	13.4	1.0	0
Urinary tract infection[a]	12.4	0	0
Asthenia	11.3	1.0	0
Dizziness	11.3	0	0
Biochemistry[b]			
Creatinine increased	74.2	0	0
AST increased	47.4	1.0	0
ALT increased	45.4	2.1	0
Lipase increased	25.8	7.2	1.0
Amylase increased[c]	17.7	3.1	0

[a]Includes cystitis.
[b]Presented values are worst-grade values regardless of baseline.
[c]Of 96 evaluable patients.

IMPORTANT SAFETY INFORMATION (cont'd)

PREGNANCY/LACTATION: Consider the benefits and risks of INREBIC for the mother and possible risks to the fetus when prescribing INREBIC to a pregnant woman. Due to the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with INREBIC, and for at least 1 month after the last dose.

RENAL IMPAIRMENT: Reduce INREBIC dose when administered to patients with severe renal impairment. No modification of the starting dose is recommended for patients with mild to moderate renal impairment. Due to potential increase of exposure, patients with preexisting moderate renal impairment require more intensive safety monitoring, and if necessary, dose modifications based on adverse reactions.

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Starting patients on INREBIC®[1]

1 Assess before starting

- Assess thiamine levels. Do not start INREBIC® in patients with thiamine deficiency; replete thiamine prior to treatment initiation and during treatment if thiamine levels are low
- Obtain the following blood tests prior to starting treatment with INREBIC®, periodically during treatment, and as clinically indicated: thiamine (vitamin B1) level, complete blood count with platelets, creatinine and BUN, hepatic panel, and amylase and lipase
- Patients who are on treatment with ruxolitinib before the initiation of INREBIC® must taper and discontinue according to the ruxolitinib prescribing information

2 Administer the right starting dose

- The recommended dosage of INREBIC® is 400 mg taken orally once daily for patients with a baseline platelet count ≥50 x 10^9/L
- Reduce the INREBIC® dose to 200 mg once daily for patients using concomitant strong CYP3A4 inhibitors
- Reduce the INREBIC® dose to 200 mg once daily for patients with severe renal impairment (CLcr 15 mL/min to 29 mL/min)
- Interrupt dose until grade 4 neutropenia is resolved to ≤grade 2 or baseline. Restart dose at 100 mg daily below the last given dose
- Interrupt dose until ≥grade 3 ALT, AST, or bilirubin are ≤grade 1 or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST, and bilirubin (total and direct) more frequently following dose reduction. If reoccurrence of a ≥grade 3 elevation, discontinue treatment with INREBIC®
- Interrupt dose until ≥grade 3 nonhematologic toxicities are resolved to ≤grade 1 or baseline. Restart dose at 100 mg daily below the last given dose

3 Support patients on INREBIC®

- If encephalopathy is suspected, immediately discontinue treatment with INREBIC® and initiate parenteral thiamine treatment. Monitor until symptoms resolve or improve and thiamine levels normalize
- The median time to onset of any grade nausea, vomiting, and diarrhea was 1 day, with 75% of cases occurring within 2 weeks of treatment
- Treat diarrhea with antidiarrheal medications promptly at the first onset of symptoms
- Consider providing appropriate prophylactic antiemetic therapy (eg, 5-HT3 receptor antagonists) during INREBIC® treatment
- INREBIC® may be taken with or without food. Administration with a high-fat meal may reduce the incidence of nausea and vomiting

To learn more, visit INREBICPRO.COM

IMPORTANT SAFETY INFORMATION (cont'd)

HEPATIC IMPAIRMENT: Avoid use of INREBIC in patients with severe hepatic impairment.

Please see additional Important Safety Information throughout. Click to see full Prescribing Information, including Boxed WARNING.

REFERENCES: 1. INREBIC® [package insert]. Summit, NJ: Celgene Corporation; 2019. **2.** Data on file. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.1.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed October 20, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org.

INREBIC®
(fedratinib) capsules
100mg