Missing Milestones Has Consequences

- EARLIER
- DEEPER
- FEWER PROGRESSIONS
- SWITCH

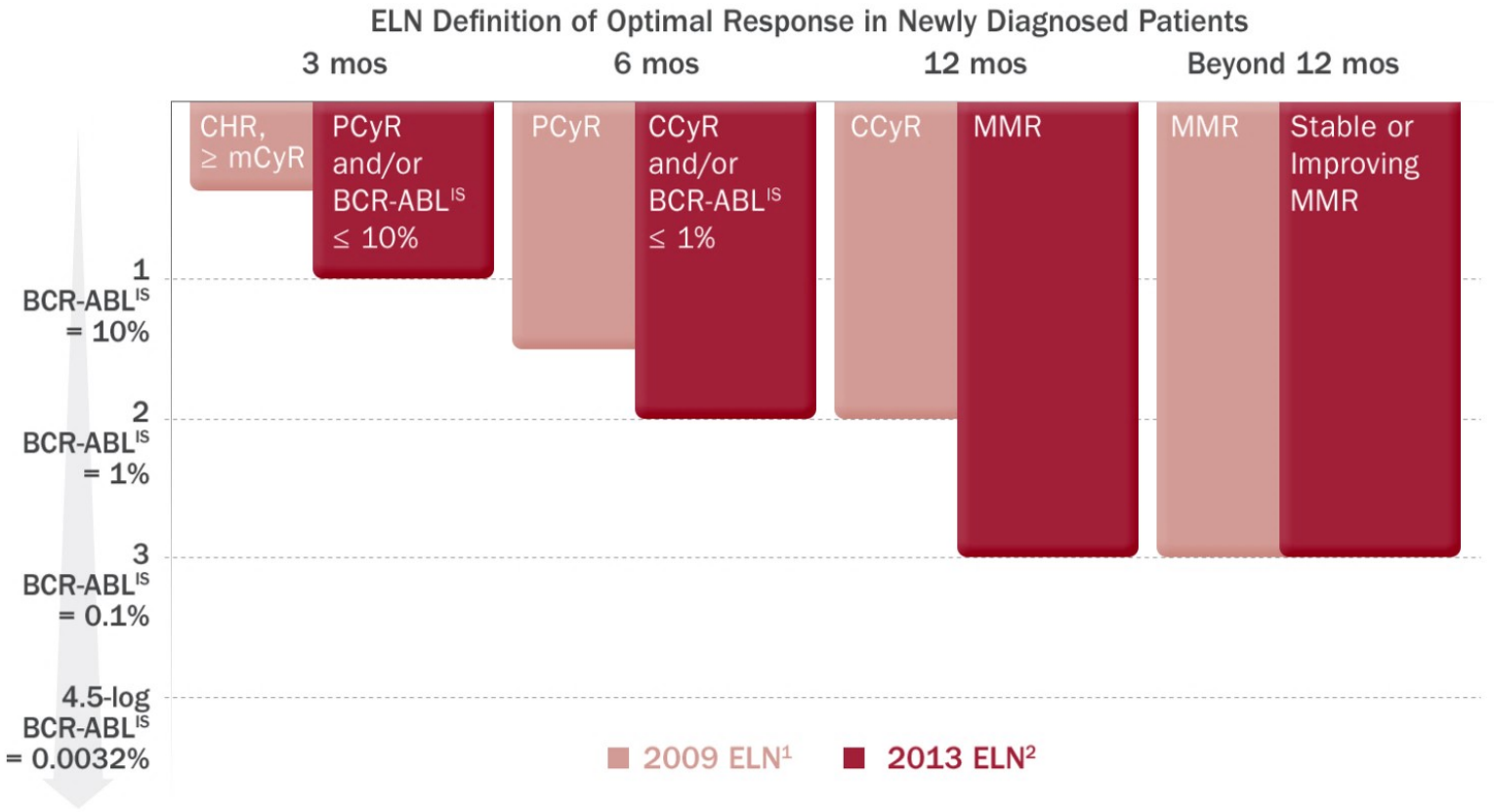
RESPONSE MATTERS.

Send Resources

MISSING MILESTONES HAS CONSEQUENCES

European LeukemiaNet (ELN) Now Recommends Earlier, Deeper Response

In 2013, ELN changed the recommended optimal response milestones for patients with Ph+ CML



How are your newly diagnosed patients doing meeting these milestones?

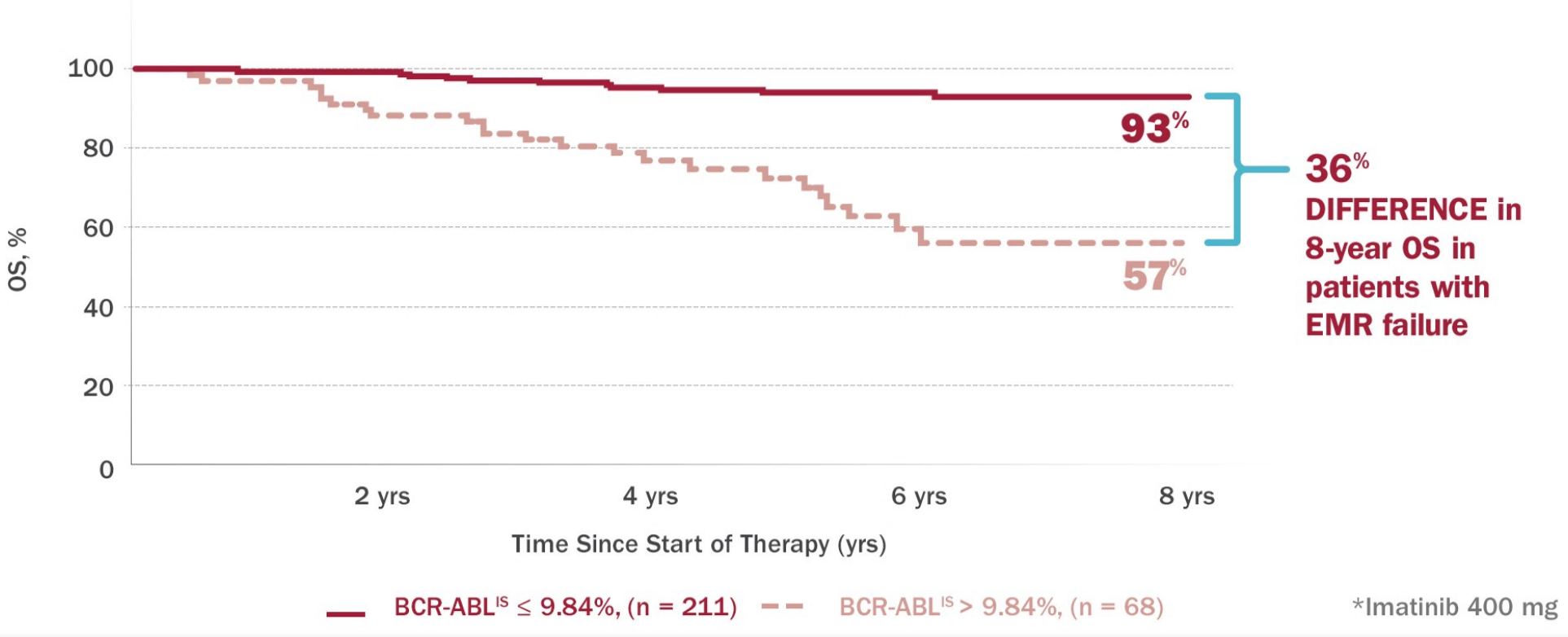
BCR-ABL^{IS} ≤ 10% at 3 months is also referred to as early molecular response (EMR).[3]

MISSING MILESTONES HAS CONSEQUENCES

Achieving EMR is Associated With Improved Overall Survival[1]

IN A RETROSPECTIVE STUDY BY MARIN ET AL

EMR at 3 months was predictive of long-term survival in newly diagnosed CML-CP patients on TKI therapy*



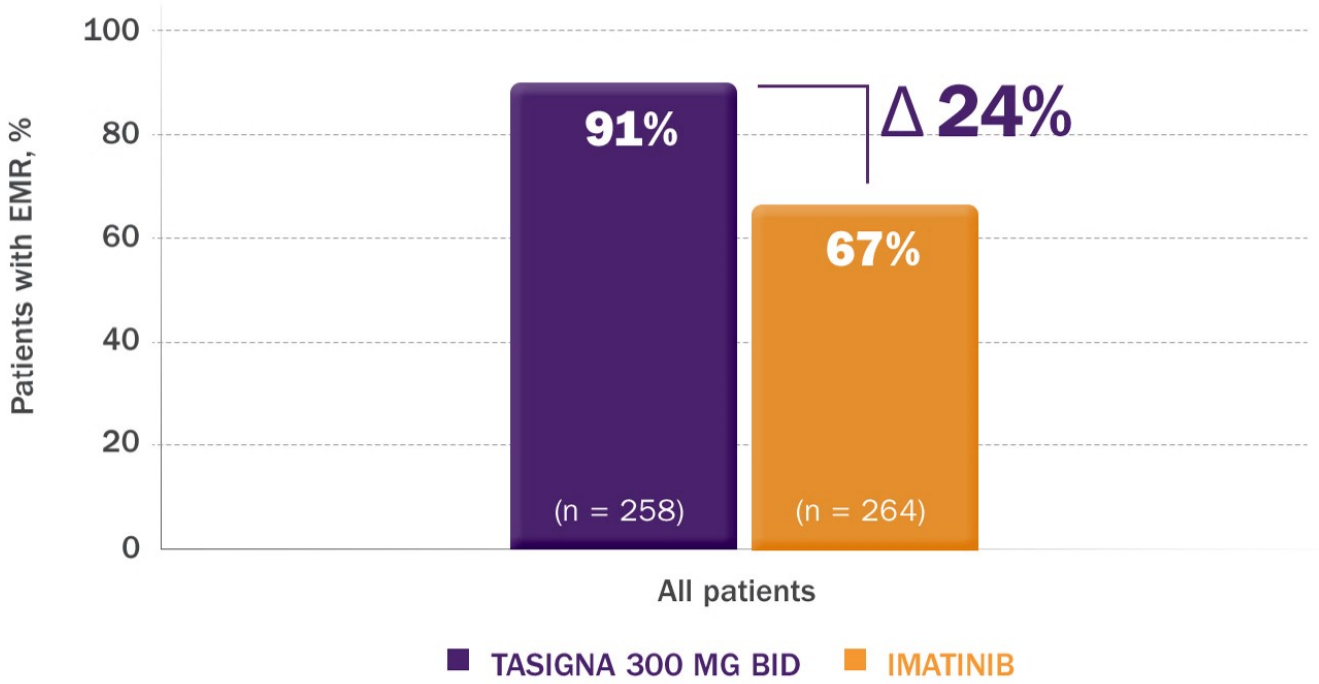
*Imatinib 400 mg

EARLIER RESPONSE MATTERS

More Patients Achieved EMR With Tasigna vs Imatinib[1,2]

ENESTND LANDMARK ANALYSIS

In a retrospective analysis in ENESTnd evaluating EMR at 3 months: MORE PATIENTS ACHIEVED EMR with Tasigna vs imatinib, regardless of Sokal score



3X as many patients failed to achieve EMR with imatinib vs Tasigna (33% vs 9%)

VIEW ADDITIONAL DATA

ENESTnd participants without evaluable PCR samples at 3 months were excluded from the Landmark Analysis.

Tasigna 400 mg BID ENESTnd study arm is not reported here as this dose is not indicated for newly diagnosed patients.

EARLIER RESPONSE MATTERS

More Patients Achieved EMR With Tasigna vs Imatinib[1,2]

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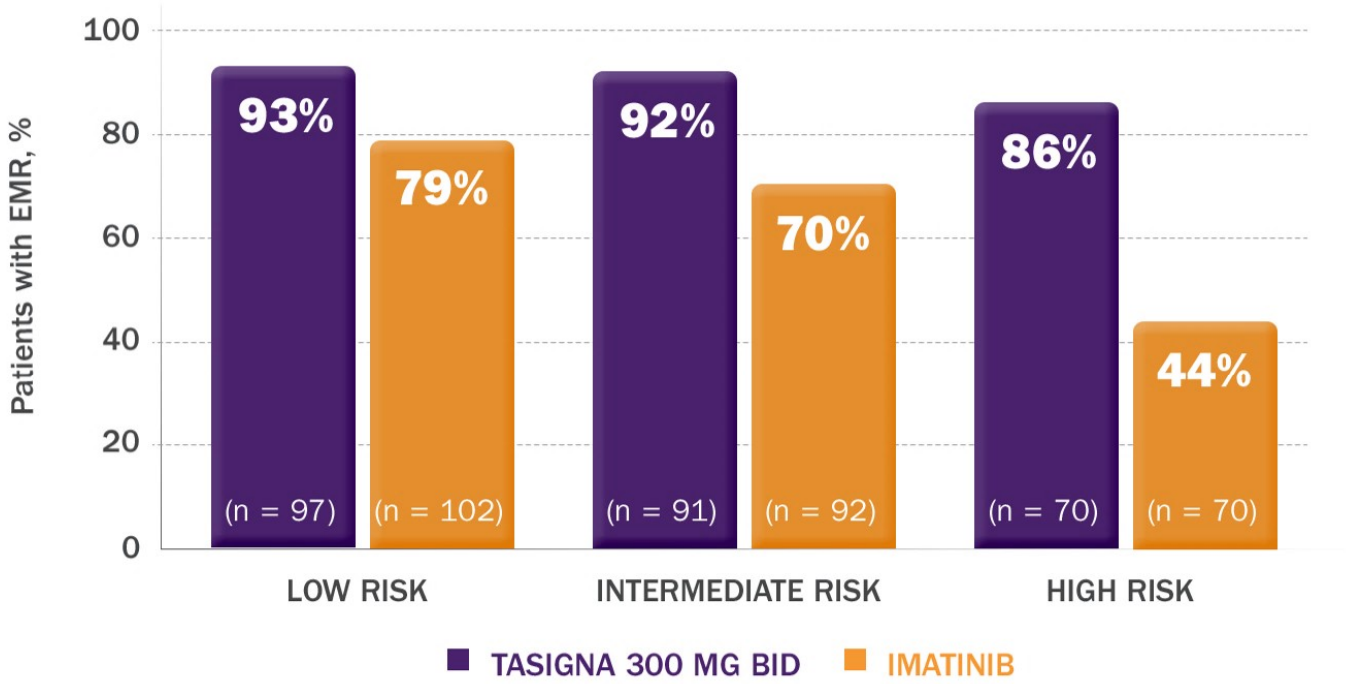

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EARLIER RESPONSE MATTERS

Patients Who Achieved EMR Showed Greater Overall Survival[1]

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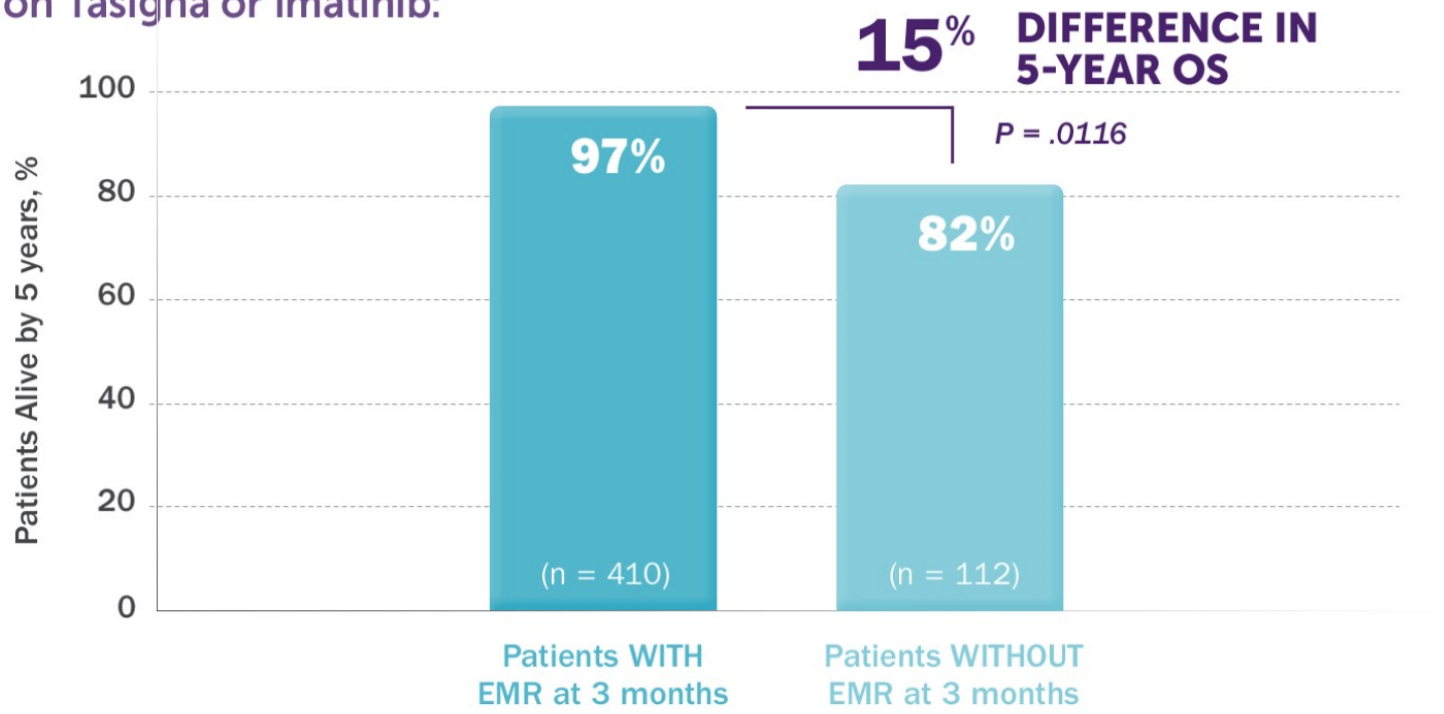
In a retrospective analysis in ENESTnd evaluating EMR at 3 months in patients on Tasigna or imatinib:



Patients who achieved EMR showed greater OS[1]

VIEW LINE GRAPH

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EARLIER RESPONSE MATTERS

Patients Who Achieved EMR Showed Greater Overall Survival[1]

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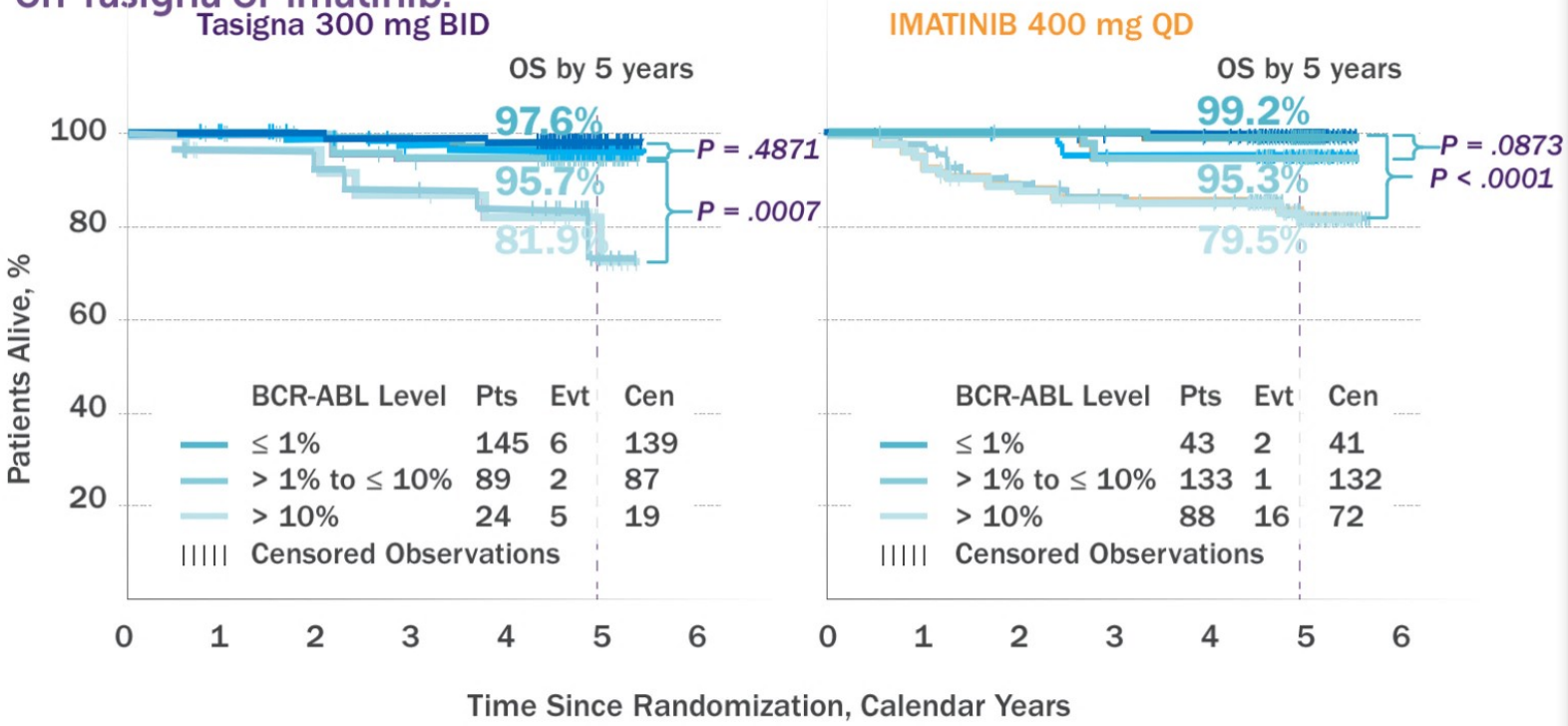


Patients who achieved EMR showed greater OS[1]

VIEW BAR GRAPH

ENESTnd participants without evaluable PCR samples at 3 months were excluded from the Landmark Analysis.

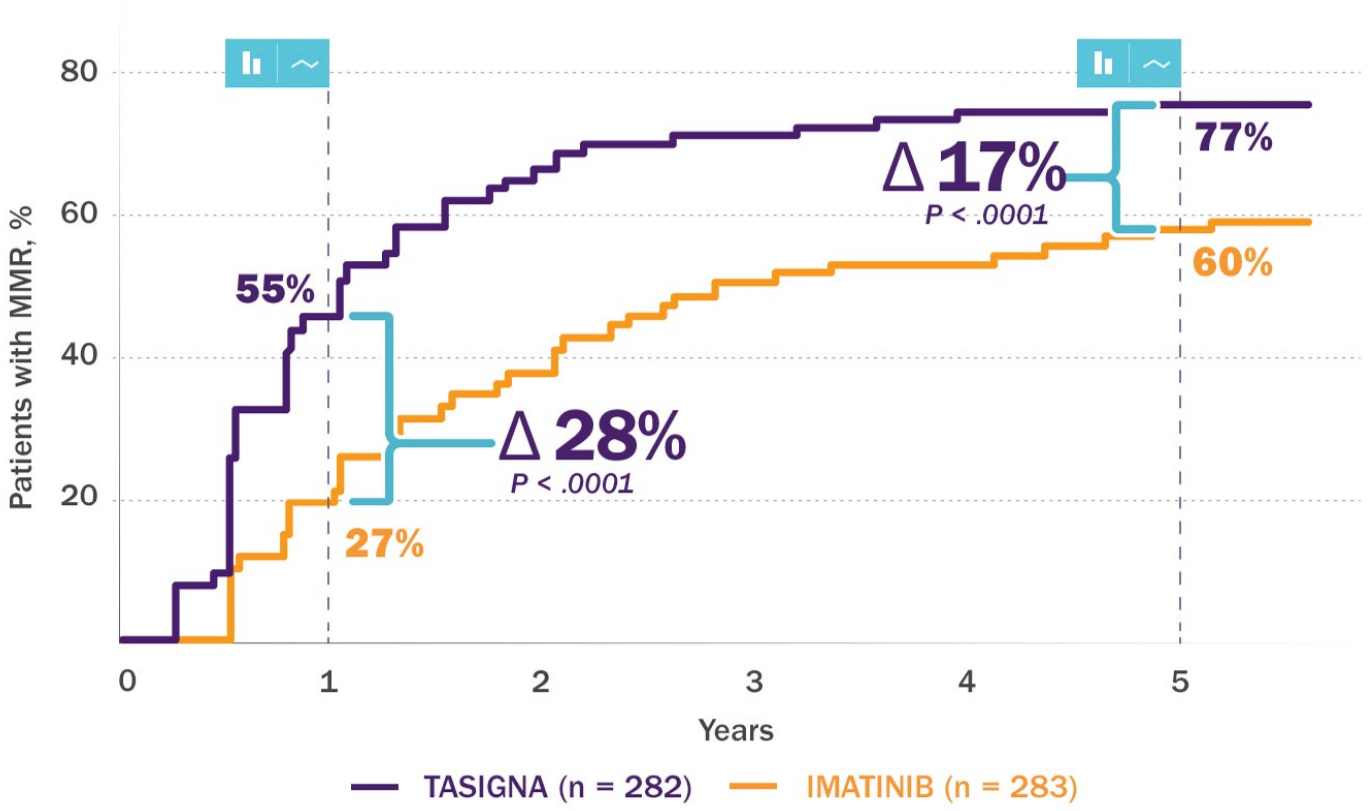
Tasigna 400 mg BID ENESTnd study arm is not reported here as this dose is not indicated for newly diagnosed patients.

DEEPER RESPONSE MATTERS

More Patients Achieved MMR With Tasigna vs Imatinib[1]

ENESTND 5-YEAR FOLLOW-UP

In ENESTnd assessment of the rates of MMR showed:



The imatinib arm **DID NOT CATCH UP** to the Tasigna arm by 5 years

MMR rates remained higher by 5 years with Tasigna vs imatinib

Tasigna 400 mg BID ENESTnd study arm is not reported here as this dose is not indicated for newly diagnosed patients.

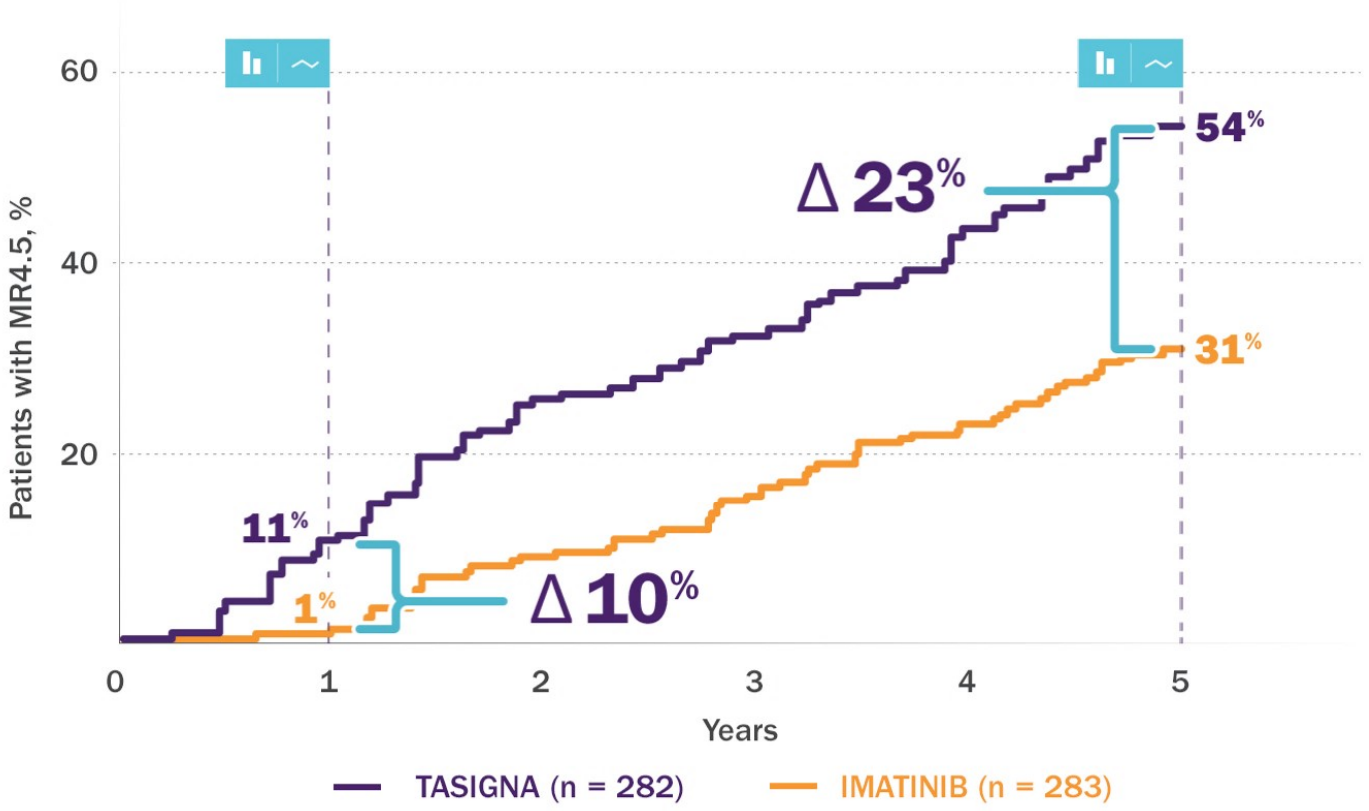
Cumulative response rates by 5 years were calculated based on sixty 28-day cycles in a database with 60 calendar months of follow-up.

DEEPER RESPONSE MATTERS

More Patients Achieved MR4.5 With Tasigna vs Imatinib[1]

ENESTND 5-YEAR FOLLOW-UP

In ENESTnd assessment of the rates of MR4.5 showed:



The imatinib arm **DID NOT CATCH UP** to the Tasigna arm by 5 years

23% more patients achieved MR4.5 by 5 years with Tasigna vs imatinib

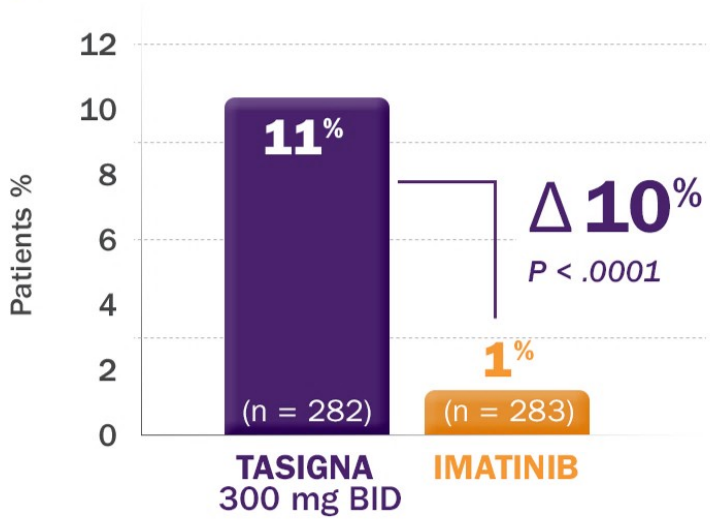
Tasigna 400 mg BID ENESTnd study arm is not reported here as this dose is not indicated for newly diagnosed patients.

Cumulative response rates by 5 years were calculated based on sixty 28-day cycles in a database with 60 calendar months of follow-up.

DEEPER RESPONSE MATTERS

More Patients Achieved MR4.5 With Tasigna vs Imatinib[1]

Percent of Patients With MR4.5 by 1 Year in ENESTnd[1]



More patients achieved MR4.5 in the first 12 months with Tasigna[1]

ENESTND 5-YEAR

In ENESTnd assess

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matinib

400 mg BID ENESTnd study
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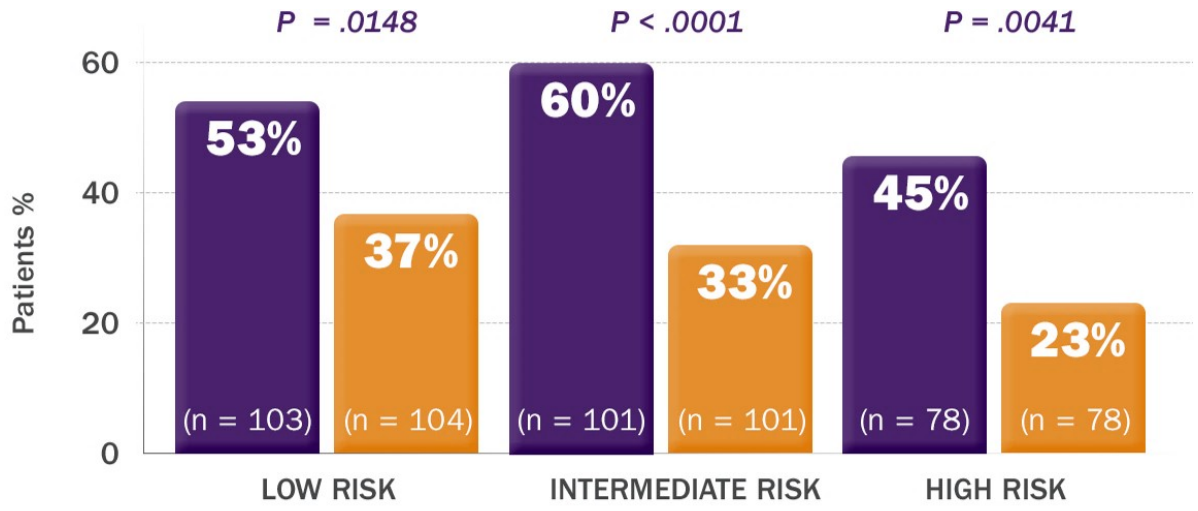
Cumulative response rates by 5 years were calculated based on sixty 28-day cycles in a database with 60 calendar months of follow-up.

DEEPER RESPONSE MATTERS

Percent of Patients With MR4.5 by 5 Years in ENESTnd[2]



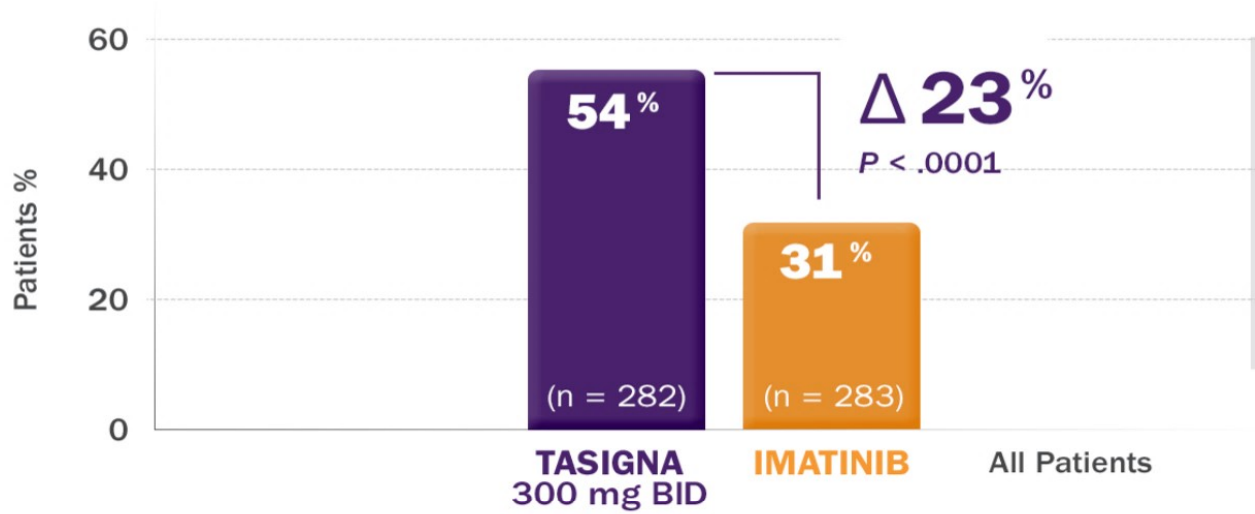
Regardless of Sokal risk score, Tasigna resulted in higher rates of MR4.5 by 5 years compared with imatinib[2]

VIEW ALL PATIENTS

DEEPER RESPONSE MATTERS

MORE PATIENTS ACHIEVED MR4.5 with Tasigna vs imatinib, regardless of Sokal score[2]

Percent of Patients With MR4.5 by 5 Years in ENESTnd[1,2]



Regardless of Sokal risk score, Tasigna resulted in higher rates of MR4.5 by 5 years compared with imatinib[2]

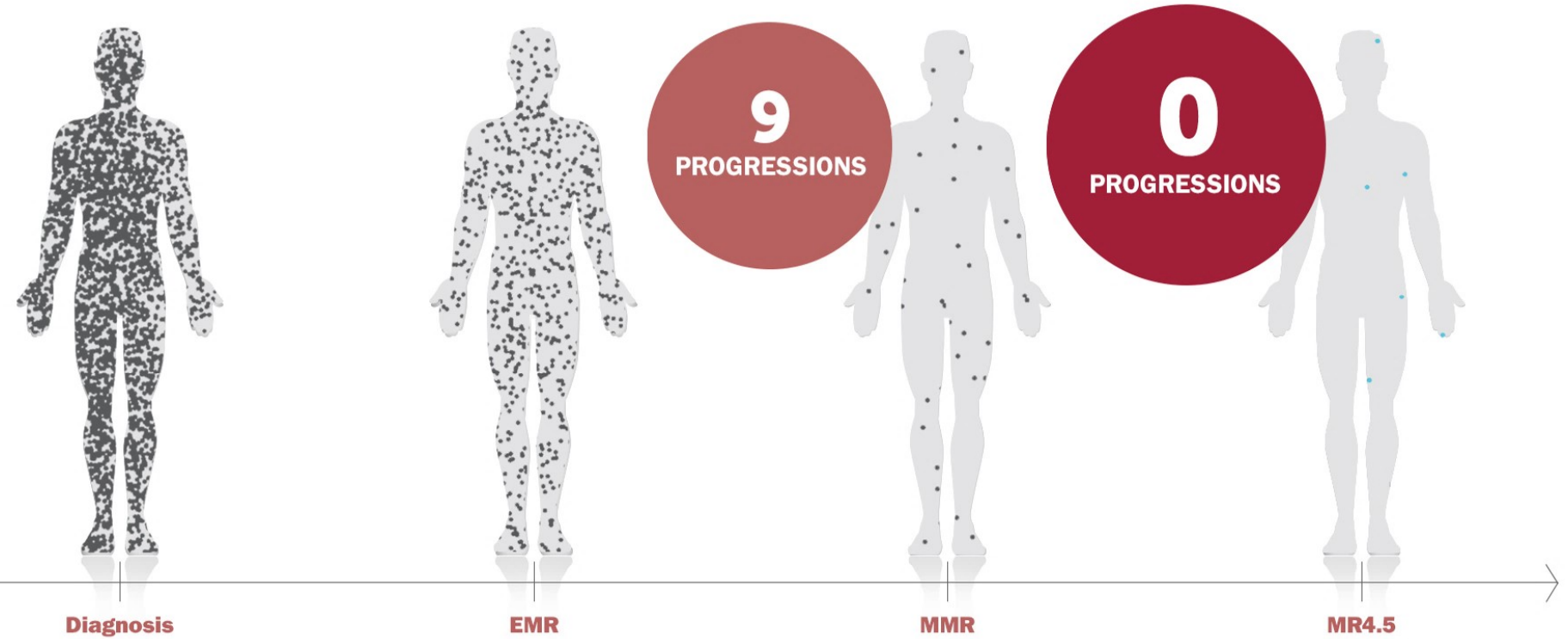
VIEW ADDITIONAL DATA

FEWER PROGRESSIONS

MR4.5 Matters When it Comes To Progression[1]

CML-STUDY IV

With a median follow-up of 3 years, assessment of progressions according to response level showed that no patient with confirmed MR4.5 progressed (n = 1524)



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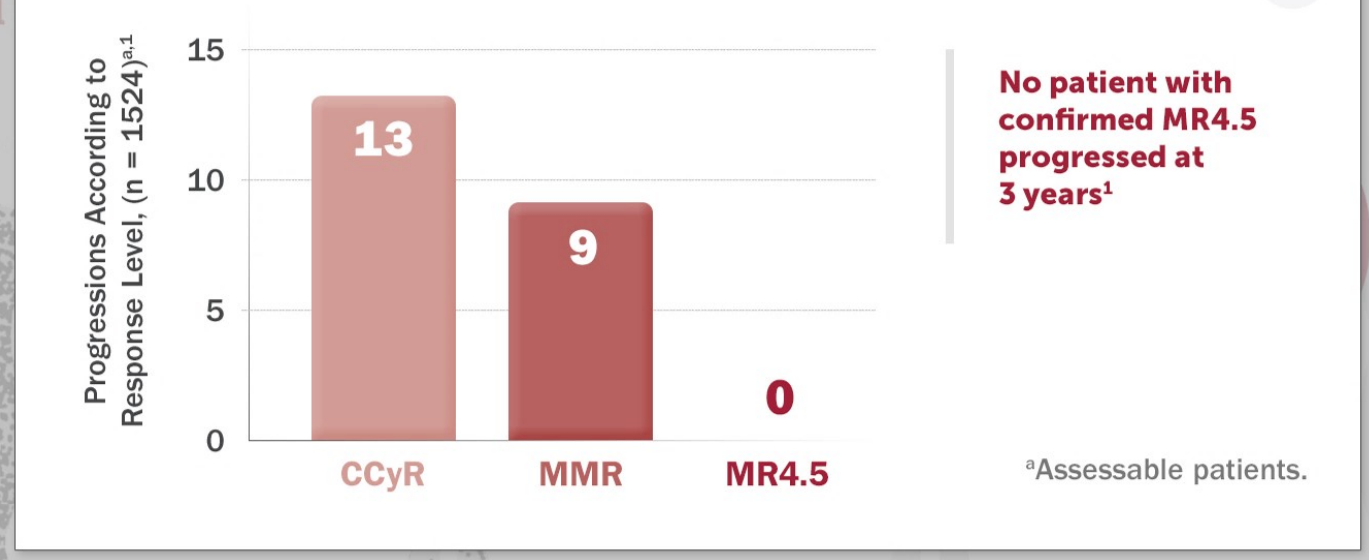
CML-STUDY IV

With a median

response level



No patient with confirmed MR4.5 progressed at 3 years[1]

[a]Assessable patients.

Diagnosis EMR MMR MR4.5

FEWER PROGRESSIONS

Fewer Patients Progressed With Tasigna vs Imatinib[2]

ENESTND 5-YEAR FOLLOW UP

In ENESTnd analysis of progressions to AP/BC while on study drug showed:

99% of patients treated with Tasigna 300 mg BID

REMAINED IN CHRONIC PHASE (n = 282)

NO NEW PROGRESSIONS while on study drug since the 2-year analysis

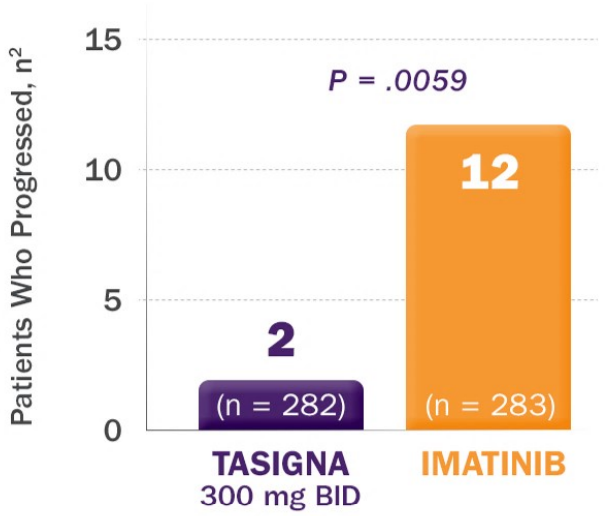
No patient with MR4.5 in any arm progressed[3]

Progression to AP/BC events included progressions to AP/BC (excluding clonal evolution) or CML-related deaths occurring on study drug.

Tasigna 400 mg BID ENESTnd study arm is not reported here as this dose is not indicated for newly diagnosed patients.

FEWER PROGRESSIONS

Fewer Patients Progressed With Tasigna vs Imatinib[2]



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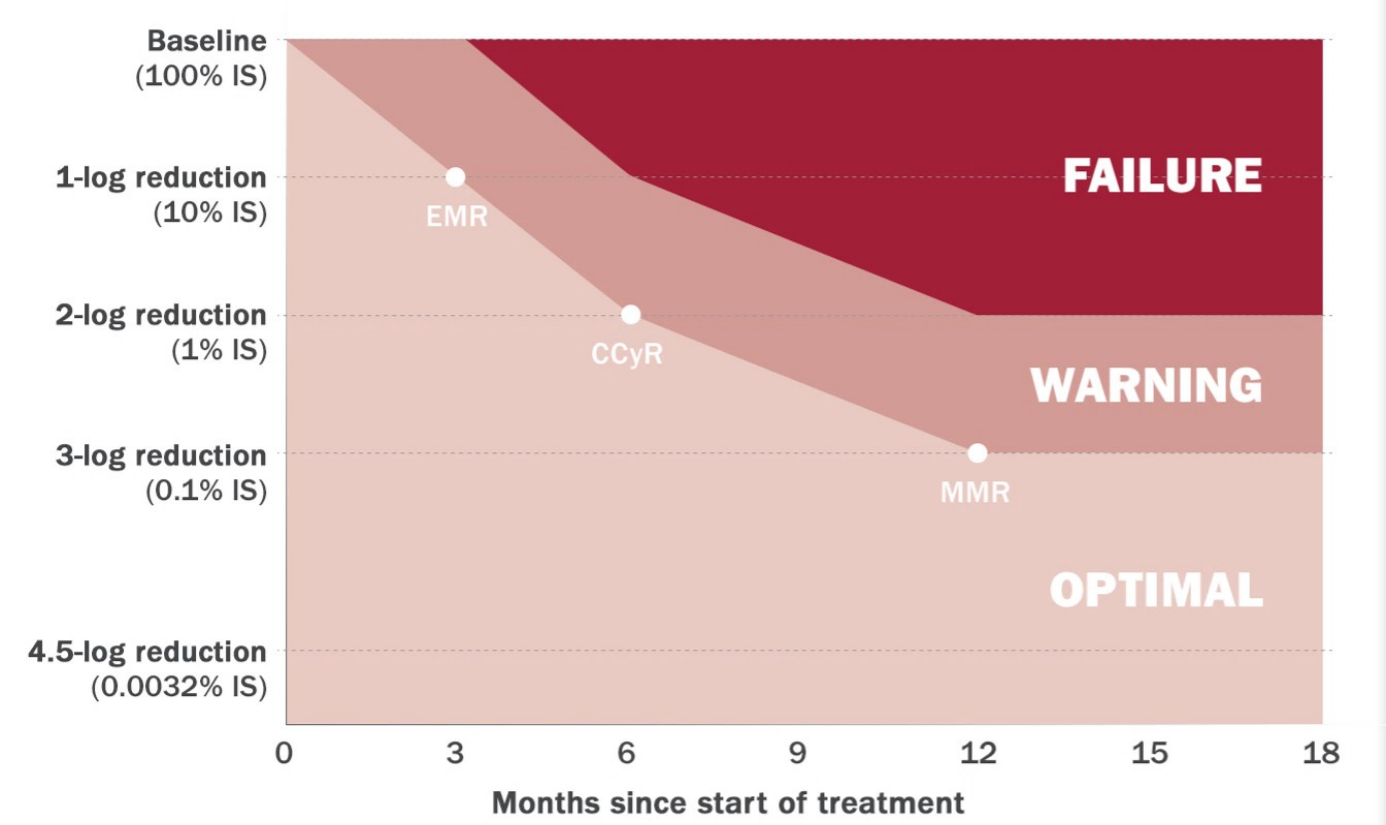
SWITCH

Current ELN Recommendations for Switching[1]

2013 ELN recommended treatment response milestones[1]



How do your patients respond to treatment after switching for treatment failure?

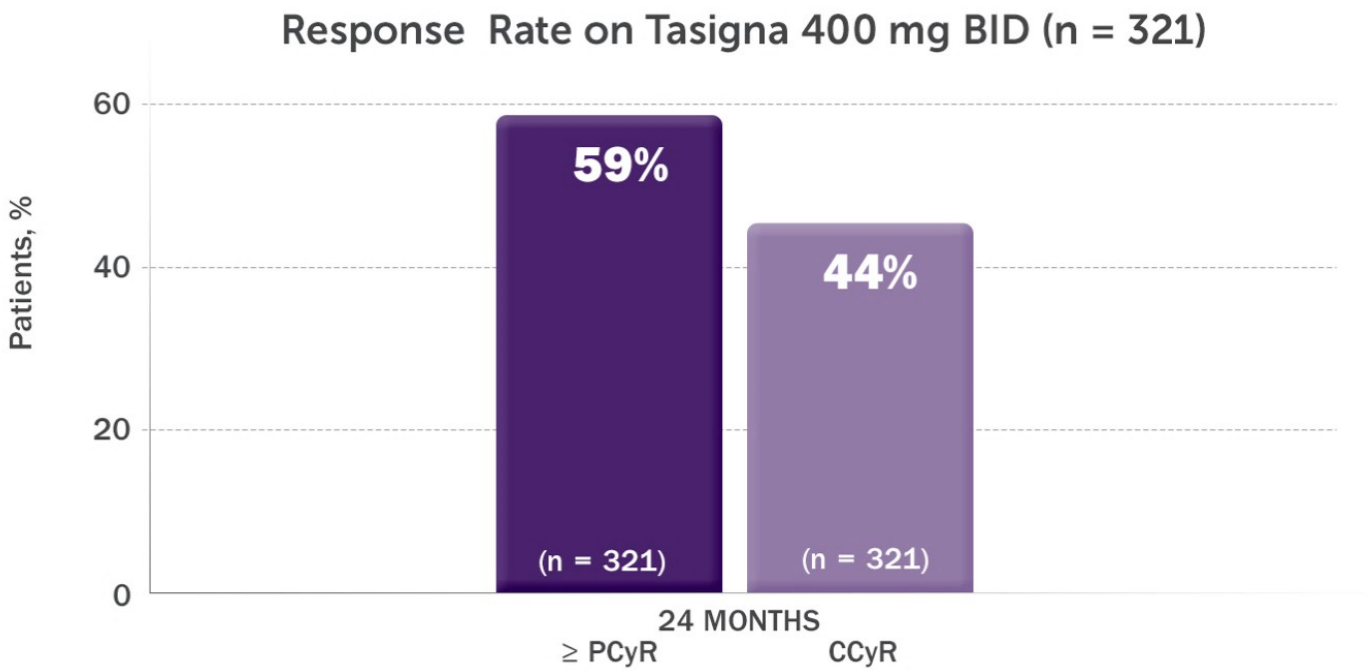
Does increased monitoring in patients with a warning response allow you to act faster in the event of treatment failure?

SWITCH

Responses in Patients Switched to Tasigna After Experiencing Resistance or Intolerance to Imatinib[2]

2101 Study

After switching to Tasigna in patients resistant and intolerant to imatinib:



ACHIEVING OPTIMAL* RESPONSES in the second line is important to prevent progression to AP/BC[1]

Most responders achieved ≥ PCyR within 3 months.

In patients who achieved CCyR, the median time to ACHIEVE CCyR was approximately 3 months.

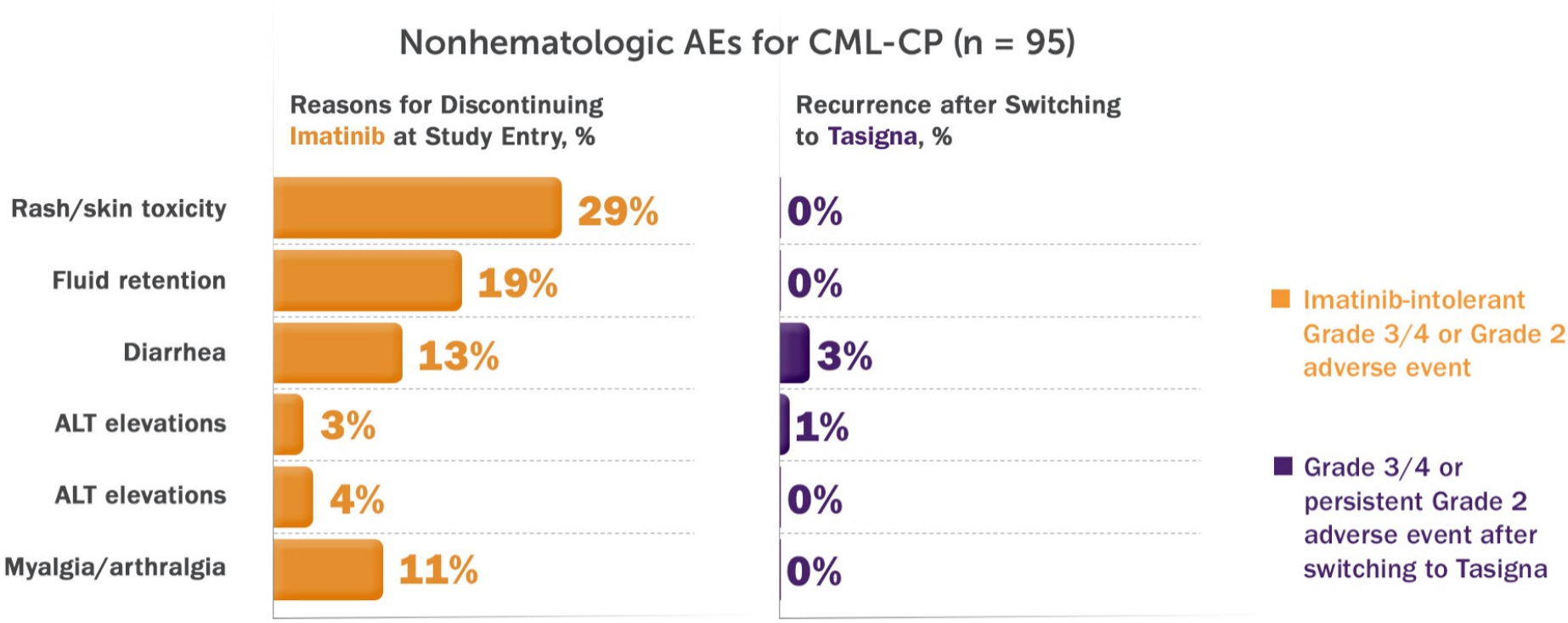
*According to ELN. ELN definition of optimal response to second-line treatment at 3 months is > mCyR (Ph+ < 65%) and/or BCR-ABL ≤10%.

SWITCH

Recurrence of Adverse Events After Switch to Tasigna[3]

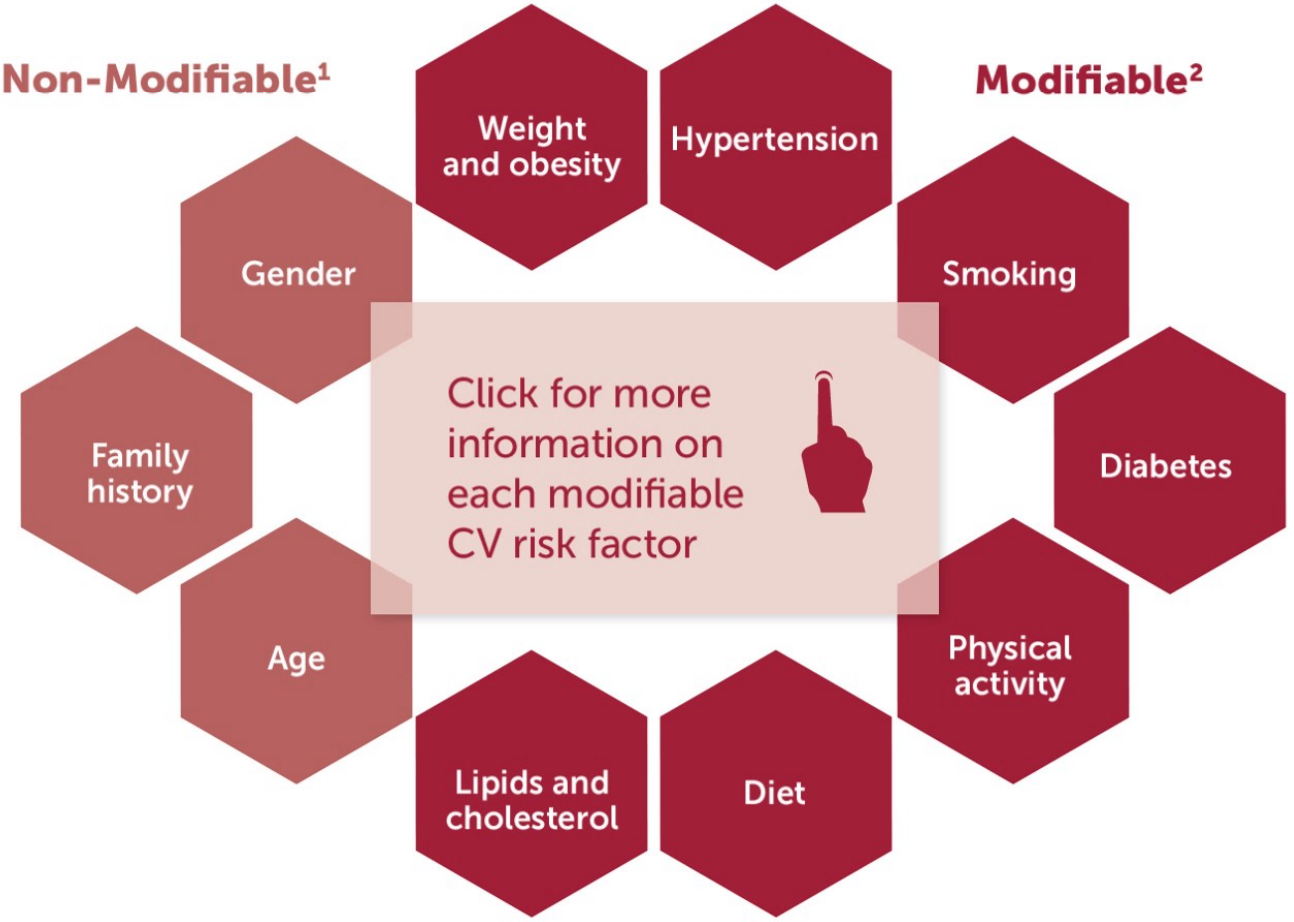
2101 STUDY

In the phase 2 study 2101 after switching to Tasigna 400 mg BID
in imatinib-resistant or —intolerant patients:



Modifiable and Non-Modifiable CV Risk Factors

The choice of treatment is an individualized treatment decision based on **a benefit:risk assessment**



CVEs have been reported in patients with Ph+ CML treated with **ALL APPROVED TKIS**[2-6]

Some CV risks can be managed[1]

Chronic management with any TKI therapy requires close monitoring[2-6]

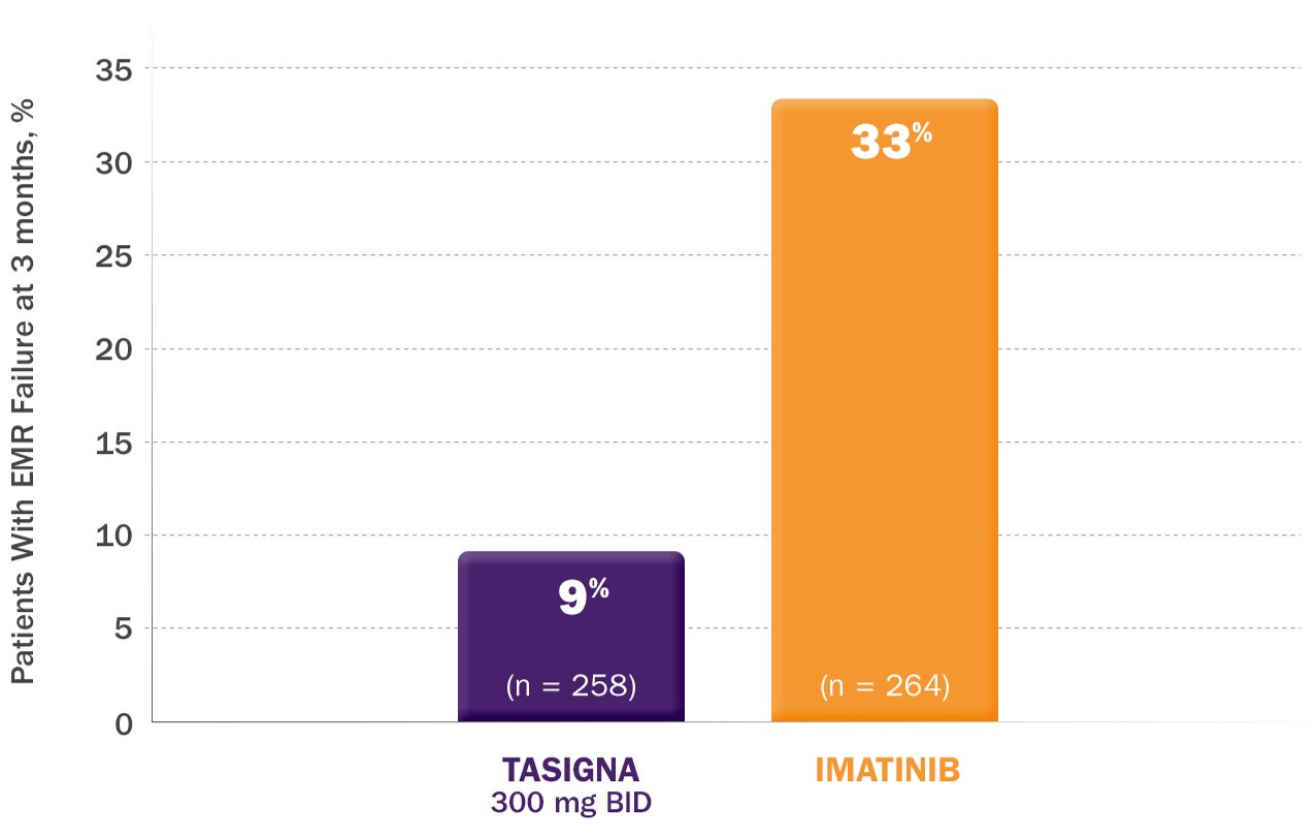
All patients treated with TKIs should be assessed for risk factors of CV disease, regularly monitored and, if appropriate, managed by standard guidelines.

FIRST-LINE CHOICE MATTERS

Your First Treatment in CML Matters

ENESTnd Landmark Analysis[1]

3X as many patients on imatinib failed to achieve EMR at 3 months vs Tasigna in an analysis in ENESTnd

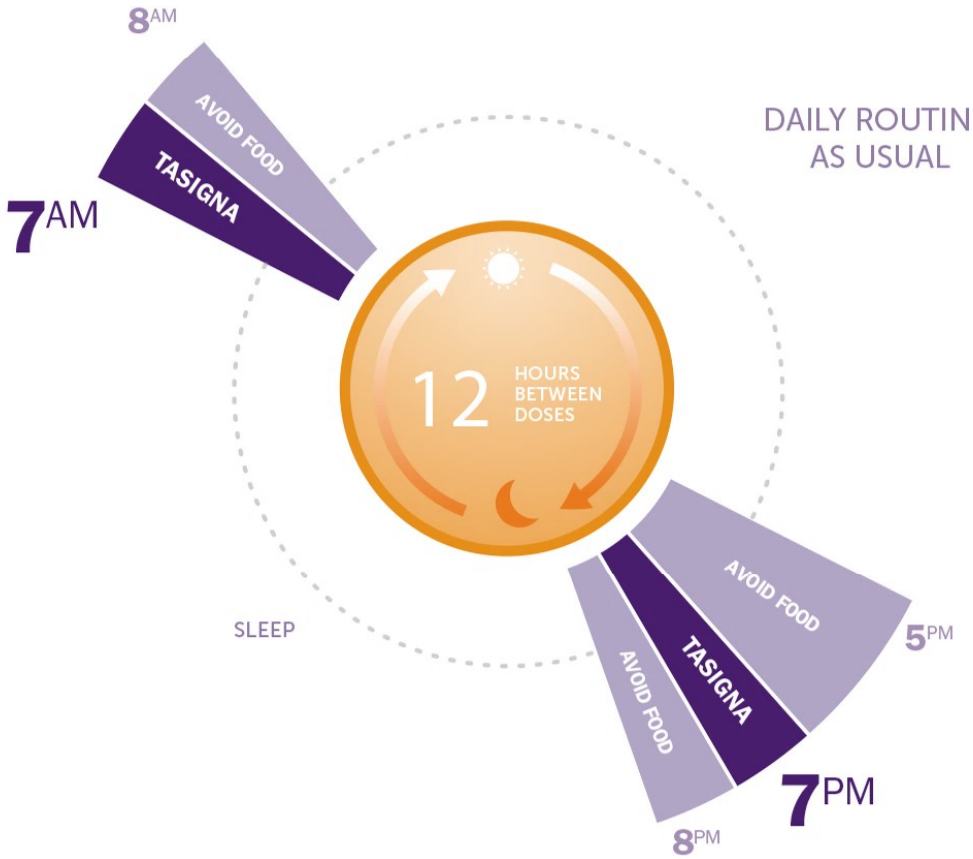


More patients
achieved EMR with Tasigna vs imatinib[1]

ROUTINE DAILY DOSING

A Dosing Regimen That Fits Into a Daily Routine[1]

Patients should take **2 Tasigna capsules in the morning** and **2 capsules in the evening.**
Doses should be about **12 hours apart.**



If a patient misses a dose, he or she should not take another dose but rather wait to take the next scheduled dose

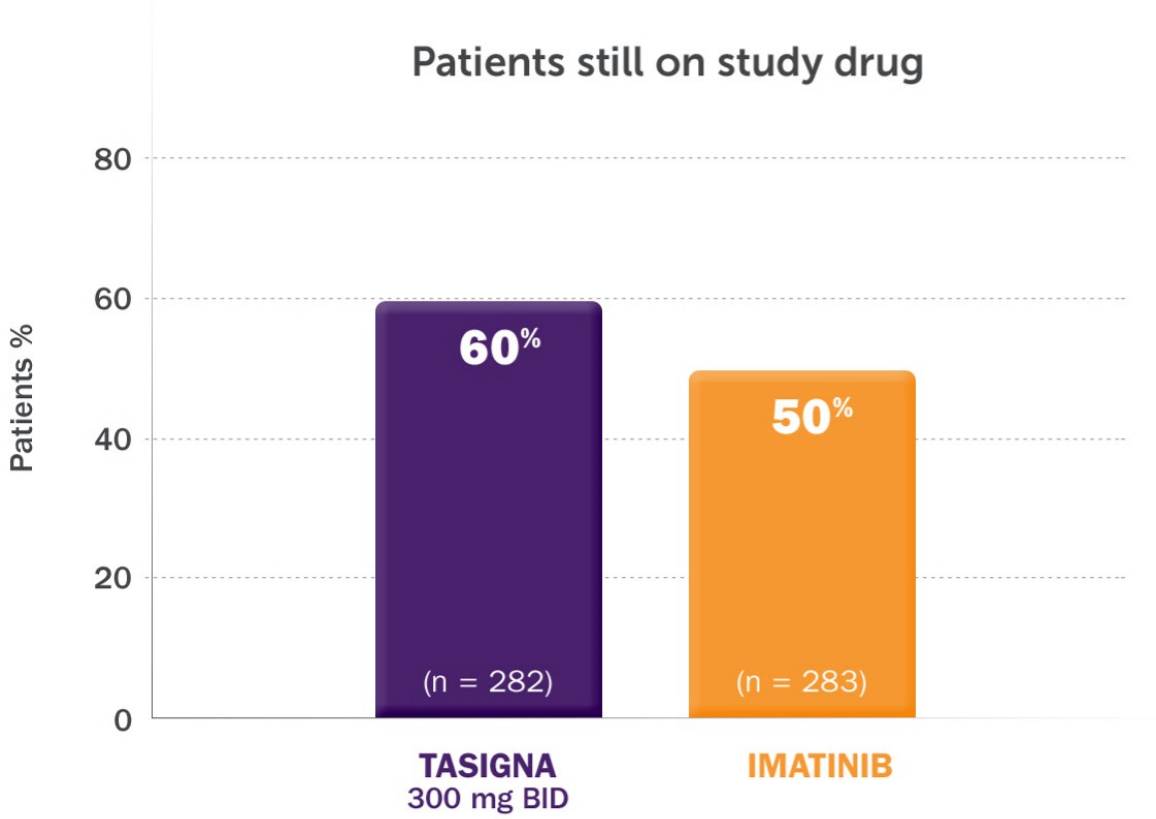
Patients must avoid food for 2 hours before and 1 hour after each dose

For full dosing information including dose adjustments please see the full prescribing information.

Starting With Tasigna Resulted in Fewer Discontinuations Compared With Imatinib*[1,2]

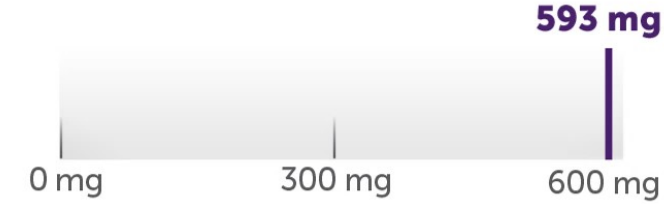
ENESTnd 5-Year Follow-up[1]

Fewer patients discontinued treatment with Tasigna vs imatinib



FEWER DISCONTINUATIONS with Tasigna vs imatinib[1]

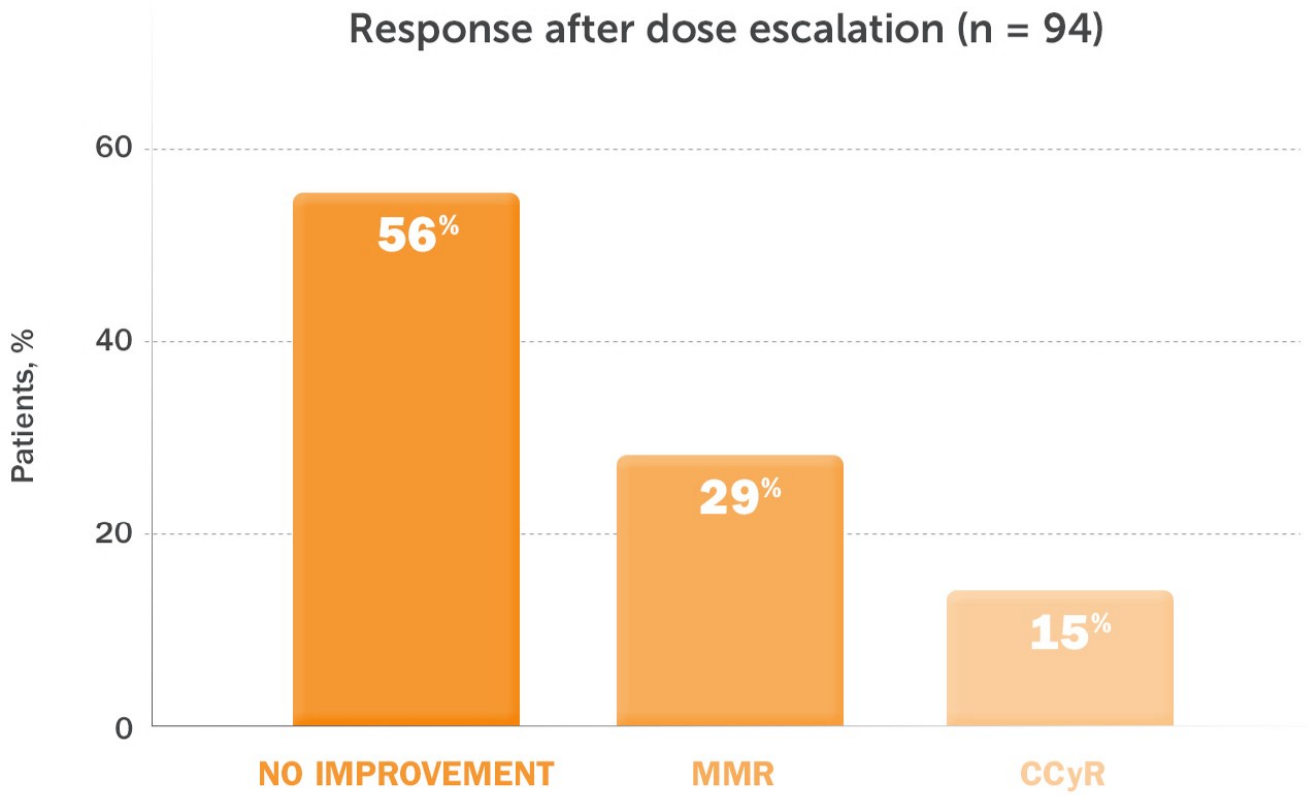
99% OF THE MEDIAN DOSE of Tasigna 300 mg BID was taken in ENESTnd



*Discontinuations for any reason

Does High-Dose Imatinib Improve Response?

In ENESTnd, patients with suboptimal response or treatment failure on imatinib 400 mg once daily were permitted to dose escalate to imatinib 400 mg twice daily [a,1]



Over half of these patients did not achieve improved responses on high-dose imatinib[b,2]

[a] The median time on imatinib 400 mg prior to dose escalation to 800 mg was 17 months (range 3-42 months).[2] Dose escalation was permitted on the imatinib arm only for patients with SoR or TF. SoR is no longer defined in the ELN recommendations.[3,4] See study design for definitions of SoR and TF in this study.

[b] The median time on imatinib 800 mg was 12 months (range < 1-39 months).[2]

Can Tasigna Be Co-administered With Some Medications?

For many patients Ph+ CML-CP has become a chronic disease requiring continuous management and TKIs are often prescribed in patients with comorbidities[1]

Coadministration is not advised in the following situations:

- Strong CYP3A4 inhibitors can increase Tasigna concentration. They should be avoided because this can lead to QT prolongation and potentially to sudden death[2]
- Strong CYP3A4 inducers can decrease Tasigna concentration. They should be avoided because this can lead to loss of response[2]
- Tasigna, by inhibiting CYP3A4 itself, can increase concentration and toxicities of other drugs, including certain statins. Doses of these substrates may need to be lowered[2]
- Concomitant use of anti-arrhythmic medicines and other drugs that may prolong the QT interval should be avoided[2]
- Taking Tasigna with food results in higher serum concentration. Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time[2]

Antacids/H2blockers/PPIs

	Concurrent use with Glivec[3]	Concurrent use with Tasigna[4]	Comment
Antacids	√	√	If necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of Tasigna
H2 Blockers	√	√[6]	When the concurrent use of an H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of Tasigna

[a] Should receive heparin instead of coumadin derivatives.
[b] Clinically meaningful drug-drug interaction between Tasigna and warfarin is less likely up to a dose of 25 mg of warfarin.

Patients who take Tasigna concomitantly with certain medications or who have certain comorbidities may require more frequent

Can Tasigna Be Co-administered With Some Medications?

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H2 Blockers	√	√[6]	When the concurrent use of an H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of Tasigna
PPIs	√[5]	√[6]	Tasigna may be used concurrently with esomeprazole or other proton pump inhibitors as needed
Warfarin			
Warfarin	X[a]	√[b]	Control of warfarin pharmacodynamic markers (INR or PT) following initiation of Tasigna therapy is recommended at least in the first two weeks

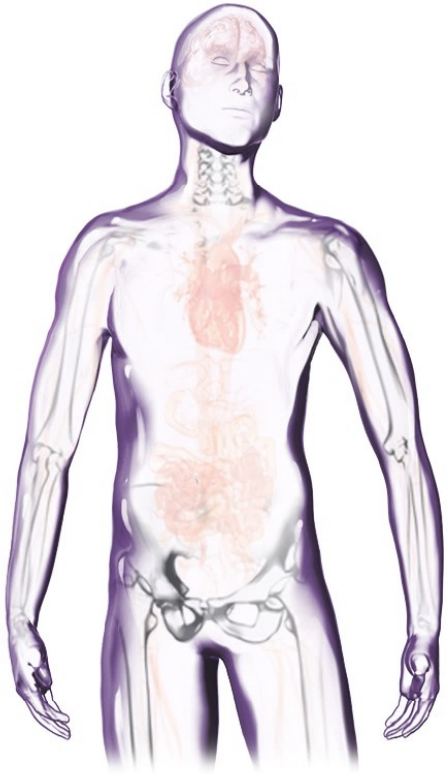
[a] Should receive heparin instead of coumadin derivatives.
[b] Clinically meaningful drug-drug interaction between Tasigna and warfarin is less likely up to a dose of 25 mg of warfarin.

Patients who take Tasigna concomitantly with certain medications or who have certain comorbidities may require more frequent monitoring. This list is not exhaustive, please refer to the currently approved prescribing information that is applicable for your country.

Tasigna Has a Manageable, Favorable Tolerability Profile[1]

In ENESTnd, 12.1% of patients taking Tasigna discontinued therapy by 5 years due to adverse events vs **13.4% of those taking imatinib.**[2] The median time on treatment was 60.5 months (range 0.1 - 70.8 months).[1]

- Fluid retention
- Gastrointestinal
- Skin and subcutaneous tissue
- Musculoskeletal
- General disorders
- Hematologic parameters
- Biochemical parameters



The Tasigna 400 mg BID ENESTnd study arm is not reported here and this dose is not indicated for newly diagnosed patients.
For further information on safety, including the serious risks associated with Tasigna, please see the safety information and full prescribing information.

1. Habucky K, Megyeri A. Tasigna (nilotinib) 150 mg and 200 mg hard capsules core data sheet version 1.3. West Sussex, United Kingdom: Novartis Europharm Limited; 2014:1-61. Table 7-1: Most Frequently Reported Non-hematologic. Adverse Drug Reactions (≥ 5% in any TASIGNA Group)
2. Larson RA, Kim D-W, Jootar S, et al. ENESTnd 5-year update: long-term outcomes of patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib vs imatinib. *J Clin Oncol.* 2014;32(5s): abstract 7073.

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Missing Milestones Has Consequences

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- SWITCH

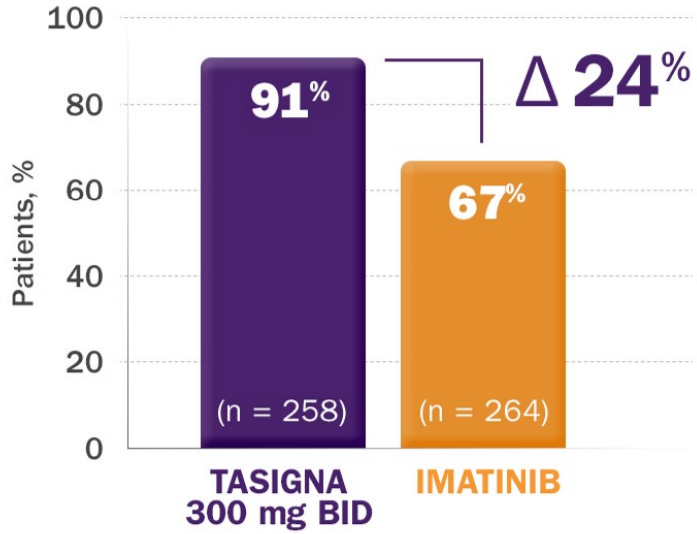
ENESTnd Landmark Analysis

Percent of Patients Who Achieved EMR

at 3 Months in ENESTnd[1]

Earlier response matters: More patients achieved EMR with Tasigna vs imatinib[1]

Patients who achieved EMR showed greater OS[1]



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