Second – Generation TKIs in First – Line Treatment.

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TABLE II. Tyrosine Kinase Inhibitors Available for Chronic Myeloid Leukemia

Agent	Indications for use	Dosing	Key toxicities	Comment
Imatinib	CP—newly diagnosed CP, AP, BP—after interferon therapy	CP—400 mg once daily (up to 800 mg) AP, BP—600 mg once daily (up to 800 mg)	Peripheral edema, myalgias, nausea	First TKI approved for CML, has the longest duration of follow up
Nilotinib	CP—newly diagnosed CP, AP—patients with resistance or intolerance to prior therapy	CP (newly diagnosed) – 300 mg twice daily CP (prior therapy), AP—400 mg twice daily	QT prolongation, pancreatitis, hyperglycemia, hepatotoxicity, vascular events	Superior to imatinib in a randomized study for newly diagnosed patients
Dasatinib	CP—newly diagnosed CP, AP, BP—patients with imatinib resistance or intolerance	CP—100 mg once daily AP, BP—140 mg once daily	Pleural effusions, hematologic, pulmonary hypertension, hemorrhage	Superior to imatinib in a randomized study for newly diagnosed patients
Bosutinib	CP, AP, BP—patients with resistance or intolerance to prior therapy	500 mg once daily	Diarrhea, hematologic, hepatotoxicity	In a randomized study versus imatinib, failed to meet the primary endpoint (though was not worse)
Ponatinib	CP, AP, BP—patients with T315I mutation CP, AP, BP—patients in which no other TKI is indicated	45 mg once daily	Hypertension, arterial and venous thrombotic events, heart failure, pancreatitis, hepatotoxicity	Only available TKI active against T315 mutations

Tyrosine Kinase Inhibitors (year of FDA approval)

- Imatinib (Gleevec) 2001
- Dasatinib (Sprycel) 2006
- Nilotinib (Tasigna) 2007
- Bosutinib (Bosulif) 2012
- Ponatinib (Iclusig) 2012

Efficacy

- faster and deeper molecular responses
- increased freedom from progression to AP\BC
- long-term OS is not statistically different

Safety

- good and consistent toxicity profile

Table 1 ELN 2013 treatment recommendations

Time	Optimal	Warning	Failure
Baseline	–	High-risk major route CCA/Ph+	–
3 months	BCR-ABLIS < 10%* Ph+ < 35% (PCyR)	BCR-ABLIS > 10%* Ph+ 36–95%	NoCHR* Ph+ > 95%
6 months	BCR-ABLIS < 1%* Ph + 0% (CCyR)	BCR-ABLIS 1–10%* Ph + 1–35%	BCR-ABLIS > 10%* Ph+ > 35%
12 months	BCR-ABLIS < 0.1%* (MMR)	BCR-ABLIS 0.1–1%*	BCR-ABLIS > 1%* Ph+ > 0%
>12 months	MMR or better	CCA/Ph-(-7, or7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+
At 1st-line failure	–	NoCHR Loss of CHR on imatinib Lack of CyRto 1st-line TKI high-risk	–
3 months of 2nd-line	BCR-ABLIS < 10%* Ph+ < 65%	BCR-ABLIS > 10%* Ph+ 65–95%	NoCHR, or Ph+ > 95%, or New muta-tions
6 months of 2nd-line	BCR-ABLIS < 10%* Ph+ < 35% (PCyR)	BCR-ABLIS < 10%* Ph+ 35–65%	BCR-ABLIS > 10%* Ph+ > 65%* New mutations
12 months of 2nd-line	BCR-ABLIS < 1%* Ph+0 (CCyR)	BCR-ABLIS 1–10%* Ph+ 1–35%	BCR-ABLIS > 10%* Ph+ > 35%* New mutations
>12 months of 2nd-line	MMR or better	CCA/Ph-(-7or7q-) or BCR-ABLIS > 0.1%	Loss of CHR, or Loss of CCyR or PCyR New mutations Loss of MMR** CCA/Ph+

*and/or
**in 2 consecutive tests, of which one ≥1%

Second-generation TKIs vs IM in newly diagnosed CML pts

H.Kontarjian et al. NEJM , June 5 , 2010

" Dasatinib vs IM in newly diagnosed CP CML "

Phase II, single center trial , 519 pts

	IM	DAS
CCyR	66%	77%
MMolR	28%	46%
Progression	3.5%	1.9%

Responses were achieved in a shorter time with Dasatinib

Second-generation TKIs vs IM in newly diagnosed CML pts

G.Saglio et al. NEJM, June 5 , 2010

" Nilotinib vs IM for newly diagnosed CML " (846 pts)

	IM	Nilo 300	Nilo 400
CCyR	65%	80%	78%
MMolR	22%	44%	43%
Progression	4%	<1%	<1%

Dasatinib Versus Imatinib Study In Treatment-naïve CML: DASISION (CA180-056). *Design*

- Primary endpoint: Confirmed CCyR by 12 months
- Secondary/other endpoints: Rates of CCyR and MMR; times to confirmed CCyR, CCyR and MMR; time in confirmed CCyR and CCyR; PFS; overall survival

Kantarjian. NEJM 362: 2260, 2010.

Nilotinib vs Imatinib in Newly Dx CML (ENESTnd)

- N = 846
- 217 centers
- 35 countries

RANDOMIZED*

Nilotinib 300 mg BID (n = 282)

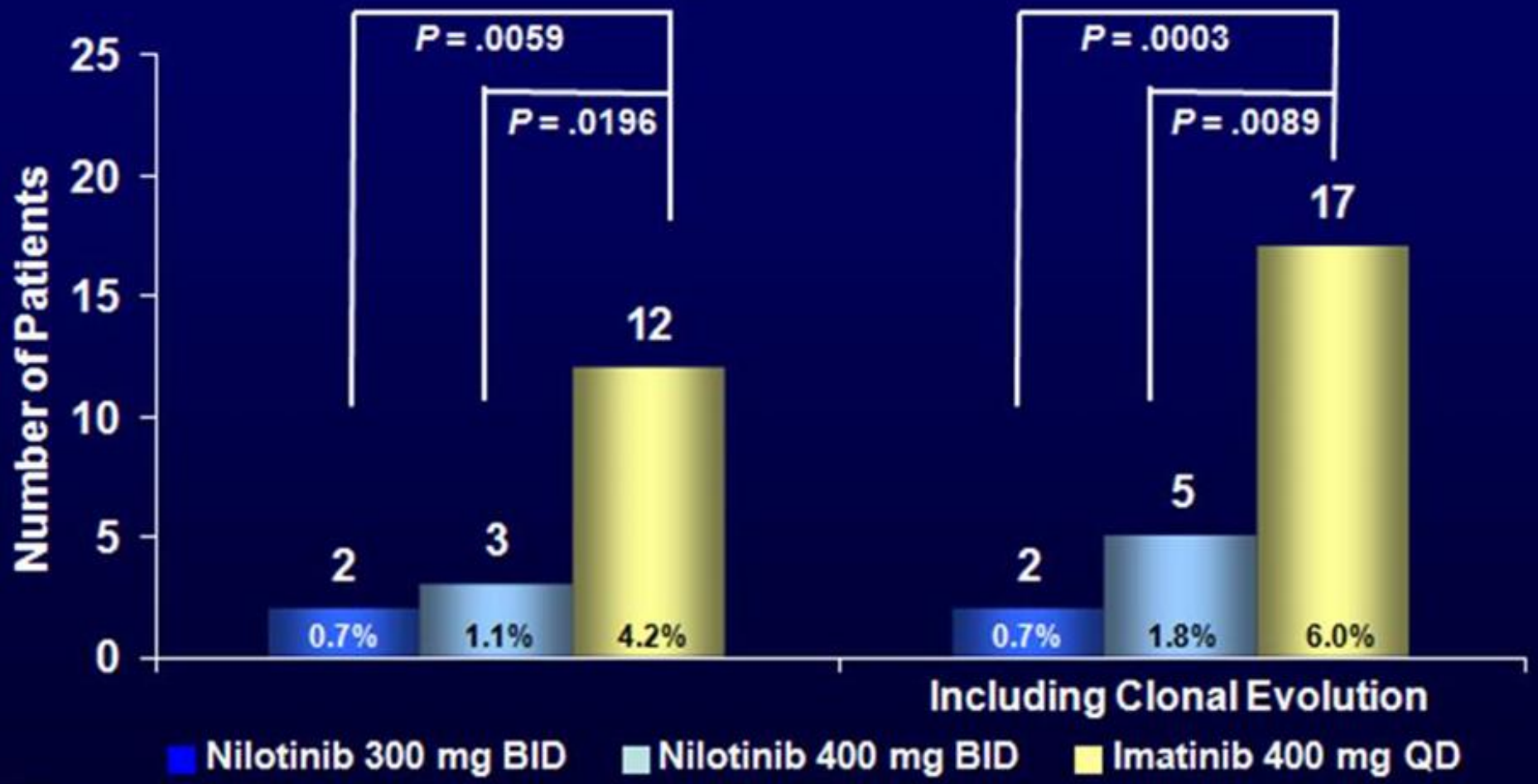
Nilotinib 400 mg BID (n = 281)

Imatinib 400 mg QD (n = 283)

Follow-up 5 years

- Primary endpoint: MMR at 12 months
- Key secondary endpoint: Durable MMR at 24 months
- Other endpoints: CCyR by 12 months, time to MMR and CCyR, EFS, PFS, time to AP/BC on

Progression to AP/BC on Core Treatment*†



*ITT population

†Progression to AP/BC or death due to CML while on core treatment

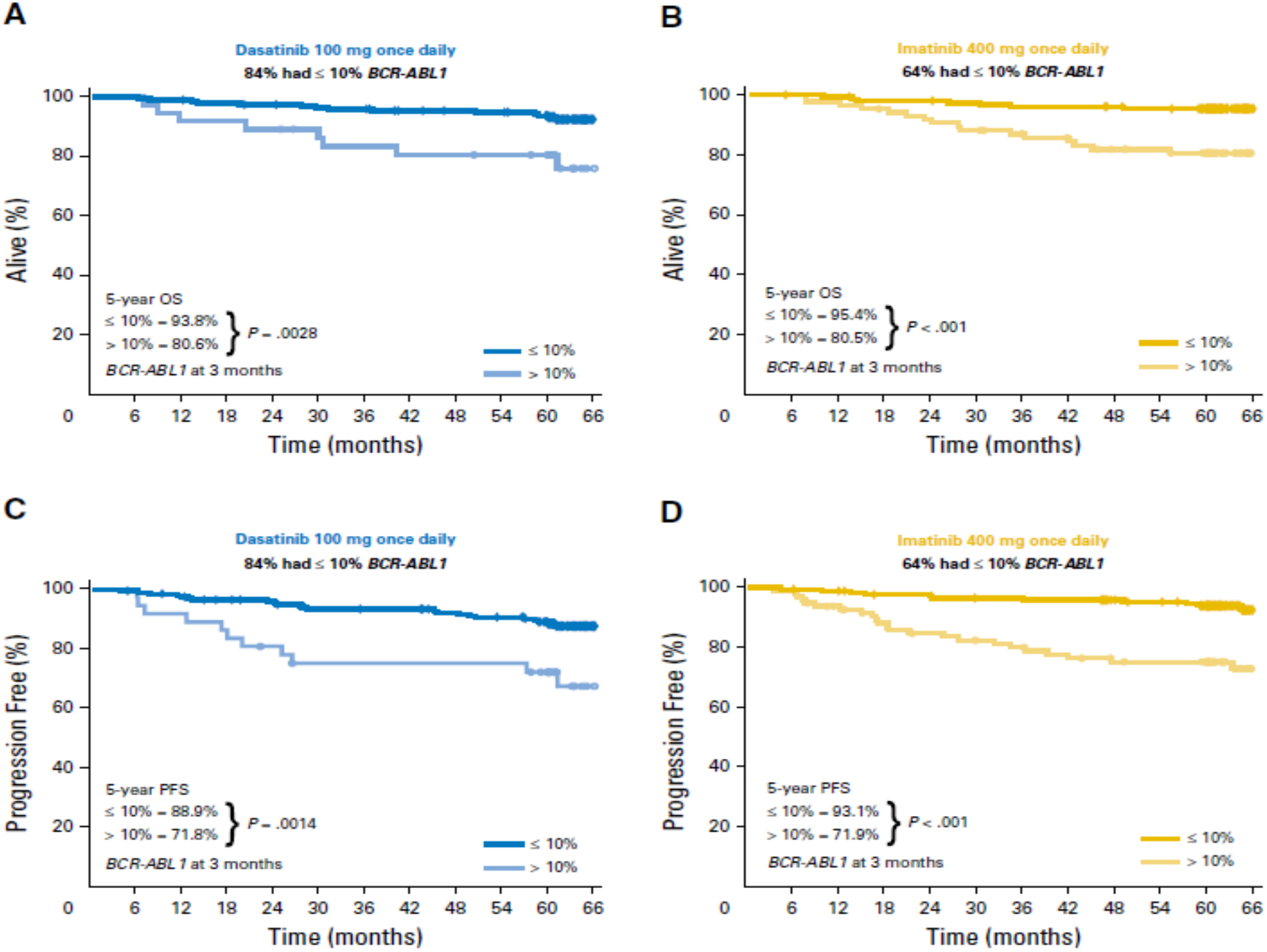
Data cut-off: 20Aug2010

Hughes TP, et al. ASH 2010. Abstract 207.

TABLE I. Summary of Pivotal Phase III Trials of Approved Tyrosine Kinase Inhibitors for the Frontline Treatment of Chronic Myeloid Leukemia

Trial	Treatment	CCyR (%)	MMR (%)	BCR-ABL < 10% at 3 months (%)	EFS/PFS (%)	OS (%)	Longest follow-up (years)
		At 6 years			At 6 years		
IRIS	Imatinib ($n = 304$)	83	86	NR	81	85	8
		At 2 years	At 5 years		At 5 years		
DASISION	Dasatinib ($n = 259$)	86	76	84	85	91	5
	Imatinib ($n = 260$)	82	64	64	86	90	
		At 2 years	At 5 years		At 5 years	At 6 years	
ENESTnd	Nilotinib 300 mg ($n = 282$)	87	77	91	95	92	6
	Nilotinib 400 mg ($n = 281$)	85	77	89	97	96	
	Imatinib ($n = 283$)	77	60	67	93	91	

NR=Not reported

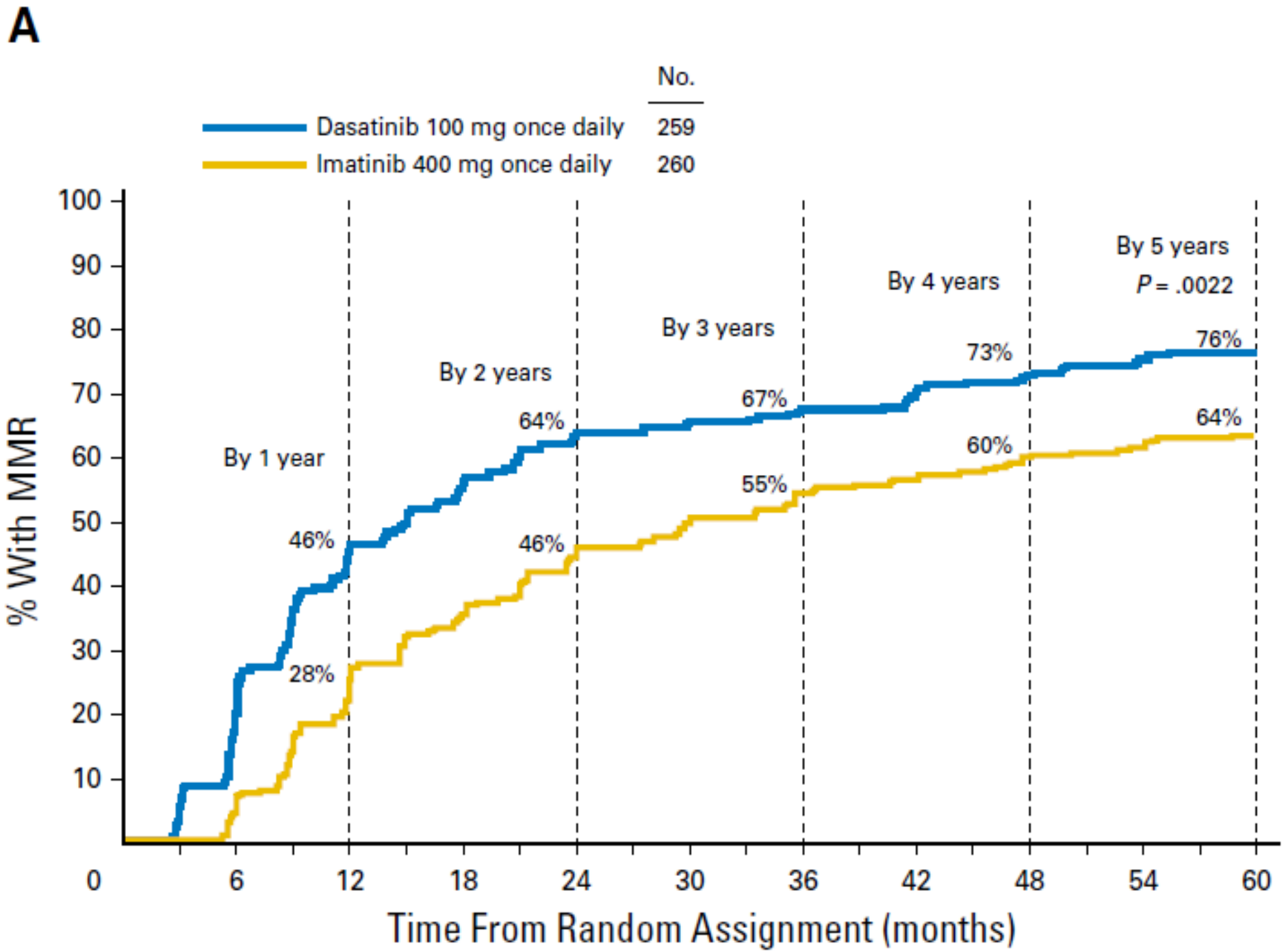

A
Dasatinib 100 mg once daily
84% had ≤ 10% BCR-ABL1
Alive (%)
100
80
60
40
20
0
5-year OS
≤ 10% – 93.8%
> 10% – 80.6%
P = .0028
BCR-ABL1 at 3 months
≤ 10%
> 10%
6 12 18 24 30 36 42 48 54 60 66
Time (months)
B
Imatinib 400 mg once daily
64% had ≤ 10% BCR-ABL1
Alive (%)
5-year OS
≤ 10% – 95.4%
> 10% – 80.5%
P < .001
BCR-ABL1 at 3 months
≤ 10%
> 10%
Time (months)
C
Dasatinib 100 mg once daily
84% had ≤ 10% BCR-ABL1
Progression Free (%)
5-year PFS
≤ 10% – 88.9%
> 10% – 71.8%
P = .0014
BCR-ABL1 at 3 months
≤ 10%
> 10%
Time (months)
D
Imatinib 400 mg once daily
64% had ≤ 10% BCR-ABL1
Progression Free (%)
5-year PFS
≤ 10% – 93.1%
> 10% – 71.9%
P < .001
BCR-ABL1 at 3 months
≤ 10%
> 10%
Time (months)

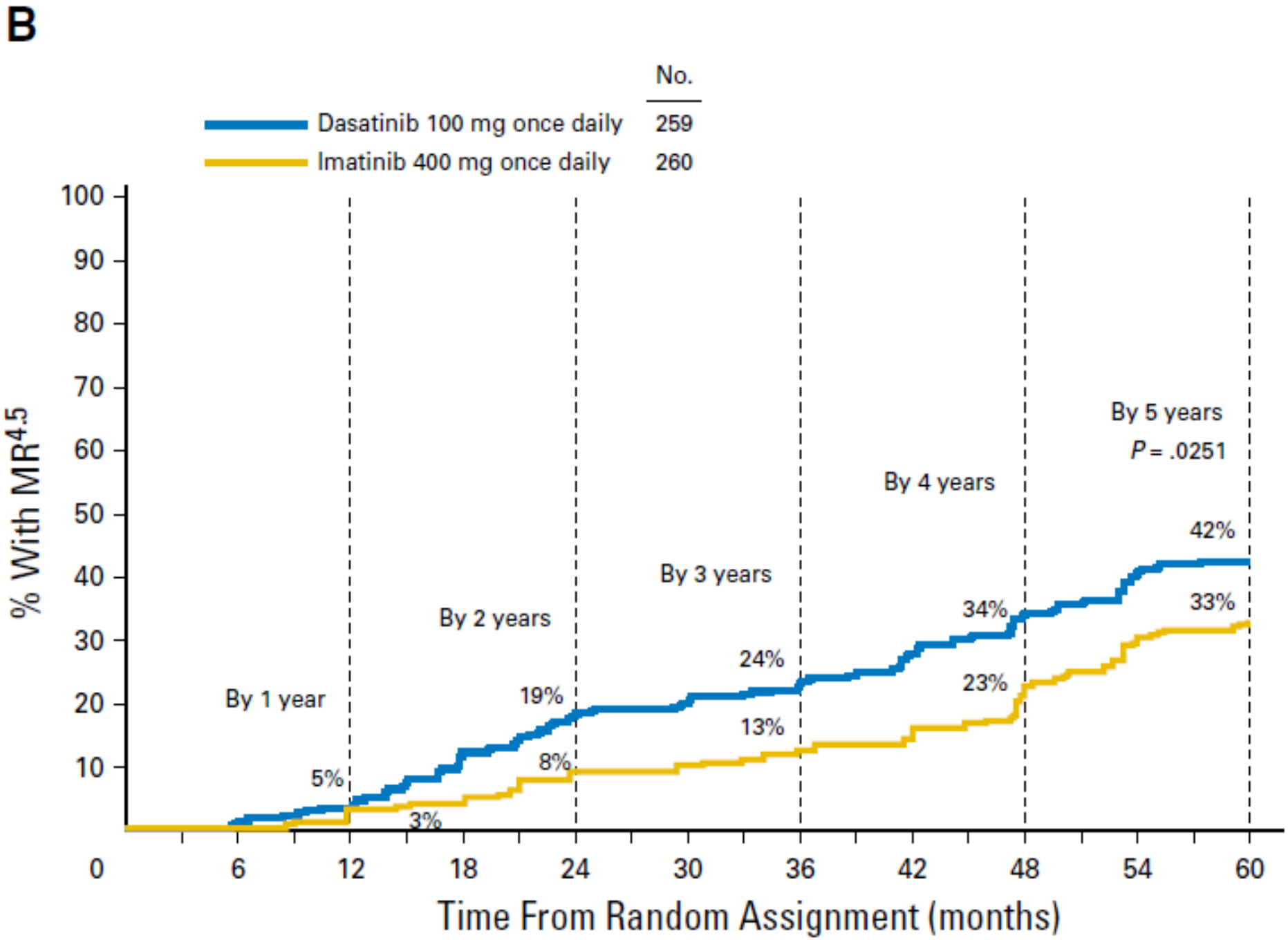
DASISION Final 5-Year Study Results

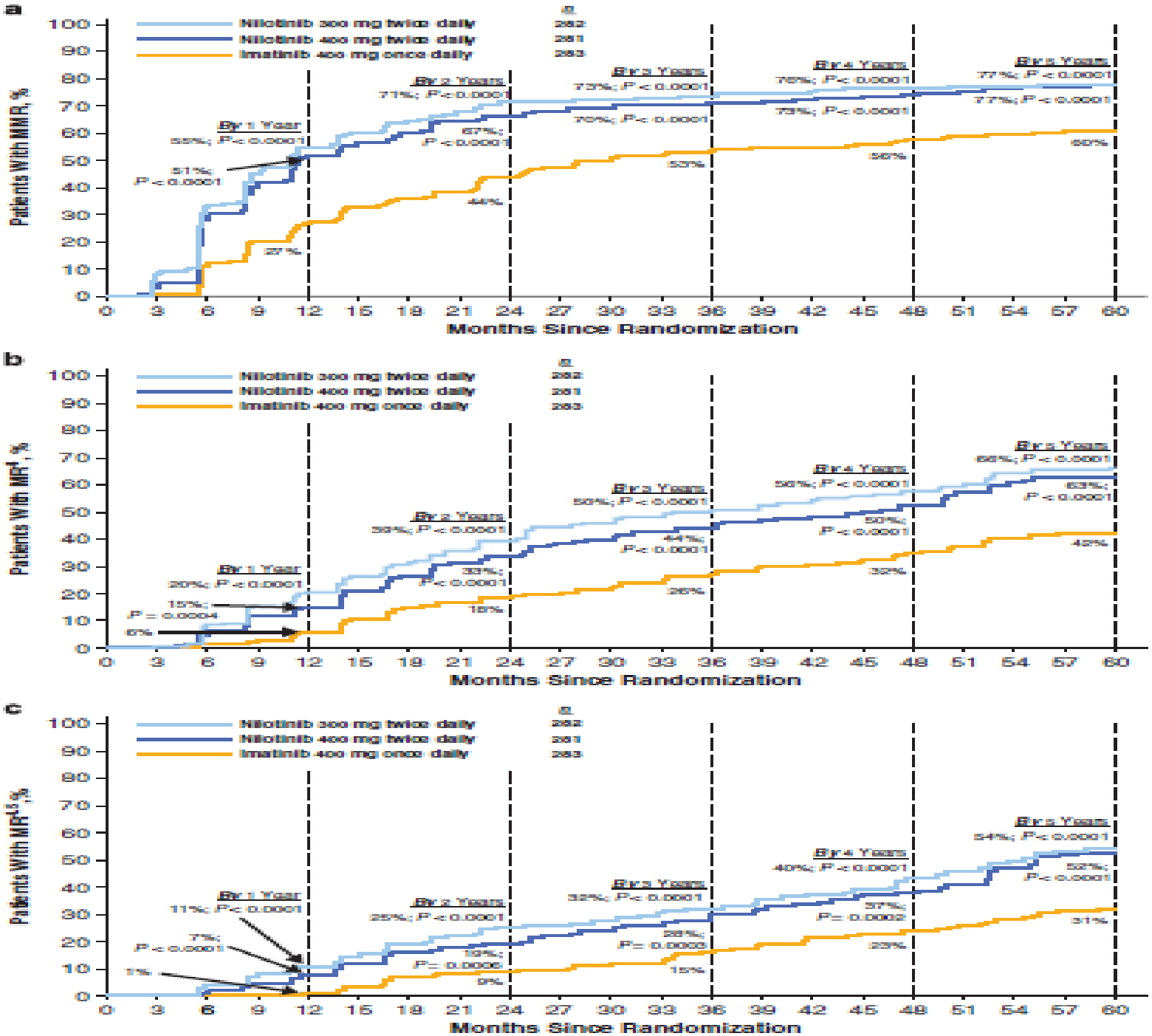
Table 2. Five-Year Responses by *BCR-ABL1* (IS) Transcript Levels at 3 Months

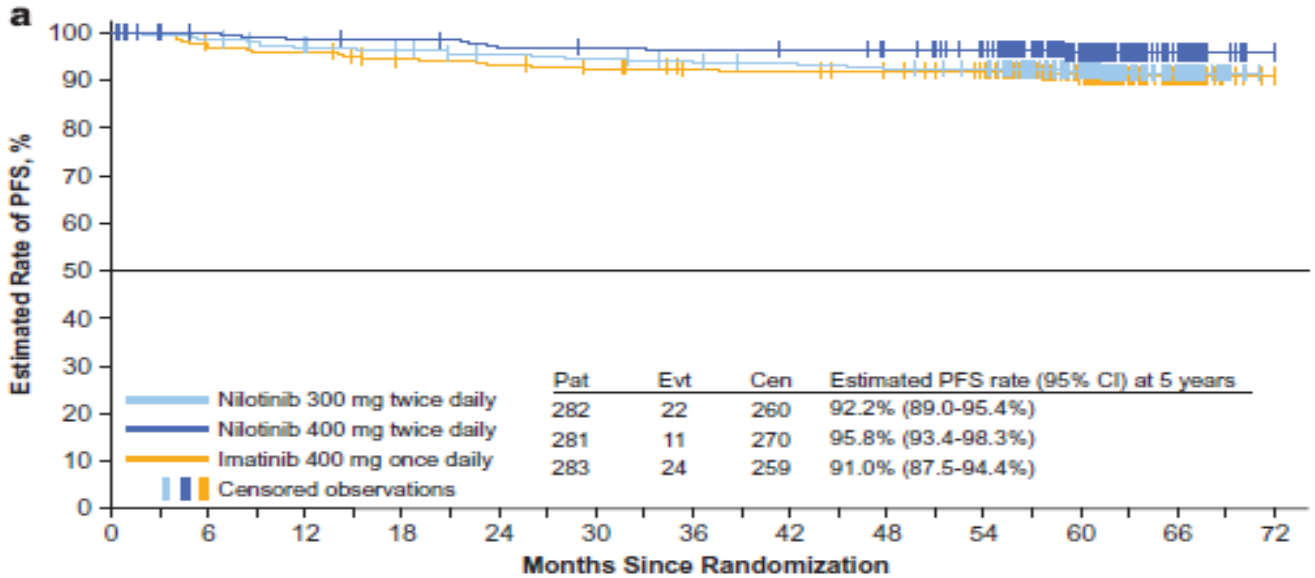
	% of Patients			
	Dasatinib 100 mg Once Daily (n = 259)		Imatinib 400 mg Once Daily (n = 260)	
Response	3-Month *BCR-ABL1* Transcript Level ≤ 10% (n = 198; 84%)	3-Month *BCR-ABL1* Transcript Level > 10% (n = 37; 16%)	3-Month *BCR-ABL1* Transcript Level ≤ 10% (n = 154; 64%)	3-Month *BCR-ABL1* Transcript Level > 10% (n = 85; 36%)
Complete cytogenetic response	94	41	92	59
Major molecular response	87	38	81	41
$MR^{4.5}$	54	5	48	12

Abbreviations: IS, International Scale; $MR^{4.5}$, molecular response with a 4.5-log reduction in *BCR-ABL1* transcripts from baseline (*BCR-ABL1* transcript level ≤ 0.0032% [IS]).


A
No.
Dasatinib 100 mg once daily 259
Imatinib 400 mg once daily 260
% With MMR
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24
30
36
42
48
54
60
Time From Random Assignment (months)
By 1 year
By 2 years
By 3 years
By 4 years
By 5 years
P = .0022
46%
28%
64%
46%
67%
55%
73%
60%
76%
64%

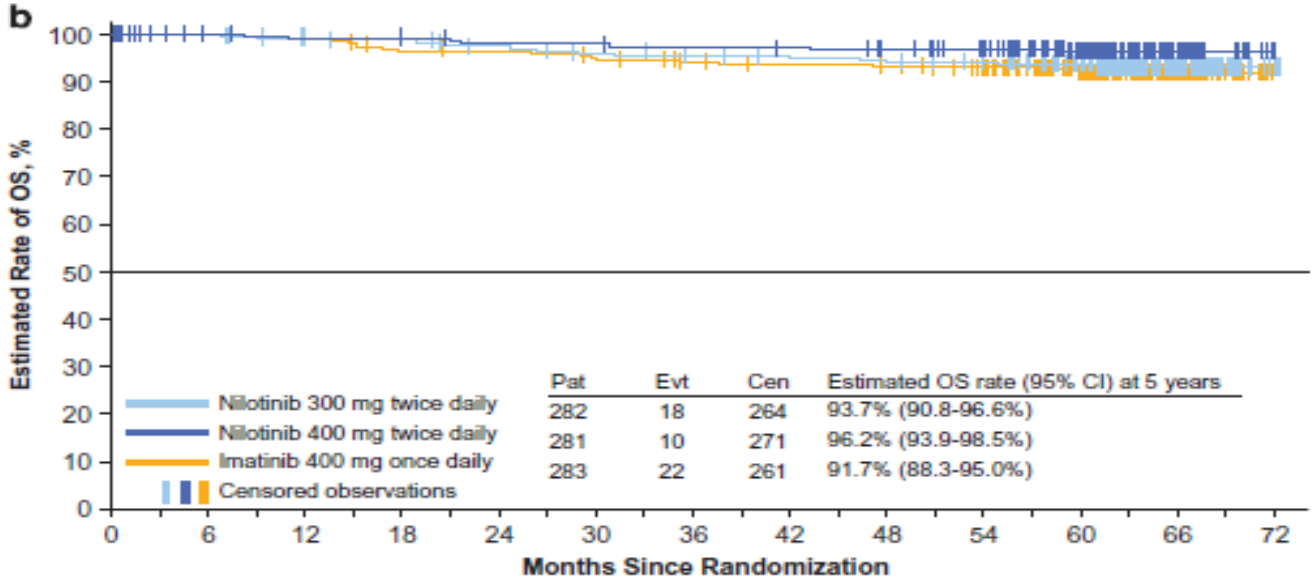

B
No.
Dasatinib 100 mg once daily 259
Imatinib 400 mg once daily 260
% With MR4.5
100
90
80
70
60
50
40
30
20
10
0
6
12
18
24
30
36
42
48
54
60
Time From Random Assignment (months)
By 1 year
By 2 years
By 3 years
By 4 years
By 5 years
P = .0251
5%
3%
19%
8%
24%
13%
34%
23%
42%
33%


a
Nilotinib 300 mg twice daily
Nilotinib 400 mg twice daily
Imatinib 400 mg once daily
n
282
281
283
Patients With MMR, %
By 1 Year
55%; P < 0.0001
51%;
P < 0.0001
27%
By 2 Years
71%; P < 0.0001
67%;
P < 0.0001
44%
By 3 Years
73%; P < 0.0001
70%; P < 0.0001
53%
By 4 Years
76%; P < 0.0001
73%; P < 0.0001
56%
By 5 Years
77%; P < 0.0001
77%; P < 0.0001
60%
Months Since Randomization
b
Patients With MR4, %
By 1 Year
20%; P < 0.0001
15%;
P = 0.0004
6%
By 2 Years
39%; P < 0.0001
33%;
P < 0.0001
18%
By 3 Years
50%; P < 0.0001
44%;
P < 0.0001
26%
By 4 Years
56%; P < 0.0001
50%;
P < 0.0001
32%
By 5 Years
66%; P < 0.0001
63%;
P < 0.0001
42%
Months Since Randomization
c
Patients With MR4.5, %
By 1 Year
11%; P < 0.0001
7%;
P < 0.0001
1%
By 2 Years
25%; P < 0.0001
19%;
P = 0.0006
9%
By 3 Years
32%; P < 0.0001
28%;
P = 0.0003
15%
By 4 Years
40%; P < 0.0001
37%;
P = 0.0002
23%
By 5 Years
54%; P < 0.0001
52%;
P < 0.0001
31%
Months Since Randomization



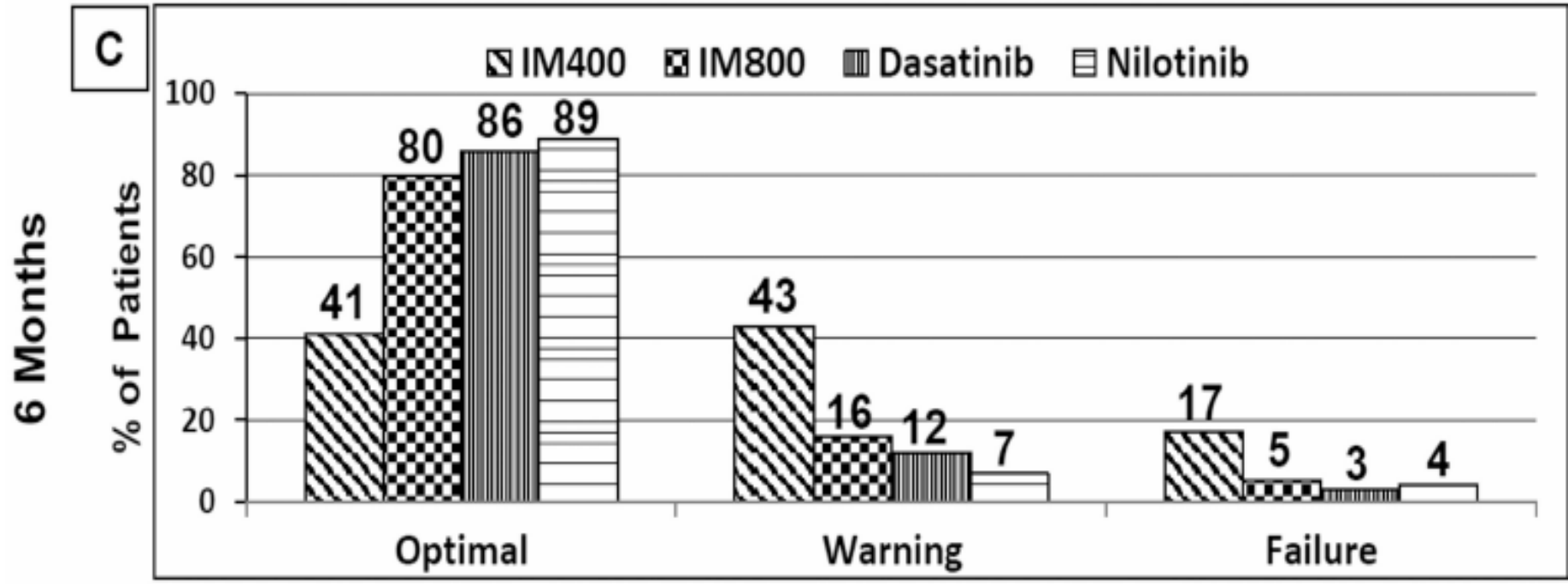
At-risk : Events

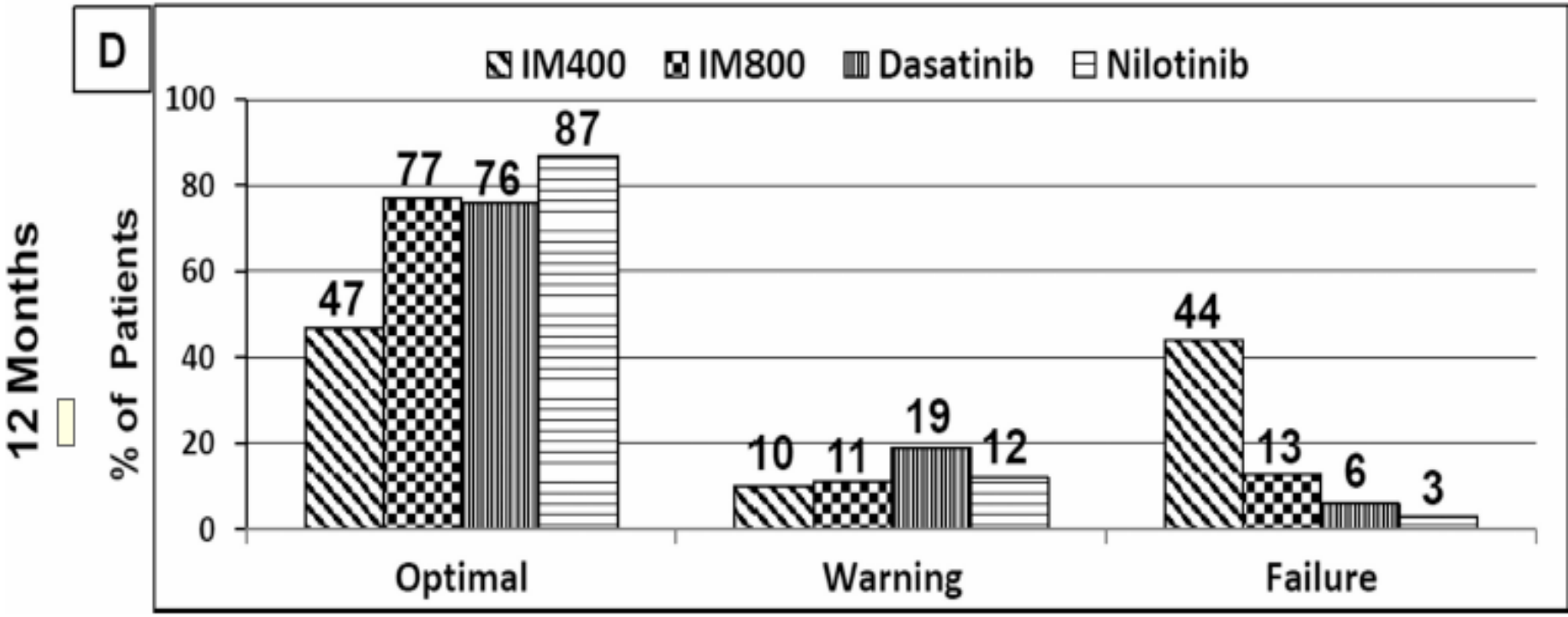
Nilotinib 300 mg twice daily	282 : 0	266 : 8	258 : 12	251 : 17	246 : 20	177 : 21	0 : 22
Nilotinib 400 mg twice daily	281 : 0	269 : 3	262 : 8	260 : 9	255 : 10	183 : 11	0 : 11
Imatinib 400 mg once daily	283 : 0	265 : 11	254 : 18	244 : 21	240 : 22	169 : 24	0 : 24



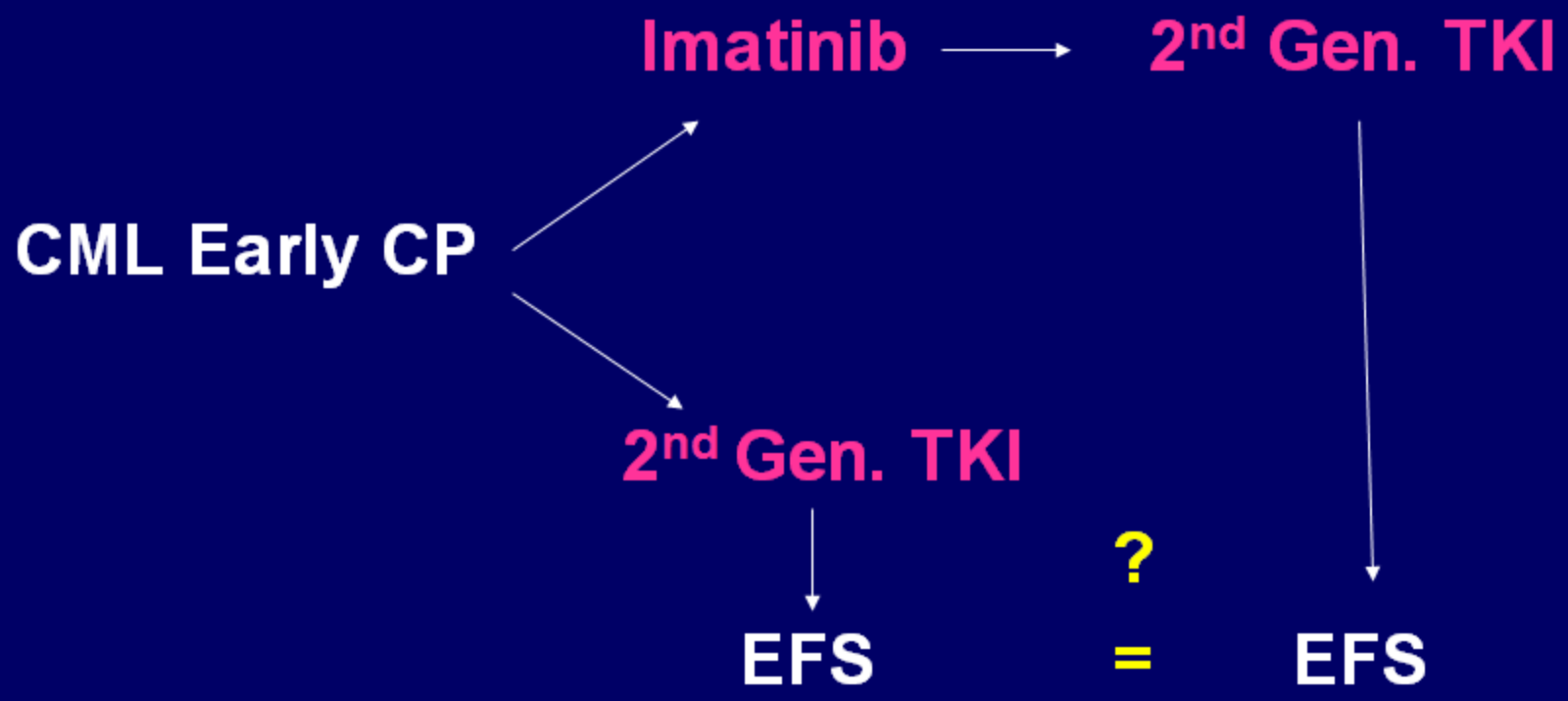
At-risk : Events

Nilotinib 300 mg twice daily	282 : 0	271 : 2	263 : 7	254 : 13	249 : 16	207 : 17	1 : 18
Nilotinib 400 mg twice daily	281 : 0	270 : 2	264 : 6	261 : 8	256 : 9	206 : 10	0 : 10
Imatinib 400 mg once daily	283 : 0	274 : 2	262 : 10	250 : 16	245 : 18	197 : 22	0 : 22


C
6 Months
% of Patients
IM400
IM800
Dasatinib
Nilotinib
100
80
60
40
20
0
41
80
86
89
43
16
12
7
17
5
3
4
Optimal
Warning
Failure


D
12 Months
% of Patients
IM400
IM800
Dasatinib
Nilotinib
100
80
60
40
20
0
47
77
76
87
10
11
19
12
44
13
6
3
Optimal
Warning
Failure

The Best Strategy for CML



1\3 of CML patients do not show an optimal response to Imatinib

Most of these patients will switch to treatment with a 2-generation TKI

40-50% of this patients will achieve an optimal response

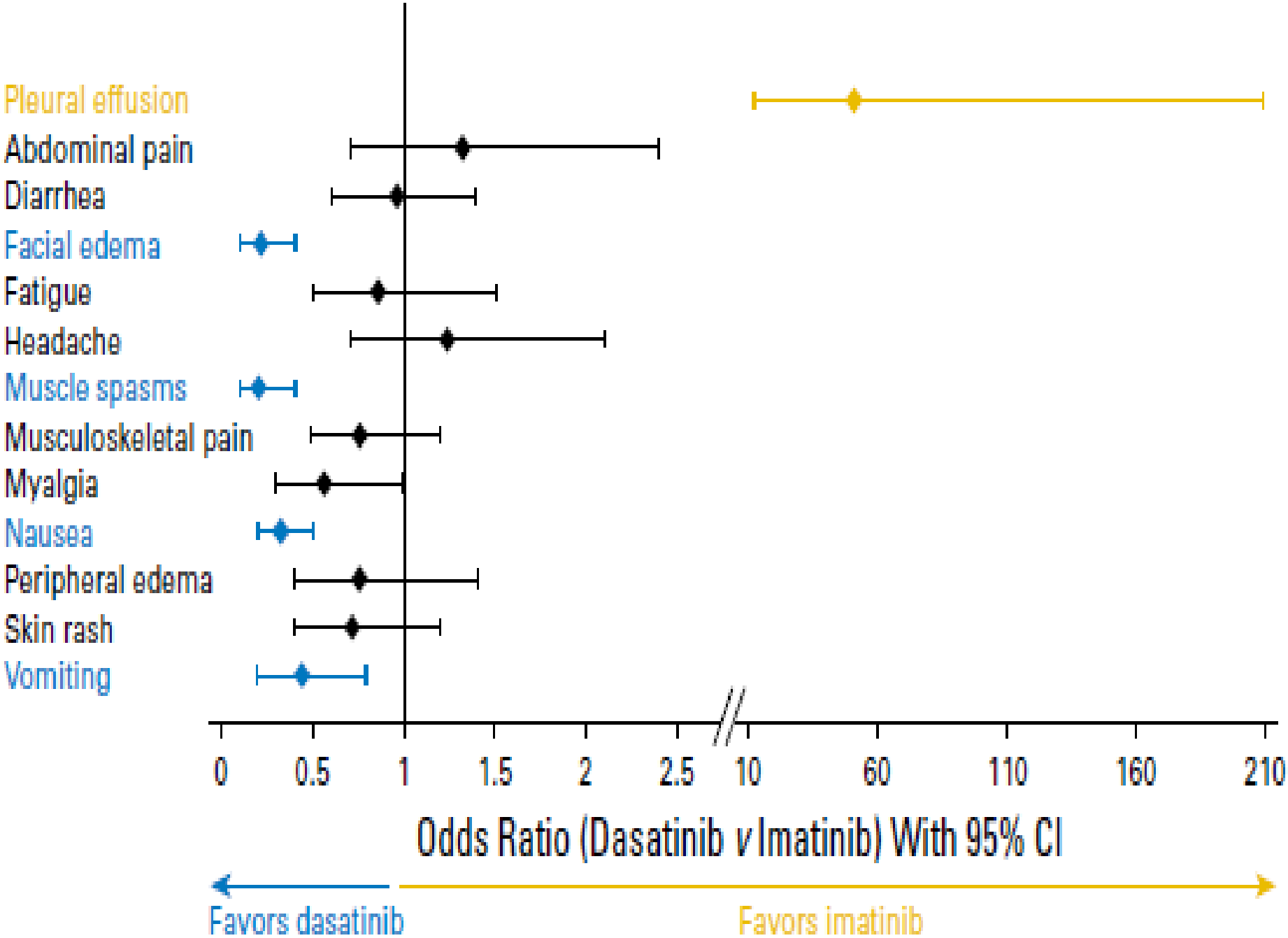
15-20% of them in a short time will progress to a more advanced phase of the disease

Table 1. Comparison of the Most Frequent Adverse Events of Any Grade (≥ 20% of Patients) and Grade 3/4 Laboratory Abnormalities (≥ 15% of Patients) in Patients With CML-CP Receiving Tyrosine Kinase Inhibitors

	Imatinib (Front line)[a]	Dasatinib		Nilotinib		Bosutinib (R/I)[f]	Ponatinib (R/I)[g]
		Front line[b]	R/I[c]	Front line[d]	R/I[e]		
Abdominal pain	X					X	X
Arterial ischemia							X
Arthralgia				X	X		X
Constipation					X		X
Cough	X				X	X	
Diarrhea	X	X	X		X	X	
Dry skin							X
Dyspnea			X				
Fatigue	X		X	X	X	X	X
Fluid retention	X	X	X				
Superficial edema	X		X				
Pleural effusion			X				
Headache	X		X	X	X	X	X
Hemorrhage	X						
Hypertension							X
Joint pain	X						
Muscle cramps	X						
Musculoskeletal pain	X		X				
Myalgia	X						X
Nasopharyngitis	X			X	X		
Nausea	X			X	X	X	X
Pain in extremity					X		
Pruritus				X	X		
Pyrexia					X	X	X
Rash	X			X	X	X	X
URTI	X						
Vomiting	X				X	X	
Grade 3/4 lab abnormalities							
Thrombocytopenia			X		X	X	X
Neutropenia	X	X	X		X		X
Anemia							
Elevated lipase					X		X
Hypophosphatemia					X		

Dasatinib Related Adverse Events :

Neutropenia grade ¾	34-70%	Headache	24%
Anemia grade ¾	10%	Fatigue	21%
Thrombocytopenia grade ¾	22%	Rash	22%
Pleural effusion (grade ¾)	10% (2%)		
Peripheral Edema	10-20%		
CHF	2%		
Diarrhea	31%		
Nausea	22%		
Vomiting	13%		


Pleural effusion
Abdominal pain
Diarrhea
Facial edema
Fatigue
Headache
Muscle spasms
Musculoskeletal pain
Myalgia
Nausea
Peripheral edema
Skin rash
Vomiting
0
0.5
1
1.5
2
2.5
10
60
110
160
210
Odds Ratio (Dasatinib v Imatinib) With 95% CI
Favors dasatinib
Favors imatinib

Myelosuppression in the main randomized trials in first line

		Neutropenia		*Thrombocytopenia*		*Anemia*	
		All grades (%)	*Grade ¾ (%)*	*All grades (%)*	*Grade 3/4 (%)*	*All grades (%)*	*Grade 3/4 (%)*
ENESTND[2]	Nilotinib 300 mg twice daily	43	12	48	10	38	3
	Imatinib 400 mg daily	68	20	56	9	47	5
DASISION[4]	Dasatinib 100 mg daily	65	21	70	19	90	10
	Imatinib 400 mg daily	52	20	62	10	84	7
BELA[22]	Bosutinib 500 mg daily	28	11	66	14	80	6
	Imatinib 400 mg daily	54	24	62	14	84	7

ide effects, grading according to NCI-CTC (Common Terminology Criteria for Adverse Events of the National Cancer Institute).

Difficult Choices

What Should we Use as Frontline Therapy for CML : Imatinib or 2nd Generation TKI?

In Conclusion : Second - generation TKIs are more potent as initial treatment :

- Faster time to cytogenetic and molecular responses

- Lower rate of transformation

- More patients achieving BCR-ABL < 10% at 3 months

- Higher and faster rates of very deep molecular responses like MR4 and MR4.5

- Good tolerability

- Only slightly higher rate of cardiovascular events

- Faster achievement of conditions allowing to reach and maintain a TFR state

The End