VII Session – Chronic Myeloid Leukemia

Bosutinib

Gianantonio Rosti, Bologna (Italy)

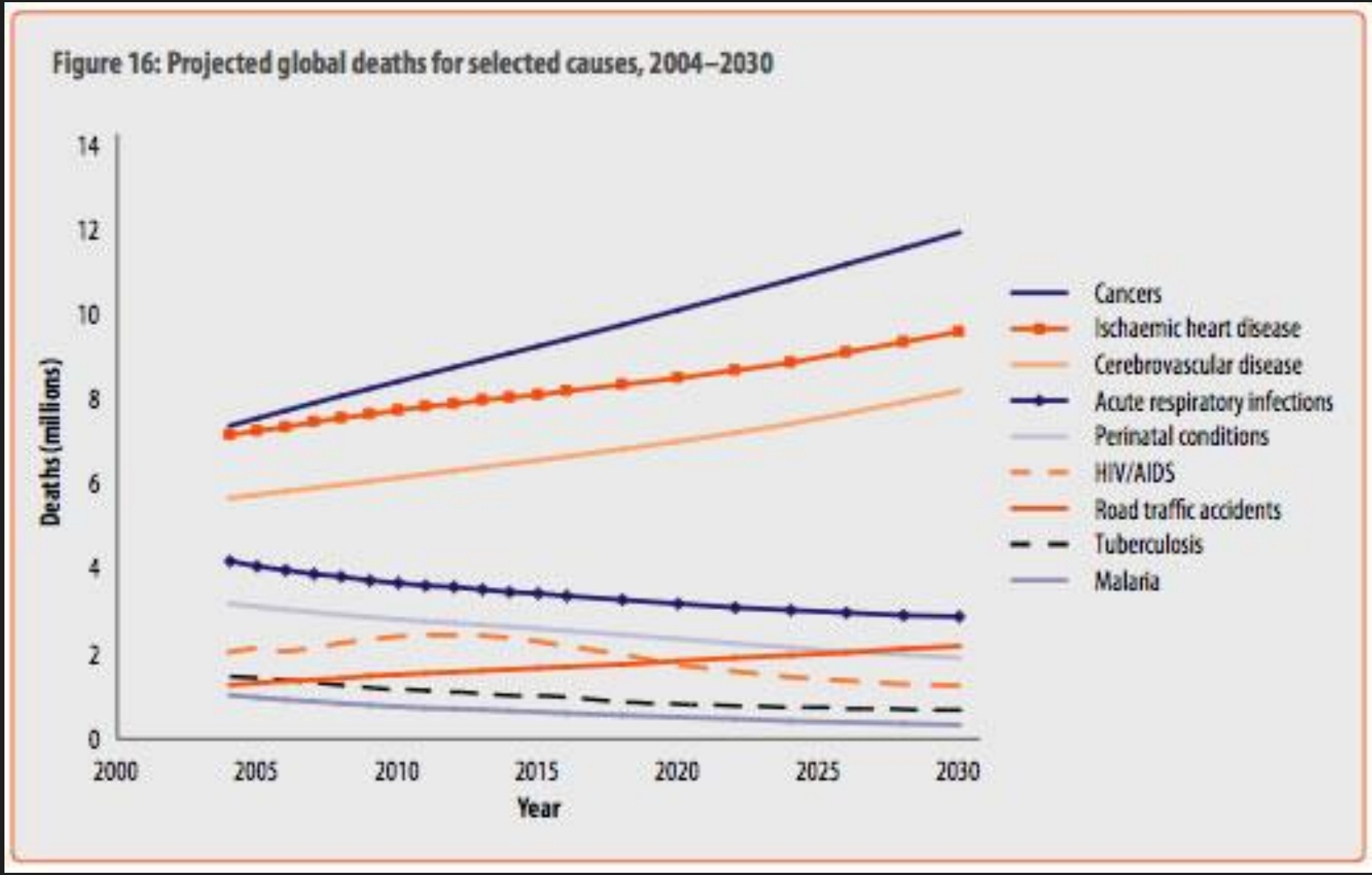
TKIs for CML therapy*

	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB	PONATINIB
Standard dose, 1st line	400 mg OD	300 mg TD	100 mg OD	NA	NA
Dose, 2nd line	3-400 mg TD	400 mg TD	70 mg TD, or 140 mg OD	500 mg OD	45 mg OD
Plasma half-life (a)	~ 20h (a)	~ 15 h (a)	~ 5 h (a)	~ 24 h	~ 19 h
Plasma conc., peak	4202 ± 1272 (a)	2329 ± 772 (a)	133 ± 74 (a)	~ 392	145 ± 73
Plasma conc, through	2062 ± 1334 (a)	1923 ± 1233(a)	5.5 ± 1.4(a)	~ 268	64 ± 29
IC50, BCR-ABL 1	260-679	10-25	0.8-1.8	42	0.5
IC50, PDGFRα	72	75	2.9	3.0	1.1
IC50, cKit	99	209	18	10000	12
IC50, Src	>1000	>1000	0.1	3.0	5.4
IC50, VEGFR2	10000	3720	NA	NA	1.5
IC50, BTK	>5000	NA	1.1	2.5	849
Food effect	weak	strong (b)	weak	weak	weak
Gastric ph elevating agents effect	no	weak	strong (c)	strong (c)	NA

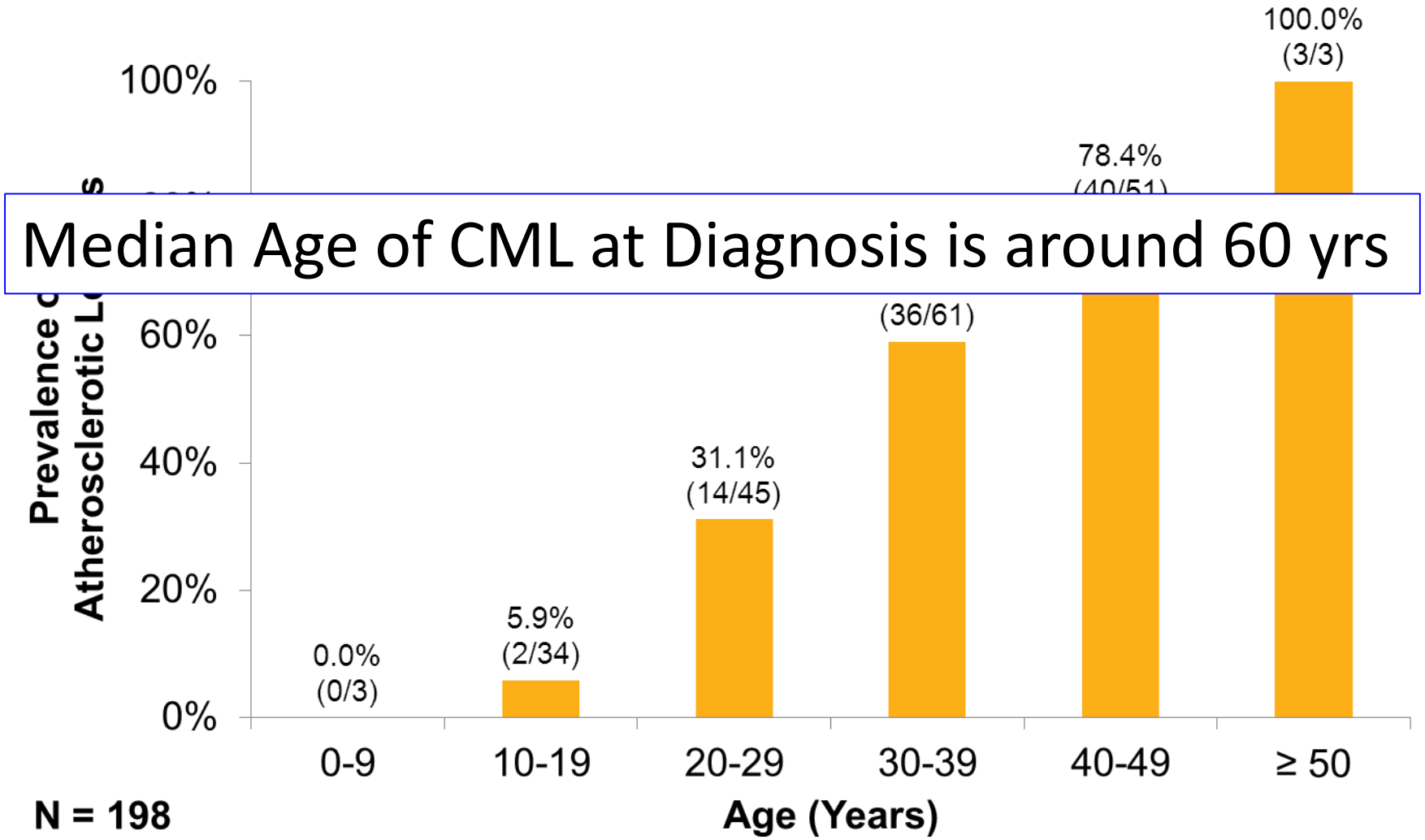
(a) For standard dose, 1st line; (b) 87% increase in AUC after a high-fat meal; (c) 60-80% reduction in AUC by H2 blocker;
OD = Once Daily TD = Twice Daily NA = not available or not known

Modified from Rosti et al, Nat Med Rev (2016)

WHO, Prediction of Cause of Death (2004-2030)



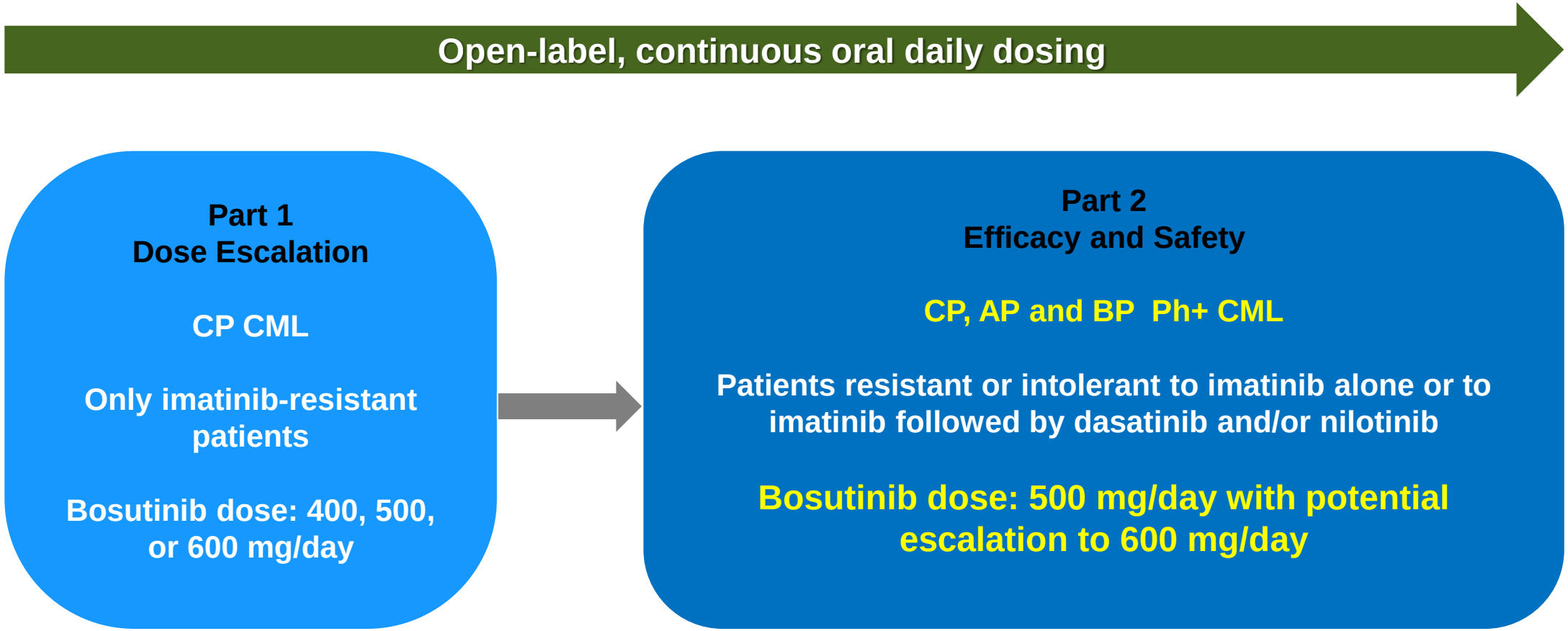
Prevalence of coronary atherosclerosis according to age



Median Age of CML at Diagnosis is around 60 yrs

Kim MS, et al. *J Atheroscler Thromb.* 2013;20:465-471.

Study 200: Phase I/II Study of Bosutinib in Previously Treated Patients with Ph+ CML



Kantarjian et al. *Blood*. 2014;123:1309-18

Study 200 (2nd line): Cumulative Cytogenetic Response to Bosutinib at 5 years

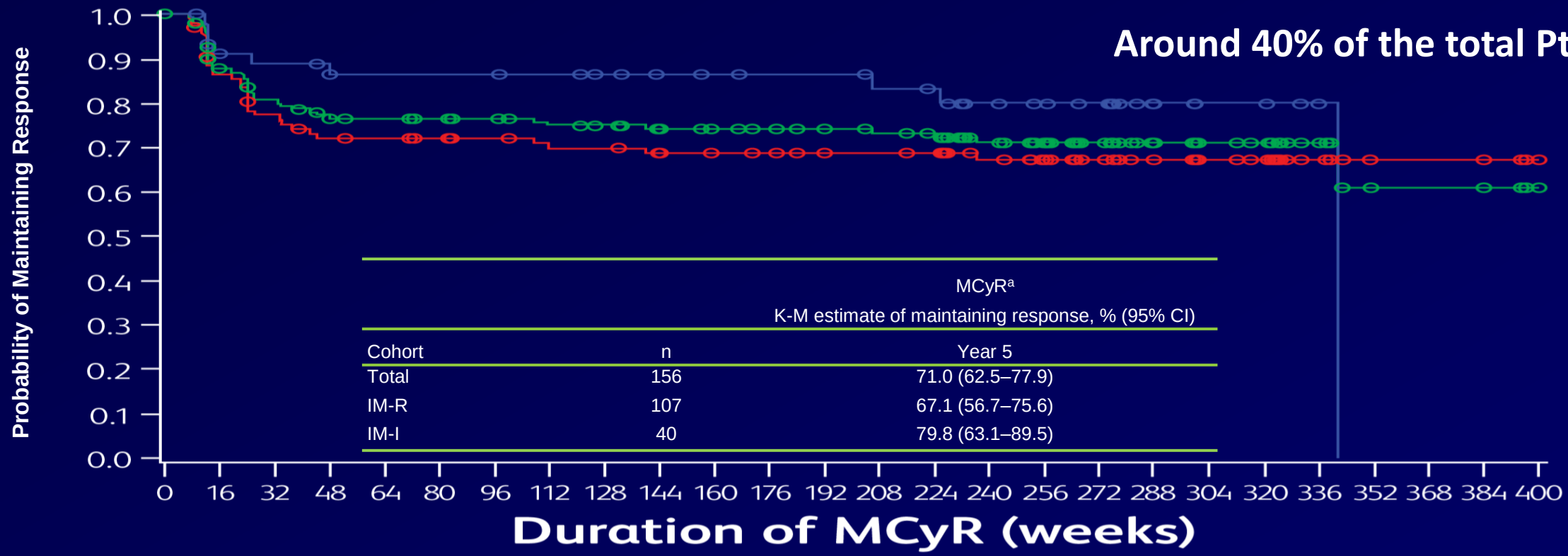
	IM-R (n=195)	IM-I (n=89)	Total (n=284)
Response	**Year 5**	**Year 5**	**Year 5**
Evaluable patients,* n	182	80	262
MCyR, n (%)	107 (59)	49 (61)	156 (60)
CCyR, n (%)	88 (48)	42 (53)	130 (50)

CCyR=complete cytogenetic response; IM-I=imatinib intolerant; IM-R=imatinib-resistant; MCyR=major cytogenetic response (complete + partial).
*To be considered a responder, the patient must have improved from their baseline assessment or maintained their baseline response. Evaluable patients had received ≥1 bosutinib dose and had a valid baseline cytogenetic assessment.

Lipton et al. ASCO 2015 , abstr. 7076

Study 200 (2nd line): Duration of MCyR Among Responders at Median Follow-up of 60 Months

Around 40% of the total Pts Pop



Cohort	n	MCyR[a] K-M estimate of maintaining response, % (95% CI) Year 5
Total	156	71.0 (62.5–77.9)
IM-R	107	67.1 (56.7–75.6)
IM-I	40	79.8 (63.1–89.5)

Subjects at Risk, n

IM-R	107	86	76	70	69	67	65	62	62	59	56	55	53	51	50	44	33	27	22	16	14	8	4	4	4	1
IM-I	49	39	38	36	35	35	35	34	32	30	29	28	28	26	25	21	19	17	8	4	4	1	0	0	0	0
Total	156	125	114	106	104	102	100	96	94	89	85	83	81	77	75	65	52	44	30	20	18	9	4	4	4	1

IM-I=imatinib-intolerant; IM-R=imatinib-resistant; KM=Kaplan-Meier; MCyR=major cytogenetic response.
Open circles indicate censored observations.
[a]42% of responders still on-treatment and at risk for an event at 5 years after initial response.
KM median duration of response not yet reached.

Lipton et al. *J Clin Oncol*. 2015; 33(suppl): Abstract 7076

Response rates in 2nd line

	Nilotinib 400 mg bid	Dasatinib 100 mg qd	Bosutinib 500 mg qd	Ponatinib 45 mg qd
At . . . months	24	24	24	15
n =	321	167	266	267
MCyR, %	59	63	59	56
CCyR, %	44	49	48	46
MMR, %	28	37	35	34

Note: Informal comparison as these are not head-to-head clinical trials.

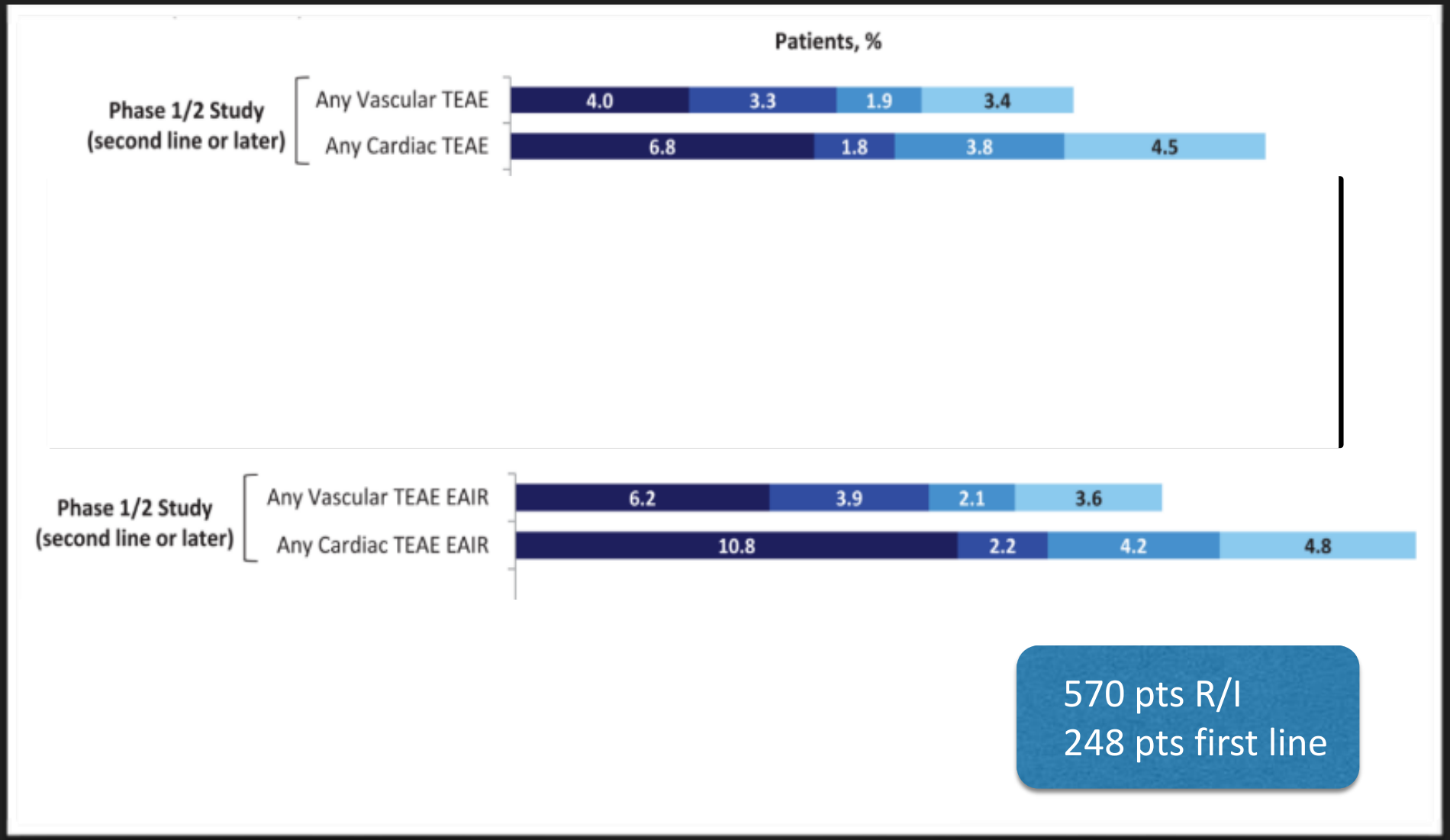
Shah NP, et al. *Haematologica.* 2010;95(2):232-240;
Kantarjian HM, et al. *Blood.* 2011;117(4):1141-1145;
Gambacorti-Passerini C, et al. *Am J Hematol.* 2014;89(7):732-42;
Hochhaus A, et al. ASH 2015. Abstract 4025.

Bosutinib 6-year Update
Summary of Clinical Activity

- CCyR: newly attained or maintained from baseline by 50% (130/262) of evaluable patients
  - IM-R patients: 48% (88/182)
  - IM-I patients: 53% (42/80)
- MCyR: newly attained or maintained from baseline by 60% (156/262) of evaluable patients
  - IM-R patients: 59% (107/182)
  - IM-I patients: 61% (49/80)
- Median durations of CCyR or MCyR not met
- Estimated probability
  - Of maintaining CCyR at year 6 = 0.67 (95% CI 0.57–0.75)
  - Of maintaining MCyR at year 6 = 0.71 (0.95 CI, 0.63–0.78)
- Most (63%–67%) patients who newly attained or maintained an MCyR from baseline did so while receiving a BOS dose of 500 mg/d

BOS, bosutinib; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; IM-I, imatinib intolerant; IM-R, imatinib-resistant; MCyR=major cytogenetic response

Incidence of treatment-emergent vascular/cardiac adverse events occurring in patients treated with bosutinib (phase 1/2 and phase 3 trials)



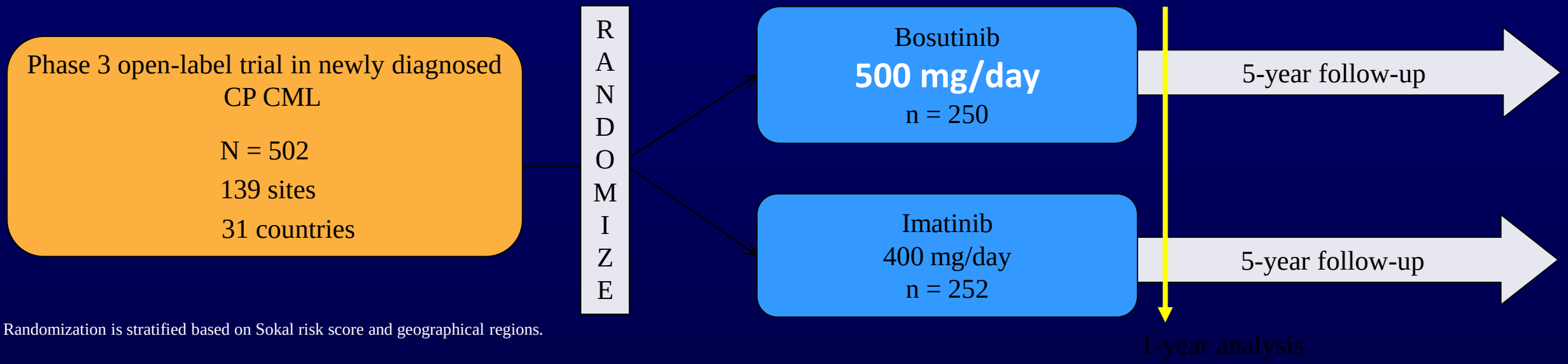
Cortes JE, et al. *Am J Hematol*. 2016;91:606-616.

Bosutinib – Therapeutic indications

Bosulif is indicated for the treatment of adult patients with:

- newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
- **Recommended dose, 500 mg once daily**

BELA Study Design



Randomization is stratified based on Sokal risk score and geographical regions.

- **Key eligibility criteria: cytogenetic diagnosis of Philadelphia chromosome–positive (Ph+) CP CML ≤6 months prior, no prior therapy other than hydroxyurea or anagrelide**
- **Primary endpoint: complete cytogenetic response (CCyR) at 12 months**
- **Key secondary and exploratory endpoints:**
  - **MMR at 12 months, time to and duration of CCyR and MMR, time to transformation to AP/BP CML, event-free survival (EFS), and overall survival (OS)**
  - **Safety and tolerability**

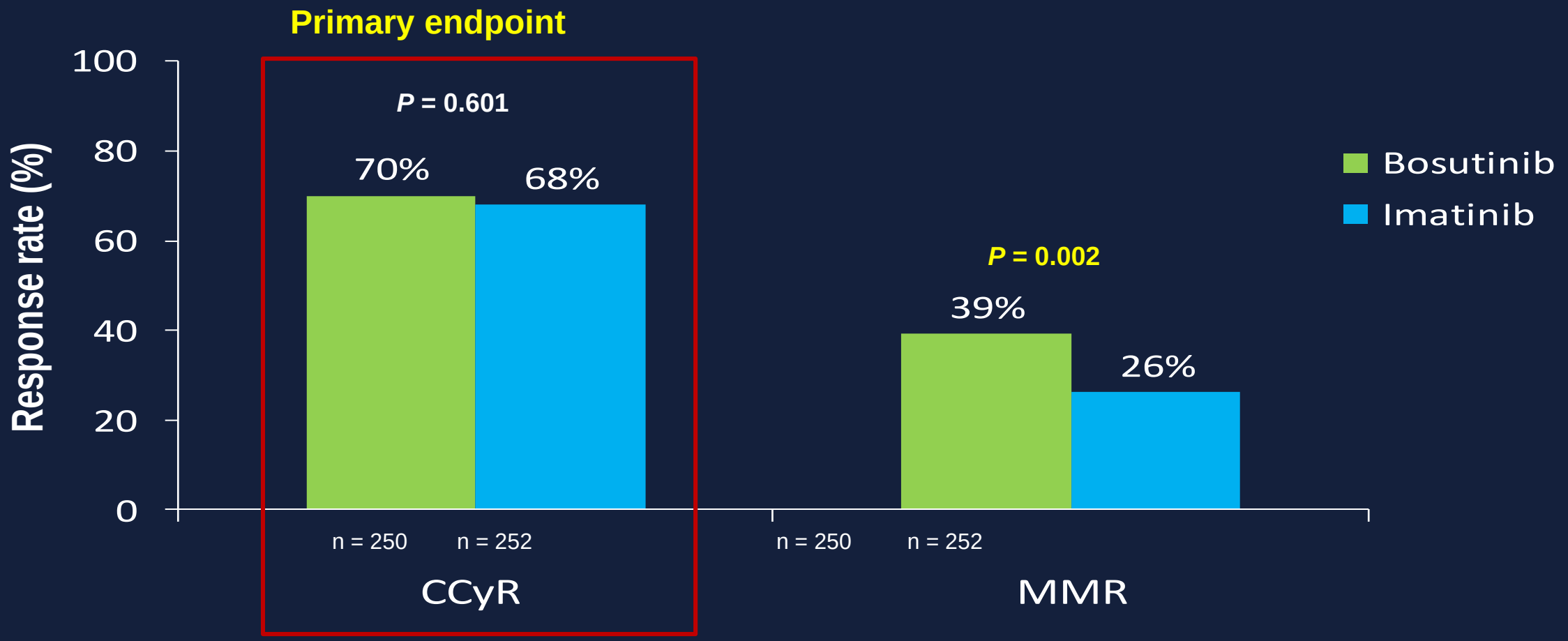
BELA – Treatment Discontinuation Reasons: Safety Population

Reason, n (%)	Bosutinib (n = 248)	Imatinib (n = 251)
Active patients	155 (62)	176 (70)
Discontinued patients	93 (38)	75 (30)
AE	61 (25)	20 (8)
Disease progression[a]	11 (4)	34 (14)
Transformation to AP/BP CML	8 (3)	15 (6)
Subject request	8 (3)	10 (4)
Lost to follow-up	6 (2)	0
Investigator request	3 (1)	5 (2)
Death	1 (<1)	1 (<1)
Protocol violation	0	2 (1)
Other	3 (1)	3 (1)

AE, adverse event; AP; advanced phase; BP, blast phase; CML, chronic myeloid leukemia.
[a]Disease progression includes both lack of efficacy and transformation to AP/BP CML.

- AEs leading to treatment discontinuation in ≥3 patients in either arm were elevated alanine aminotransferase (ALT; n = 11 vs n = 1), thrombocytopenia (n = 4 each), vomiting (n = 4 vs n = 0), neutropenia (n = 3 each), pleural effusion (n = 3 vs n = 0), and elevated lipase (n = 3 vs n = 0)

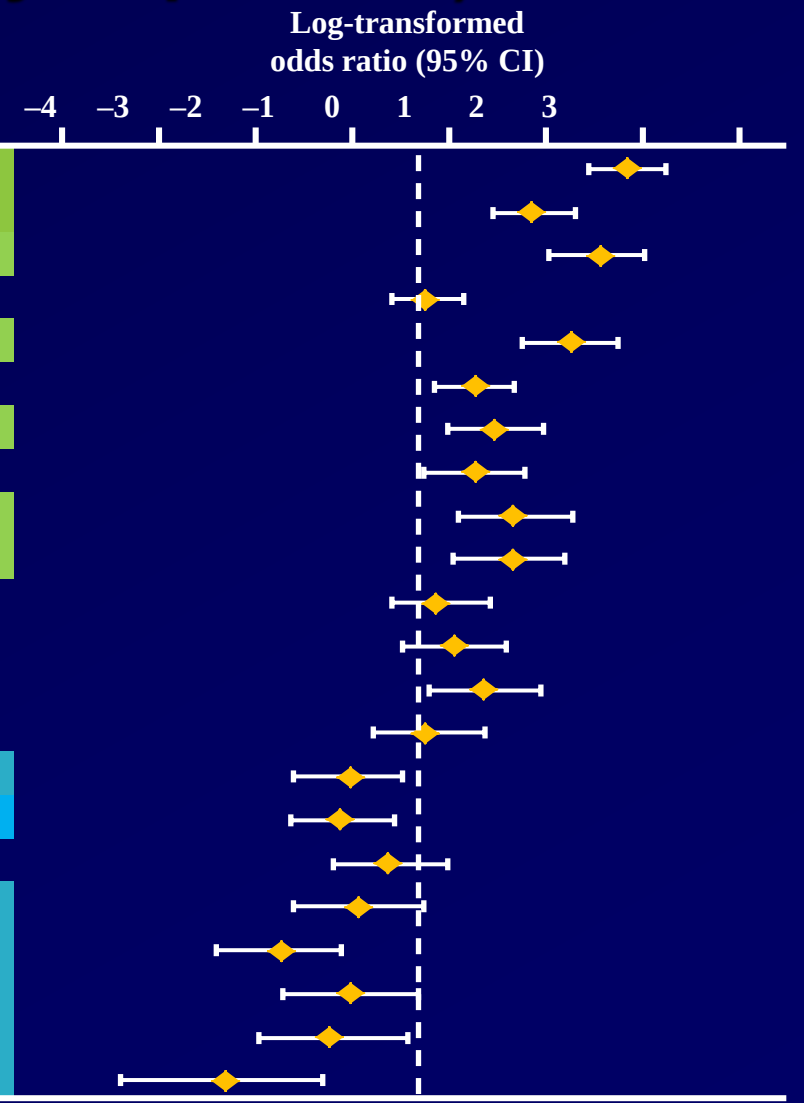
BELA trial – BOS 500 mg vs IM 400 mg
Responses at 12 Months: ITT Population



Cortes et al. J Clin Oncol 2012; 30:3486-3492

BELA 30 Months: Treatment-emergent AEs Reported for ≥10% of Patients (Safety Population)

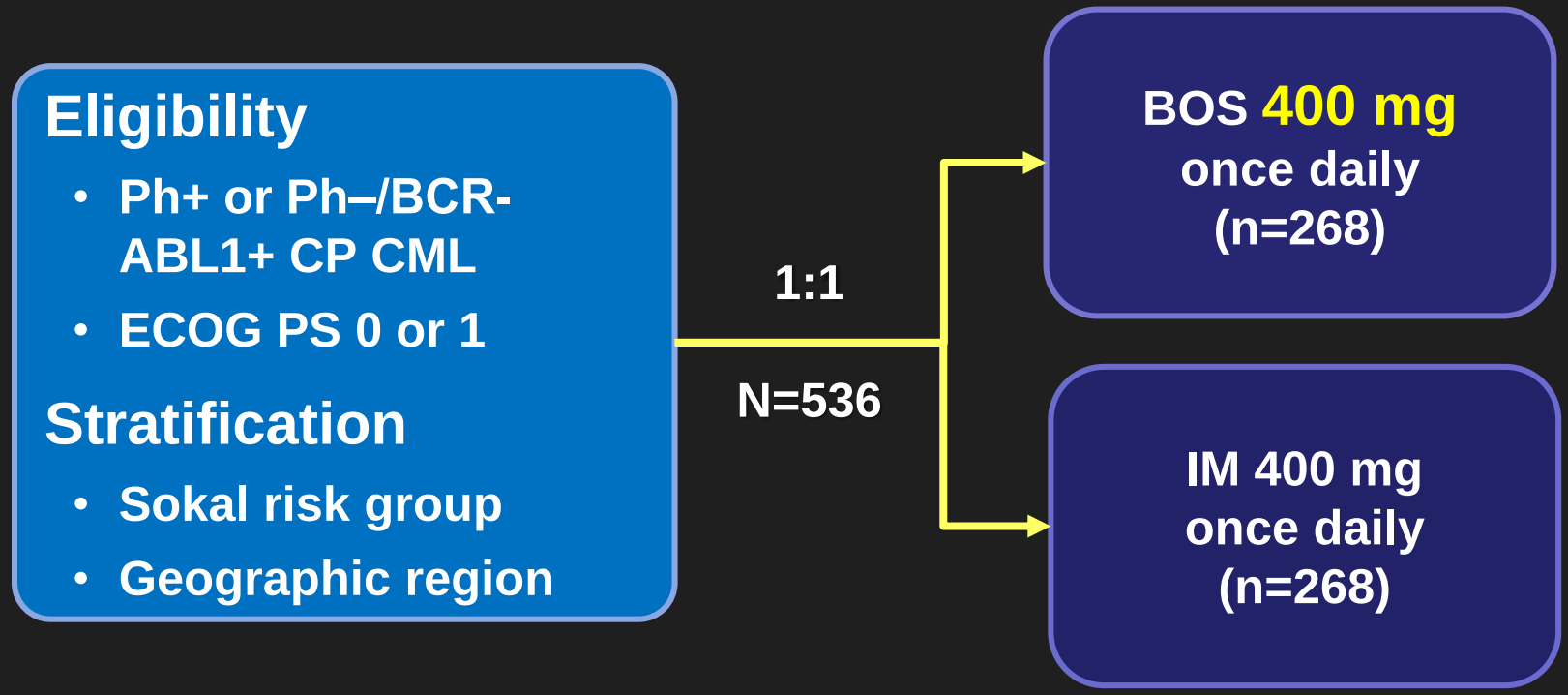
AE, n (%)	Bosutinib (n = 248)	Imatinib (n = 251)
Diarrhea	173 (70)	65 (26)
Vomiting	82 (33)	41 (16)
Increased ALT	81 (33)	23 (9)
Nausea	80 (32)	91 (36)
Increased AST	69 (28)	24 (10)
Rash	61 (25)	49 (20)
Pyrexia	46 (19)	30 (12)
Increased lipase	36 (15)	28 (11)
Upper abdominal pain	36 (15)	19 (8)
Abdominal pain	34 (14)	19 (8)
Fatigue	32 (13)	34 (14)
Headache	32 (13)	30 (12)
Upper respiratory tract infection	30 (12)	21 (8)
Cough	23 (9)	27 (11)
Hypophosphatemia	20 (8)	49 (20)
Increased creatine kinase	20 (8)	51 (20)
Arthralgia	19 (8)	32 (13)
Myalgia	13 (5)	30 (12)
Muscle cramps	12 (5)	56 (22)
Peripheral edema	12 (5)	30 (12)
Bone pain	9 (4)	27 (11)
Periorbital edema	4 (2)	36 (14)



Green highlighting adverse events numerically higher with bosutinib
Blue highlighting adverse events numerically higher with imatinib

Brummendorf et al.
Haematologica. 2012;97(Suppl 1):Abstract 0587

BFORE Study Design



Primary Endpoint

- MMR rate at 12 mo

Secondary/Other Endpoints

- CCyR by 12 mo
- MMR by 18 mo
- Response duration
- EFS and OS
- MMR at 3, 6, 9 mo
- MR^4, $MR^{4.5}$ at 3, 6, 9, 12 mo
- Time to response
- Time to transformation

- Ongoing, open-label, phase 3 study
- 536 patients were enrolled at 151 centers in 26 countries July 2014 to August 2015
- Expected study duration of 5 years
  - Data presented are up to and including the last randomized patient's 12-mo visit

BFORE, Oct 2017

ClinicalTrials.gov: NCT02130557.

Response Rates

	% (95% CI)		Odds Ratio (95% CI)	*P* Value
	BOS	IM		
MMR at 12 mo (mITT)	47.2 (40.9–53.4)	36.9 (30.8–43.0)	1.55 (1.07–2.23)	0.02
MMR at 12 mo (ITT)	*46.6 (40.7–52.6)*	*36.2 (30.4–41.9)*	*1.57 (1.10–2.22)*	*0.01*
BCR-ABL1 ratio ≤10% at 3 mo (mITT)	75.2 (69.8–80.6)	57.3 (51.0–63.5)	NA	<0.0001
CCyR by 12 mo (mITT)	77.2 (72.0–82.5)	66.4 (60.4–72.4)	1.74 (1.16–2.61)	<0.01

- MMR rate at 12 mo higher with BOS vs IM in all Sokal risk groups: high (34% vs 17%), intermediate (45% vs 39%), and low (58% vs 46%)

BFORE, Oct 2017

NA=not available. High Sokal risk group: n=53 BOS, n=54 IM; intermediate: n=107 BOS, n=92 IM; low: n=86 BOS, n=95 IM.

Treatment Status (Safety)

	BOS (n=268)	IM (n=265)
Completed 12 mo of treatment, %	82	82
Discontinued treatment within 12 mo, %	18	18
Discontinued treatment, %	22	27
Adverse event*	14	9
Related to study treatment†	13	9
Not related to study treatment	1	<1
Suboptimal response/treatment failure	2	6
Investigator request	2	5
Patient request	2	1
Disease progression to AP/BP	<1	2
Death	0	2
Other‡	2	3

- Patients who completed 12 mo of treatment continued on in the study

*Only discontinuations with adverse event as the primary reason are included. †By investigator's assessment. ‡Includes protocol deviation, lost to follow up/failed to return, other.

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	BOS (n=268)	IM (n=265)
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Patient request	2	1
Disease progression to AP/BP	<1	2
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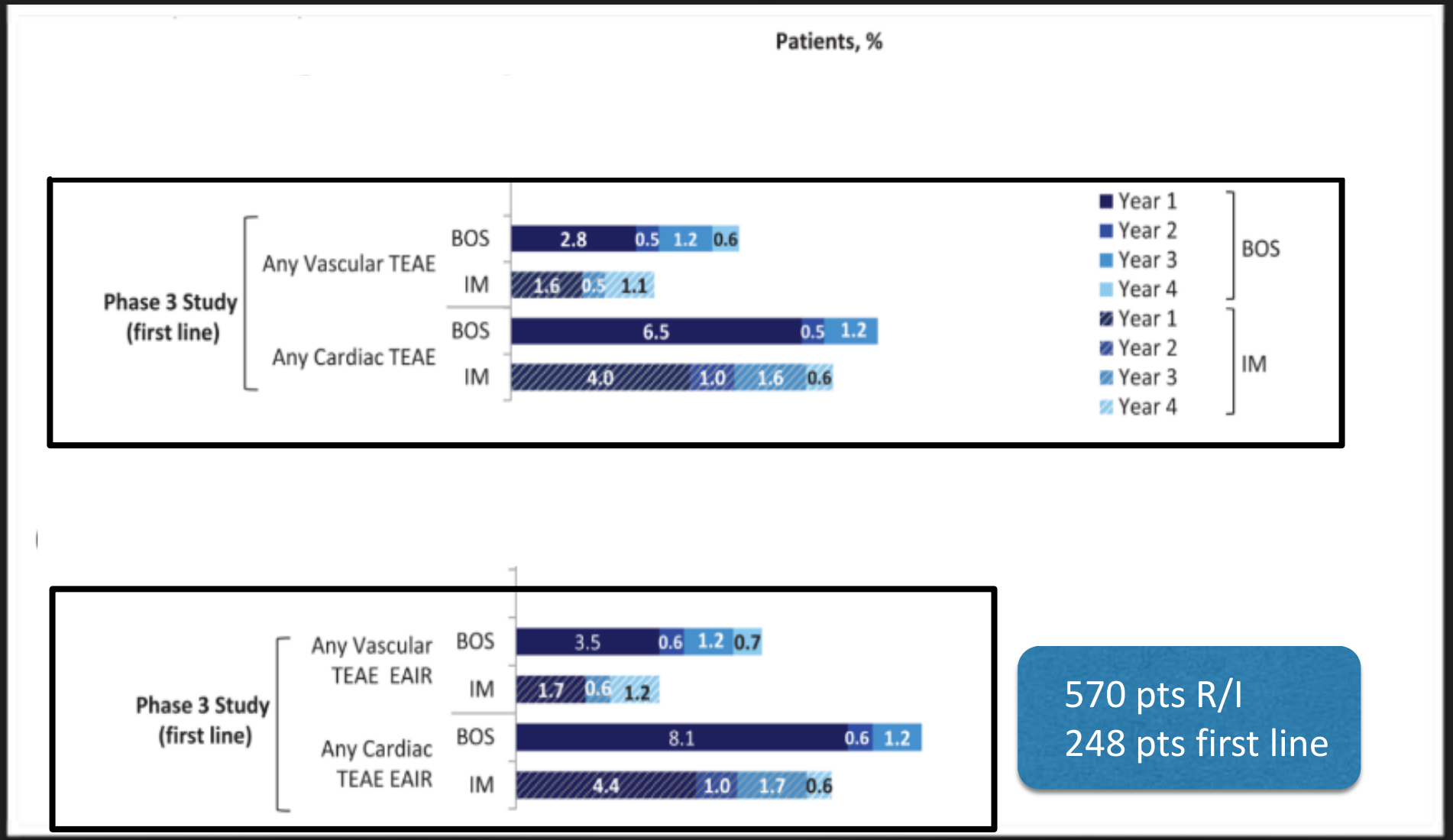
Incidence of treatment-emergent vascular/cardiac adverse events occurring in patients treated with bosutinib (phase 1/2 and phase 3 trials)



570 pts R/I
248 pts first line

Cortes JE, et al. *Am J Hematol*. 2016;91:606-616.

VOLUME 33 · NUMBER 35 · DECEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Tyrosine Kinase Inhibitor–Associated Cardiovascular Toxicity in Chronic Myeloid Leukemia

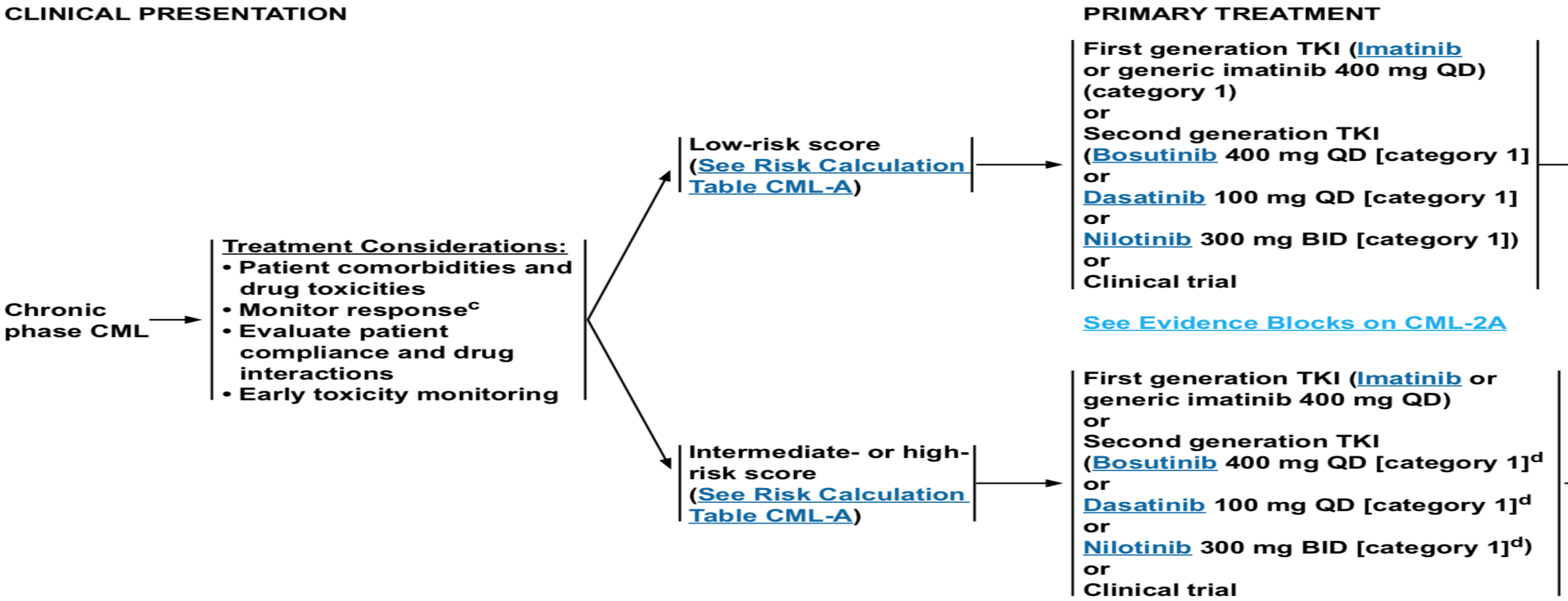
Javid J. Moslehi and Michael Deininger

Table 1 Commonly reported non-hematologic adverse effects of tyrosine-kinase inhibitors in prospective clinical trials

	Imatinib [1[a], 8, 29[a], 34, 71, 15, 16[a]]		Dasatinib [10, 23, 36, 38, 66[a], 17]		Nilotinib [11, 24, 39, 40, 51, 18, 19]		Bosutinib [9, 25, 70, 20]		Ponatinib [21, 22, 37, 58[a], 55]	
Adverse event	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Cardiac (non-ischemic)	3–8 %	<1 %	2–5.8 %	–	<1–3 %	–	4–6 %	2 %	2–29 %	2–14 %
CHF	<1–[a]2 %	[a]<1 %	1–2 %	<1–2 %	NR	NR	NR	NR	7 %	4 %
Arrhythmia/rolonged QT	2–4 %	–	2 %	–	1–2 %	–	2 %	<1 %	2 %	2 %
Hypertension	<1–4 %	<1 %	NR	NR	NR	NR	6 %	2 %	9–68 %	2–39 %
	<1–2 %	<1 %	3–9 %	NR	2–15 %	NR	<1–3 %	<1–3 %	7–[a]24 %	7–14 %
Angina	[a]<1–11 %	<1 %	NR	NR	<1 %	–	NR	NR	16 %	–
CV/arterial ischemic event	<1[a]–2 %	<1 %	4–9 %	NR	3–6 %	3–6 %	<1 %	<1 %	4–13 %	4–8 %
PAOD	<1 %	NR	NR	NR	1.5–6 %	1–6 %	NR	NR	5–[a]7 %	2–6 %
Cerebrovascular	<1 %	NR	<1 %	NR	<1 %	<1 %	<1 %	NR	4–[a]7 %	2–4 %

Moslehi JJ, et al. *J Clin Oncol*. 2015;33:4210-4218.

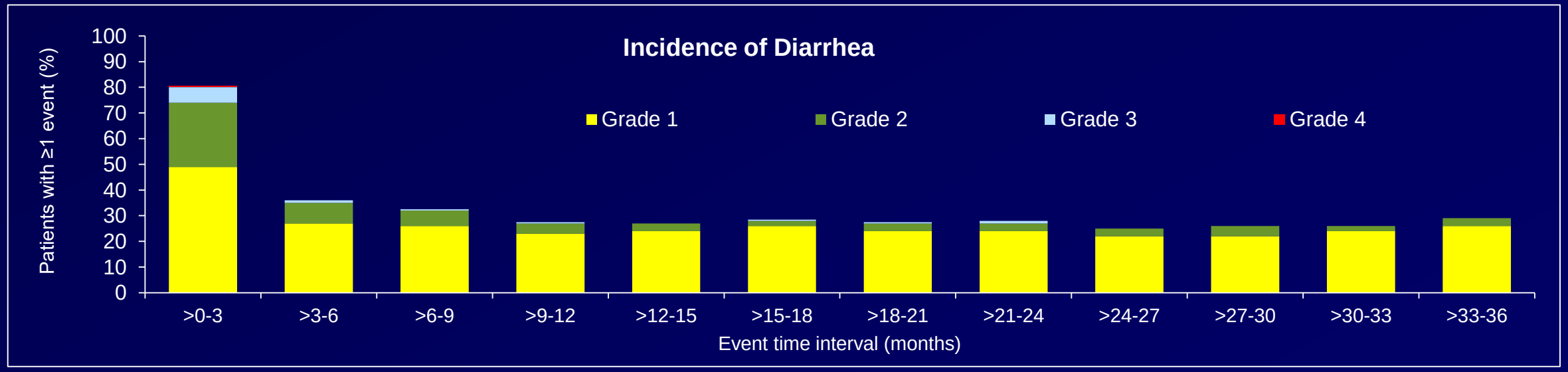
NCCN, V.4, 2018



Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Study 200: Characteristics and Management of Diarrhea

- Most common AE (82%) but mostly mild to moderate
  - Rates generally consistent across cohorts (CP2L: 86%, CP3L: 83%, ADV: 74%)
  - Grade 1/2: 73%; grade 3/4: 8%
  - <2% of drug-related cases rated as serious
  - Incidence of all grades declined markedly after first 3 months
- Predictable time course: early and transient
  - Median time to first event: 2.0 days
  - Median duration: 1-2 days per event
- Manageable with antidiarrheal medication in 65% of affected patients
  - 14% of affected patients managed by dose interruption, 6% by dose reduction
  - 1% discontinued due to diarrhea



CP2L: Chronic phase CML second-line; CP3L: Chronic phase CML third-line; ADV: advanced Ph+ leukemia

Kantarjian et al. *Blood*. 2014;123:1309-18

Retrospective analysis of 2 clinical trials

	Study 200		BELA
	Bosutinib CP2L (n=284)	Bosutinib CP3L (n=119)	Bosutinib CP1L (n=248)
Median duration of treatment, mo	26	9	55
Patients with dose reduced to 400 mg, %	47	45	42
Median time to dose reduction to 400 mg, d	52	62	64
Median duration of treatment at 400 mg, d	198	75	78
Patients with dose reduced to 300 mg, %	18	18	23
Median time to dose reduction to 300 mg, d	162	150	139
Median duration of treatment at 300 mg, d	116	164	271

- Across CP populations, 42%-47% of bosutinib patients had dose reduction to 400 mg and 18%-23% had dose reduction to 300 mg
- Median time to dose reduction, 52-162 d
- Median duration of treatment at reduced dose, 75-271 d

Kota V, et al. *Blood*. 2016;128(22). Abstract 1921.

CCyR Before and After Dose Reduction

	Study 1		Study 2
	Bosutinib CP2L (n=284)	Bosutinib CP3L (n=119)	Bosutinib CP1L (n=248)
Patients with dose reduced to 400 mg/d	**n=132**	**n=53**	**n=103**
CCyR, %			
Newly obtained CCyR following dose reduction	**36**	**21**	**40**
CCyR before and after dose reduction	**13**	**8**	**26**
CCyR before but not after dose reduction	**4**	**0**	**3**
Patients with dose reduced to 300 mg/d	**n=50**	**n=22**	**n=56**
CCyR , %			
Newly obtained CCyR following dose reduction	**16**	**14**	**18**
CCyR before and after dose reduction	**30**	**18**	**45**
CCyR before but not after dose reduction	**2**	**0**	**9**

- Among CP patients:
  - 21%-40% newly obtained and 8%-26% maintained CCyR following dose reduction to 400 mg
  - 14%-18% newly obtained and 18%-45% maintained CCyR following dose reduction to 300 mg

Kota V, et al. *Blood*. 2016;128(22). Abstract 1921.

GIMEMA CML WORKING PARTY

Phase II Clinical Trial

BOSUTINIB EFFICACY SAFETY TOLERABILITY (BEST) STUDY IN ELDERLY CHRONIC MYELOID LEUKEMIA PATIENTS FAILING FRONT-LINE TREATMENT WITH OTHER TYROSINE KINASE INHIBITORS

42 Centers actively recruiting

NCT02810990

Study Design

Phase 2, single-arm, multicentre.

Bosutinib is given orally, once daily:

- 200 mg OAD, for 2 weeks, (“run-in” period)

then

- 300 mg OAD , for the next 14 weeks

then

- 300 mg OAD, if BCR-ABL1 ≤ 1% at week 12

or

- 400 mg OAD, if BCR-ABL1 > 1% at week 12

In responsive patients (based on Q-PCR results), the bosutinib dose will be maintained (300 mg OD or 400 mg OD).

BCR-ABL Inhibitor Activity Against BCR-ABL Single Mutants

BCR-ABL MUTANT	PONATINIB	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB
Native	3	201	15	2	71
M244V	3	287	12	2	147
L248R	8	10000	549	6	874
L248V	4	586	26	5	182
G250E	5	1087	41	4	85
Y253H	5	4908	179	3	40
E255K	6	2487	127	9	181
E255V	16	8322	784	11	214
V299L	4	295	24	16	1228
T315A	4	476	50	59	122
T315I	6	9773	8091	10000	4338
F317C	3	324	16	45	165
F317I	7	266	25	40	232
F317L	4	675	21	10	82
F317V	10	1023	26	104	1280
M351T	4	404	15	2	97
E355A	7	441	18	3	74
F359C	6	728	47	2	70
F359I	11	324	64	3	76
F359V	4	346	41	2	59
H396R	4	395	23	2	60
E459K	5	612	38	4	127

Criteria Used to Classify Drug Potency

Effective C_{ave} at rec. dose	28*	444	131	11	159
IC50 <75% of C_{ave}	<21	<333	<98	<8	<119
IC50 75-150% of C_{ave}	21-32	333-500	98-147	8-12	119-179
IC50 150-300% of C_{ave}	33-95	501-1499	148-442	13-37	180-537
IC50 >300% of C_{ave}	>95	>1499	>442	>37	>537

Gozgit, et al. *Blood.* 2013;122 (abstr 3992).

Summary

- **Bosutinib 1L** induce significantly higher 12-mo response rates than imatinib (MMR, 47% vs 37%, P=0.02; CCyR, 77% vs 66%, P<0.01)
- In patients resistant to or intolerant of TKIs, an optimal response may be achieved with **Bosutinib 2L (CCyR 50%) and 3L (CCyR 32%)**
- **Bosutinib 2L** is active like dasatinib and nilotinib but more safe (particularly, cardiovascular safety)
- Dose adjustements are important to optimize treatment results (stable response after dose reduction)
- Results suggest the **lower BOS dose (400 mg)** may be associated with better tolerability and improved outcomes
- **Run-in BOS 200 mg than escalate to 300 mg or 400 mg according to milestones and tolerability ***
- **QOL at BOS 300 mg is perfect***

*** Personal opinion not (yet) scientifically validated**

VII Session – Chronic Myeloid Leukemia

Bosutinib

Gianantonio Rosti, Bologna (Italy)

Summary of Safety Data

- All-grade AEs: BOS 98% and IM 97%
  - GI events and transaminase elevations more common with BOS
    - Diarrhea common (70%); only 2 patients discontinued BOS because of this AE
  - Musculoskeletal AEs more common with IM (BOS 29% vs IM 59%)
- Grade ≥3 AEs: BOS 56% and IM 43%
  - ALT increase (19%) and thrombocytopenia (14%) most common with BOS
  - Neutropenia (12%) most common with IM
- Dose interruptions (56% vs 36%) and reductions (35% vs 17%) due to AEs more common with BOS
  - Median duration of dose delay: BOS 23 d, IM 15 d
  - Median dose intensity: BOS 392 mg/d, IM 400 mg/d
- Treatment discontinuations due to AEs: BOS 14% vs IM 9%
  - Most commonly ALT/AST elevations for BOS (5%) and myelosuppression for IM (2%)
- Dose escalation for suboptimal response: BOS 17% vs IM 28%

TKIs for CML Therapy*

	Main Adverse Events	Main Complications
Imatinib	Fatigue Myalgia Fluid retention	None
Dasatinib	Thrombocytopenia Pleural effusion	Pulmonary Hypertension
Nilotinib	Skin rash Glucose metabolism Bilirubine and lipase elevation	Arterial Occlusive Events
Bosutinib	Diarrhea Nausea Liver (AST/ALT)	None
Ponatinib	Thrombocytopenia Skin rash Lipase elevation	Arterial Occlusive Events

Gianantonio Rosti, CML Educational Session, 2014 EHA (Milan)

How I treat CML in 2018

1. Careful evaluation of the RISKS (either CML related and CV ones)
2. “Young” CML pt: 2° GenTKIs frontline
3. ANY age NON low risk (only high risk?): 2° Gen TKIs frontline
4. ANY TKI used first: TIGHT monitoring, particularly months 1-6
5. TFR proposed to ALL “eligible” pts after a minimum of 5 years of treatment and > 2 yrs of DMR ($MR^{4.0}$, better if $MR^{4.5}$)

COPD, chronic obstructive pulmonary disease

Evidence of declining renal function were observed in 1ts and 2nd /3rd line pts (at similar degree (pts with advanced phase disease and those ≥65 years cohort, had greater median declines in eGFR, approaching 25 mL/min/1.73 m^2 after 36 months of treatment.

Greatest median change in eGFR at the latest time point analyzed (36/48 months)

Median changes in eGRF relatively small (10-18 mL/min/1.73 m^2)

Changes in serum creatinine and eGFR were comparable for bosutinib and imatinib.

Changes in serum creatinine and eGFR were generally similar for patients enrolled in the first-line study, Study 3000-WW, and those enrolled in the second-line (and more advanced phase) study, Study 200-WW.

Vascular TEAEs:
(Exposure-Adjusted Rate and SOC Incidence)

	Phase 1/2 Study		BELA				Total	
	BOS (n=570)		BOS (n=248)		IM (n=251)		Pooled BOS (n=818)	
	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4
Exposure-adjusted vascular TEAE rate*	0.08	0.03	0.04	0.01	0.03	0.01	–	–
Any vascular TEAEs, %	15	6	12	2	10	2	14	5
Cardiovascular	4	2	2	1	2	<1	4	2
Cerebrovascular	2	1	1	<1	1	<1	2	1
Peripheral Vascular	9	3	9	1	6	1	9	2

*Computed as the number of patients with events/total patient-year where total patient-year=sum of time to first TEAE for patients with cardiac TEAEs plus time on treatment for patients without cardiac TEAEs.
TEAEs graded by NCI CTCAE v3.0; coded and classified by MedDRA (v≥15.0)

- **Only 1 patient treated with BOS reported PAOD (considered by investigator unrelated to BOS)**

PAOD= peripheral arterial occlusive disease; SOC=system organ class.

Cortes et al, ESH-iCMLf 2014, abstract 1782

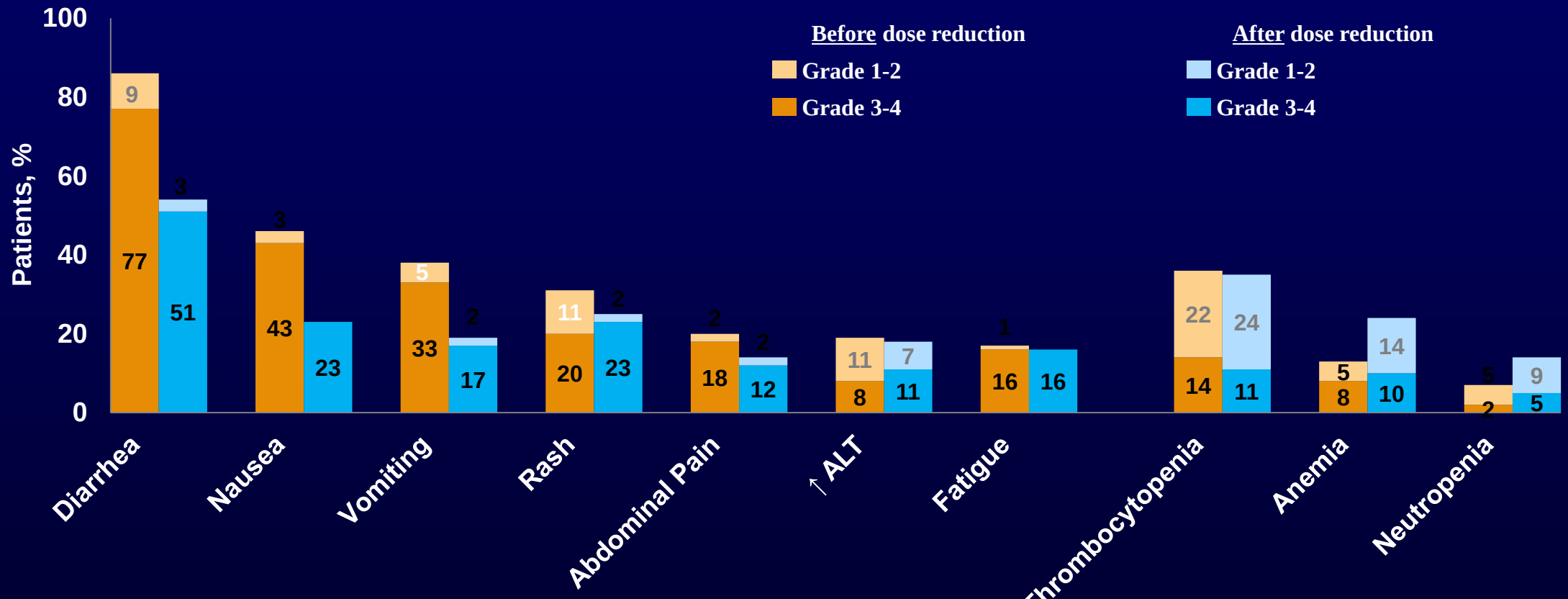
Treatment-Emergent AEs (Safety)

	BOS (n=268)		IM (n=265)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any AE, %*	98	56	97	43
Gastrointestinal	81	11	62	3
Diarrhea	70	8	34	1
Nausea	35	0	39	0
Abdominal pain	18	2	7	<1
Musculoskeletal	30	2	59	2
Muscle spasms	2	0	26	<1
Myalgia	3	<1	15	1
Liver function	40	24	14	4
ALT increased	31	19	6	2
AST increased	23	10	6	2
Periorbital edema	1	0	14	0
Hematologic	46	16	43	20
Thrombocytopenia	35	14	20	6
Neutropenia	11	7	21	12

- Cardiovascular events were infrequent (BOS 3% vs IM 0.4%; grade ≥3: 1.5% vs 0%)

*All-causality adverse events (AEs) with ≥20% incidence in either arm or a >10% difference between arms.

CP2L: Treatment-Emergent AEs Before and After Dose Reduction to 400 mg/d



Kota V, et al. *Blood*. 2016;128(22). Abstract 1921.

MMR Before and After Dose Reduction Among Patients on First-Line Treatment

	Study 2 Bosutinib CP1L (n=248)
Patients with dose reduced to 400 mg/d	**n=103**
MMR, %	
Newly obtained MMR following dose reduction	**41**
MMR before and after dose reduction	**21**
MMR before but not after dose reduction	**1**
Patients with dose reduced to 300 mg/d	**n=56**
MMR, %	
Newly obtained MMR following dose reduction	**27**
MMR before and after dose reduction	**38**
MMR before but not after dose reduction	**2**

- Among CP1L patients:
  - 41% newly obtained and 21% maintained MMR following dose reduction to 400 mg
  - 27% newly obtained and 38% maintained MMR following dose reduction to 300 mg

Kota V, et al. *Blood*. 2016;128(22). Abstract 1921.

Status Attivazione e Arruolamento
Aggiornato a Maggio 2018

Numero di Centri aperti = 37
Numero di Centri prossimi all'apertura = 3
Numero di Centri in attesa di completamento dell'iter regolatorio = 3

Numero di pazienti arruolati = 40
Numero pazienti previsti = 65

FPFV = **21/11/2016**
(Centro di Bologna)

LMC:
l'esperienza che conta

Milano, 26 settembre 2018
Michelangelo Hotel

Il Ruolo di Bosutinib

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Response rates

	Percentage (95% CI)		Odds ratio (95% CI)	*P* value
	BOS	IM		
MMR at 12 mo (mITT)	47.2 (40.9–53.4)	36.9 (30.8–43.0)	1.55 (1.07–2.23)	.02
MMR at 24 mo (mITT)	62	53		.05
MMR at 12 mo (ITT)	*46.6 (40.7–52.6)*	*36.2 (30.4–41.9)*	*1.57 (1.10–2.22)*	*.01*
MMR at 24 mo (ITT)	*61*	*51*		*.01*
BCR-ABL1 ratio ≤10% at 3 mo (mITT)	75.2 (69.8–80.6)	57.3 (51.0–63.5)	NA	<.0001
CCyR by 12 mo (mITT)	77.2 (72.0–82.5)	66.4 (60.4–72.4)	1.74 (1.16–2.61)	<.01

MMR rate at 12 mo higher with BOS vs IM in all Sokal risk groups: high (34% vs 17%), intermediate (45% vs 39%), and low (58% vs 46%)

NA, not available.
High Sokal risk group: n = 53 BOS, n = 54 IM; intermediate: n = 107 BOS, n = 92 IM; low: n = 86 BOS, n = 95 IM.
Cortes JE, et al. *J Clin Oncol.* 2018;36:231-237.

Predicted PK Parameters For A Range of Doses

Parameter	Mean	Median (range)	SD	%CV
AUC, ng/mL-h				
200	1,645	1,376 (124-9,213)	1,080	66
300	2,721	2,294 (281-13,369)	1,707	63
400	4,087	3,374 (560-24,637)	2,683	66
500	5,216	4,322 (735-22,326)	3,316	64
C_{max}, ng/mL				
200	80.6	69.3 (6.8-406)	49.3	61
300	134	116 (12.9-579)	77.7	58
400	201	170 (41.7-1,151)	124	62
500	255	215 (43.9-1,019)	152	59
C_{min}, ng/mL				
200	56.6	46.0 (3.0-363)	41.3	73
300	93.2	76.7 (7.6-539)	65.4	70
400	140	112 (8.6-926)	102	73
500	180	147 (16.2-841)	123	70

%CV, percent coefficient of variance; AUC, area under the concentration-time curve; C_{max}, maximum observed concentration; C_{min}, minimum observed concentration; SD, standard deviation

Hsyu PH et al. *Drug Metab Pharmacokinet*. 2014;29(6):441-8

Treatment Summary[a]

Parameter	IM-R (n=195)	IM-I (n=89)	Total (n=284)
Patients remaining on treatment, n (%)	82 (42)	34 (38)	116 (41)
Median (range) duration of follow-up,[b] mo	46.8 (0.6–96.3)	58.5 (0.6–93.2)	51.4 (0.6–96.3)
Median (range) duration of treatment,[b] mo	27.6 (0.2–94.9)	24.2 (0.3–83.0)	25.6 (0.2–94.9)
Patients with ≥1 dose interruption due to AEs, n (%)	131 (67)	76 (85)	207 (73)
Patients with ≥1 dose reduction due to AEs, n (%)	89 (46)	52 (58)	141 (50)
Patients with dose escalation to 600 mg/d,[c] n (%)	33 (17)	3 (3)	36 (13)
Primary reason for treatment discontinuation by Year 5,[d] n (%)	113 (58)	55 (62)	168 (59)
AE	30 (15)	34 (38)	64 (23)
PD	39 (20)	8 (9)	47 (17)
Unsatisfactory response (efficacy)	18 (9)	3 (3)	21 (7)
Patient request	12 (6)	7 (8)	19 (7)
Death	4 (2)	1 (1)	5 (2)
Investigator request	2 (1)	1 (1)	3 (1)
Lost to follow-up	3 (2)	0	3 (1)
Symptomatic deterioration	2 (1)	0	2 (1)
Other	3 (2)	1 (1)	4 (1)

AE=adverse event; IM-I= imatinib intolerant; IM-R=imatinib resistant;PD=progressive disease

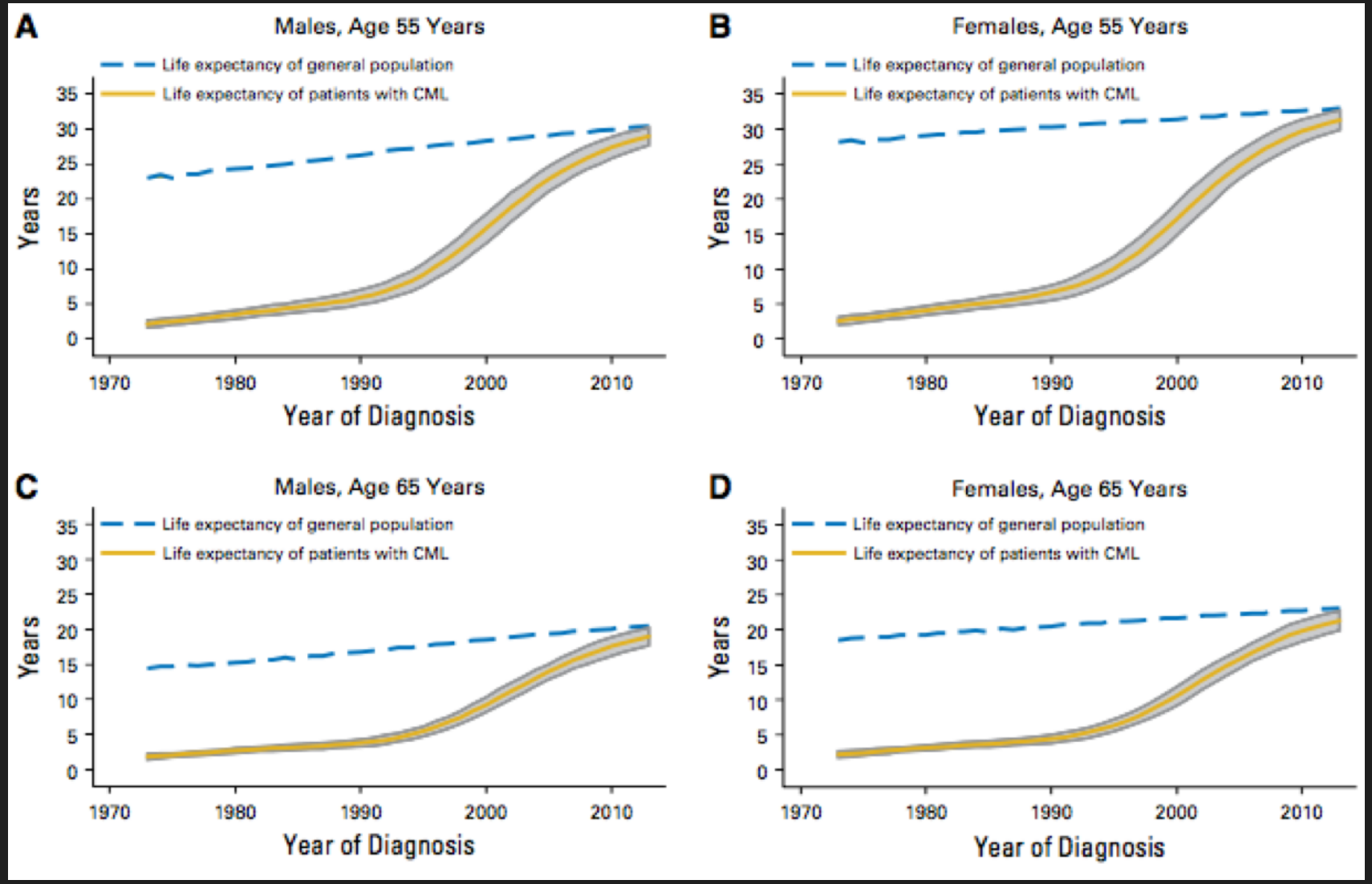
[a]In both Parts 1 and 2, patients received treatment until PD, death, unacceptable toxicity, or withdrawal of consent.

[b]One month is defined as 30.4 days.

[c]Dose escalation to bosutinib 600 mg/day was permitted for lack of efficacy if no grade 3/4 drug-related AE had occurred; does not include 11 patients who started treatment at bosutinib 600 mg/day.

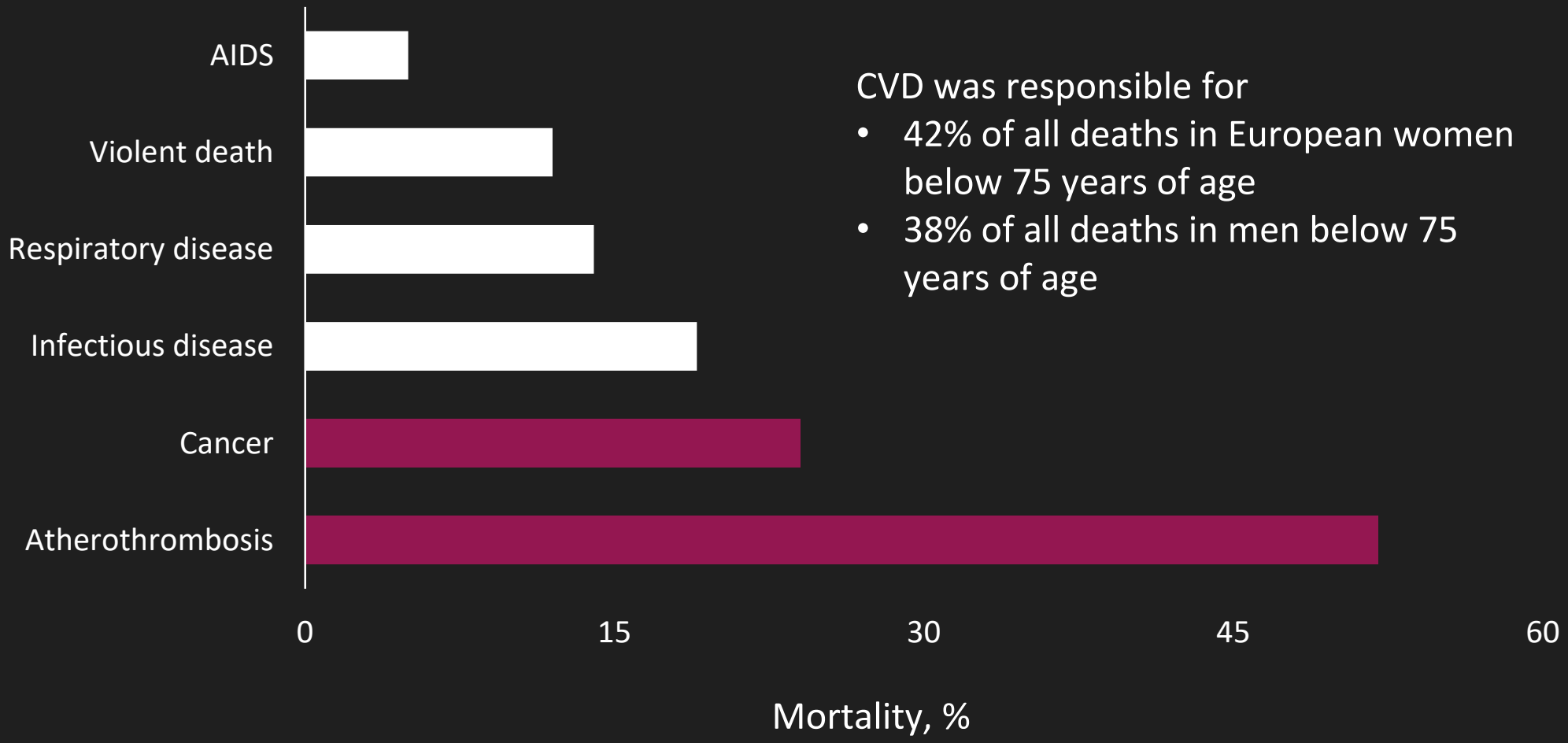
[d]65 patients had an AE leading to treatment discontinuation by year 5; however, in only 64 was this the primary reason for discontinuation.

Expected survival of CML vs normal population



Bower H, et al. *J Clin Oncol*. 2016;34:2851-2857.

Atherosclerosis is the leading cause of death in the world



CVD was responsible for

- 42% of all deaths in European women below 75 years of age
- 38% of all deaths in men below 75 years of age

World Health Organization. World Health Report. 2010.