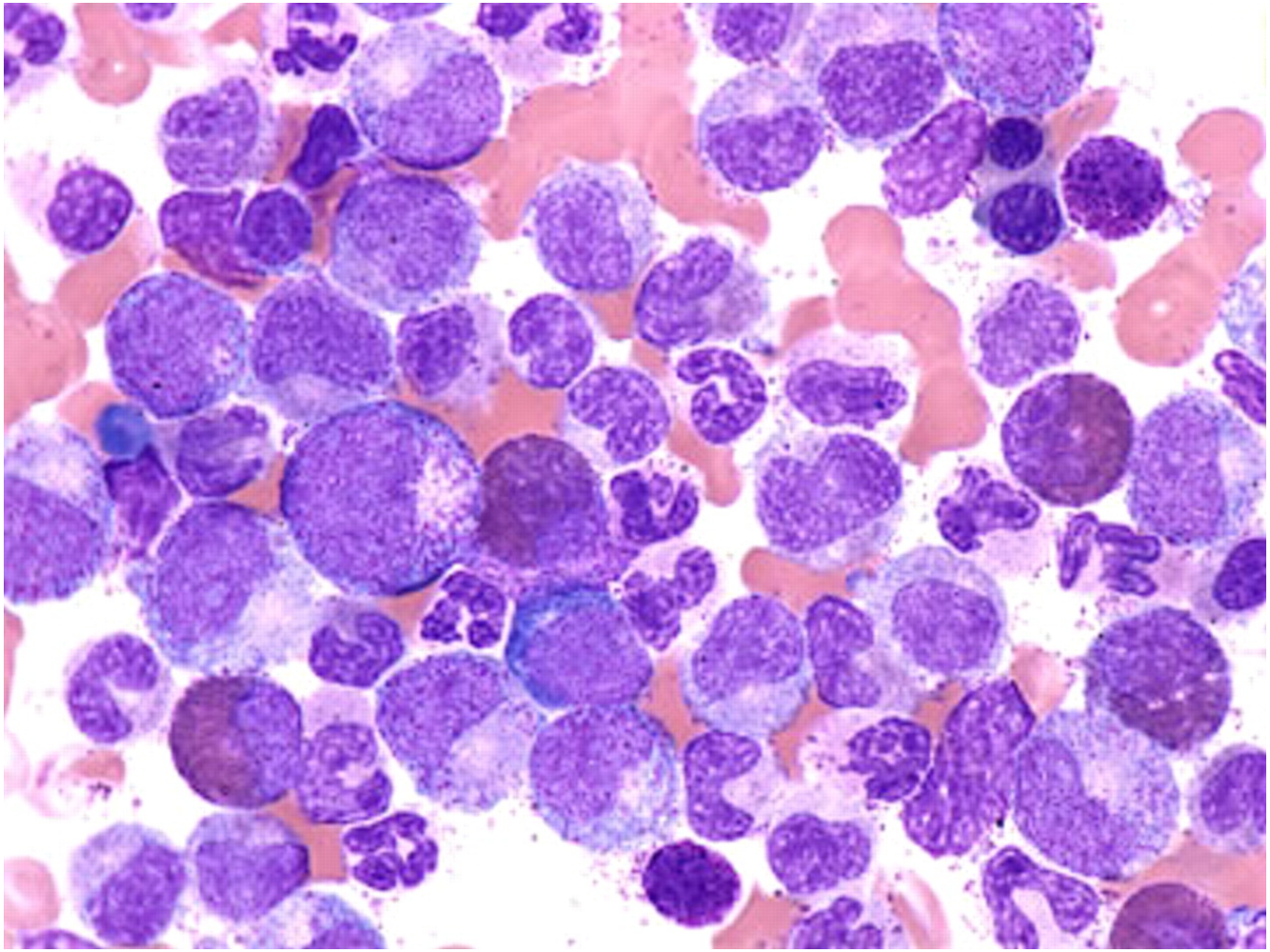
Management of CML in blast crisis

Lymphoma Tumor Board

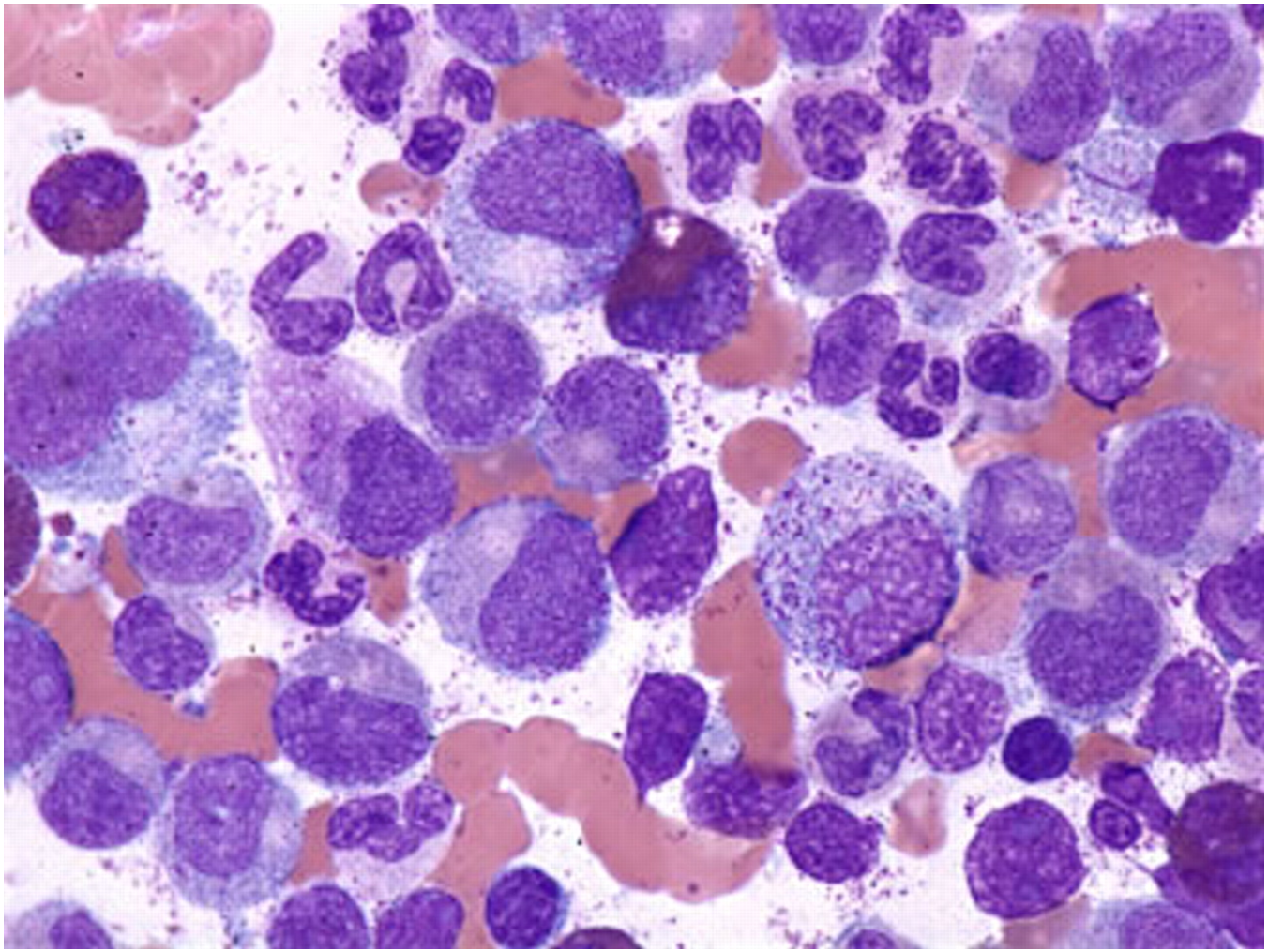
October 7, 2016

Chronic Phase CML - 2.



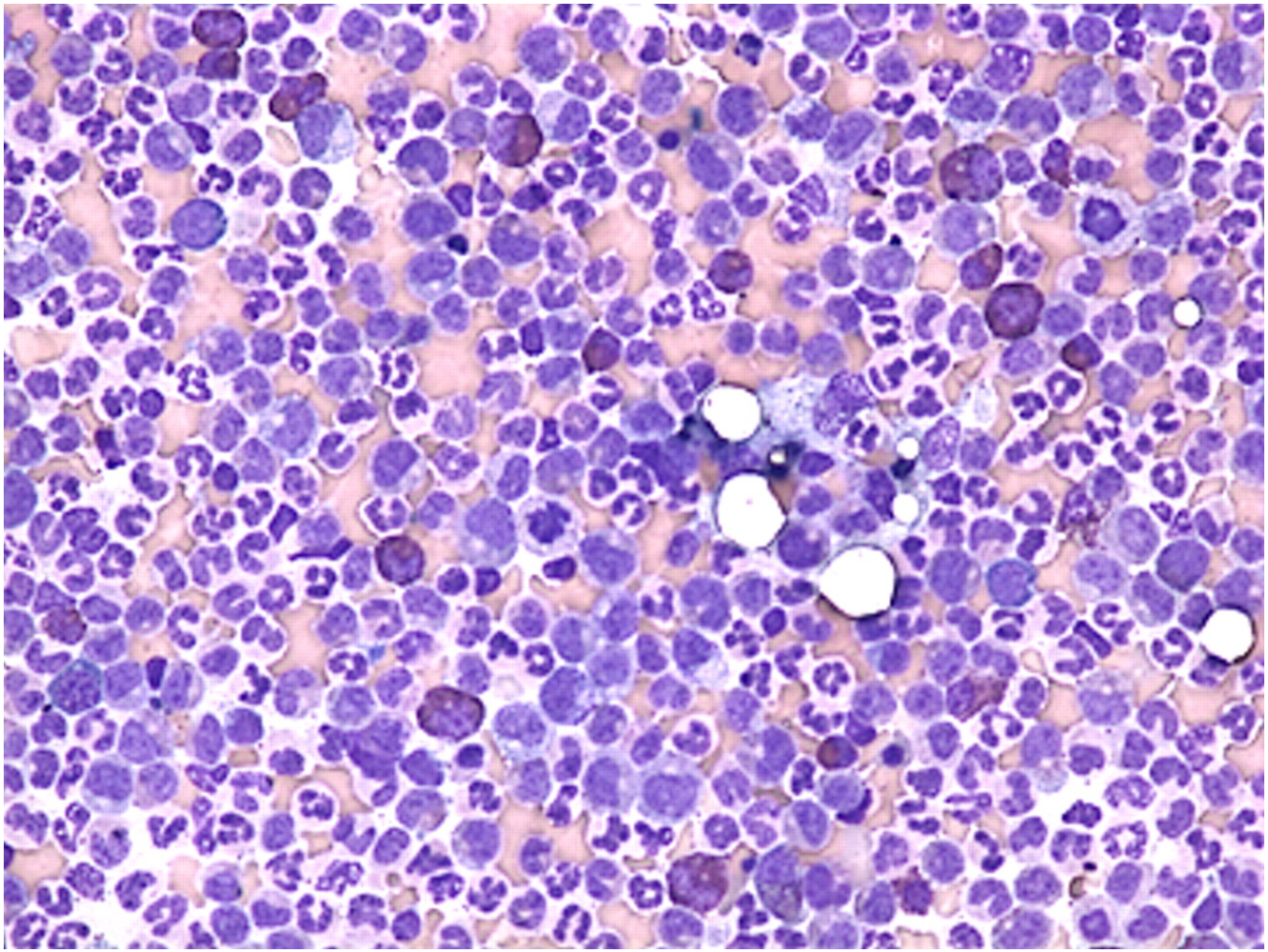
Peter Maslak, ASH Image Bank 2011; 2011-2455

Chronic Phase CML - 3.



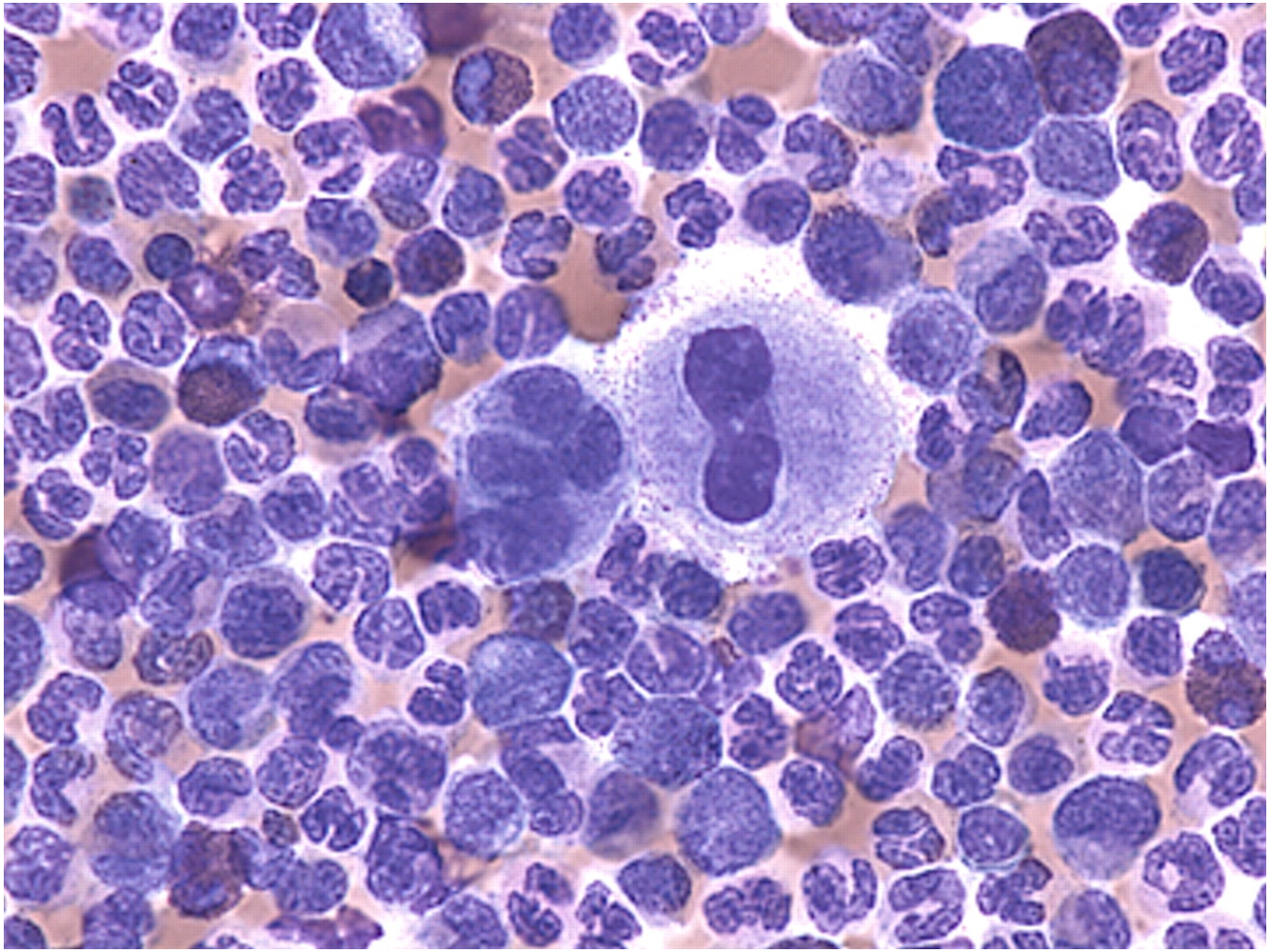
Peter Maslak, ASH Image Bank 2011; 2011-2456

Chronic Phase CML - 1.



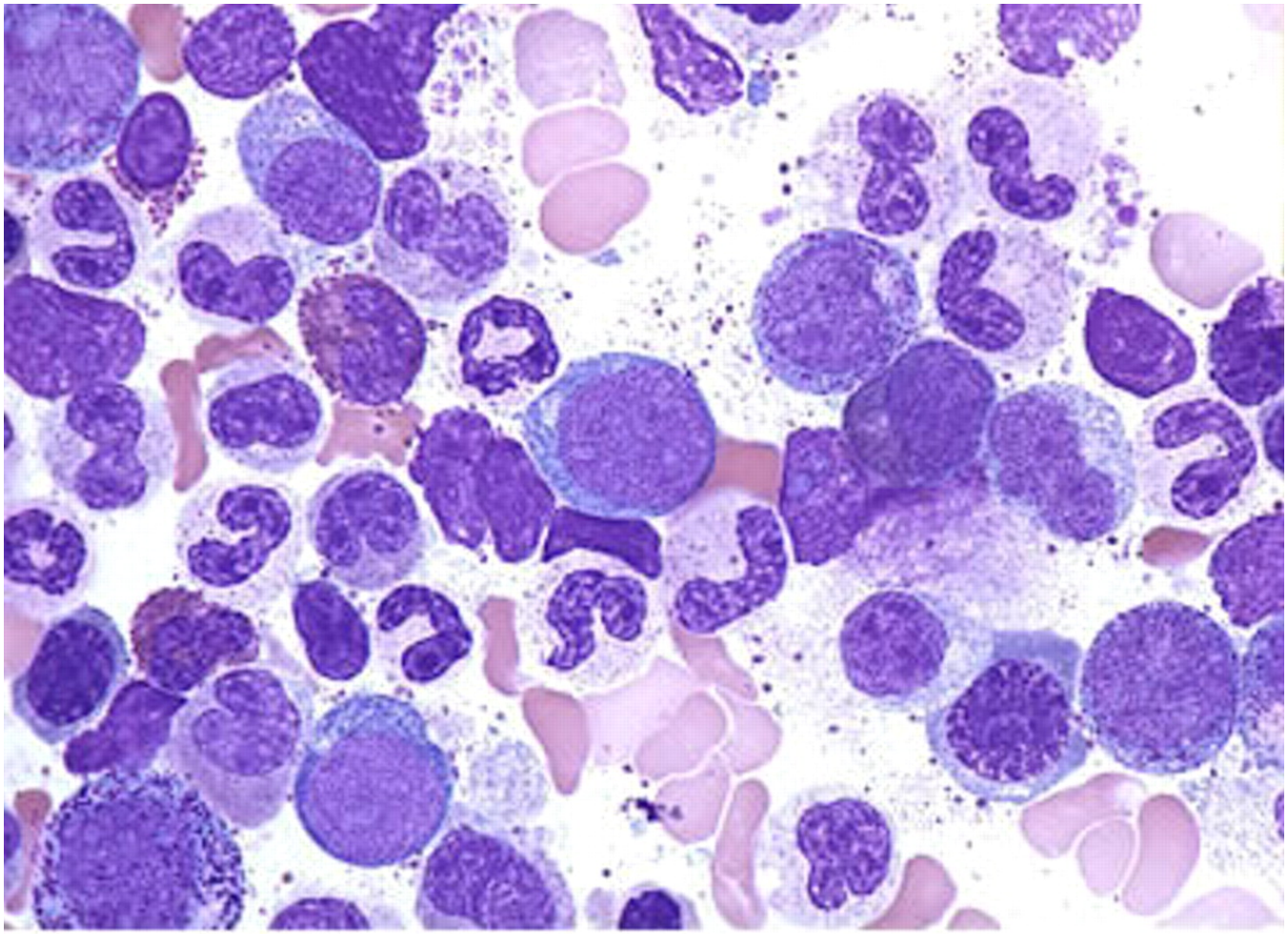
Peter Maslak, ASH Image Bank 2011; 2011-2823

Chronic Phase CML - 3.



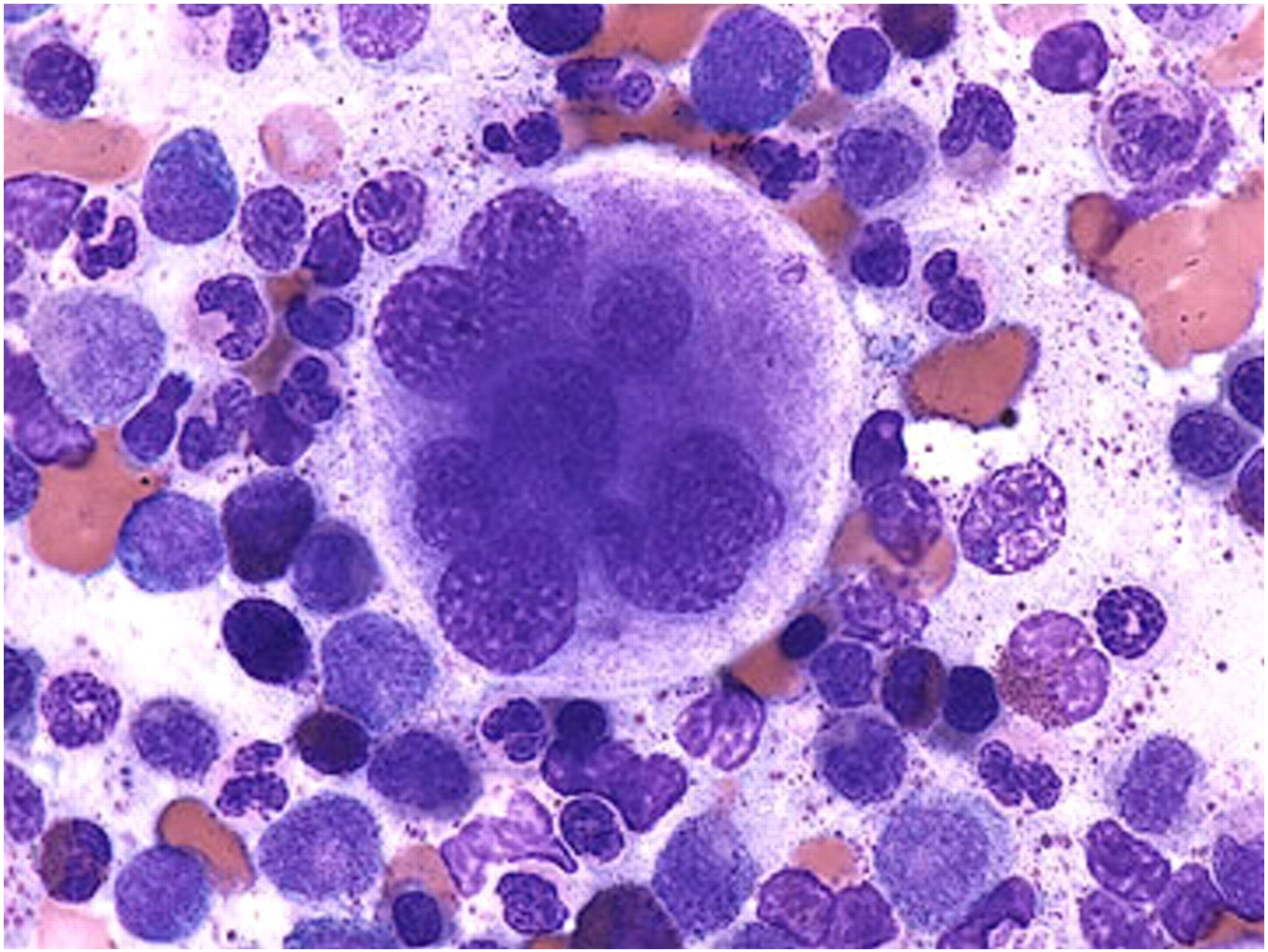
Peter Maslak, ASH Image Bank 2011; 2011-2825

Accelerated Phase CML - 2.



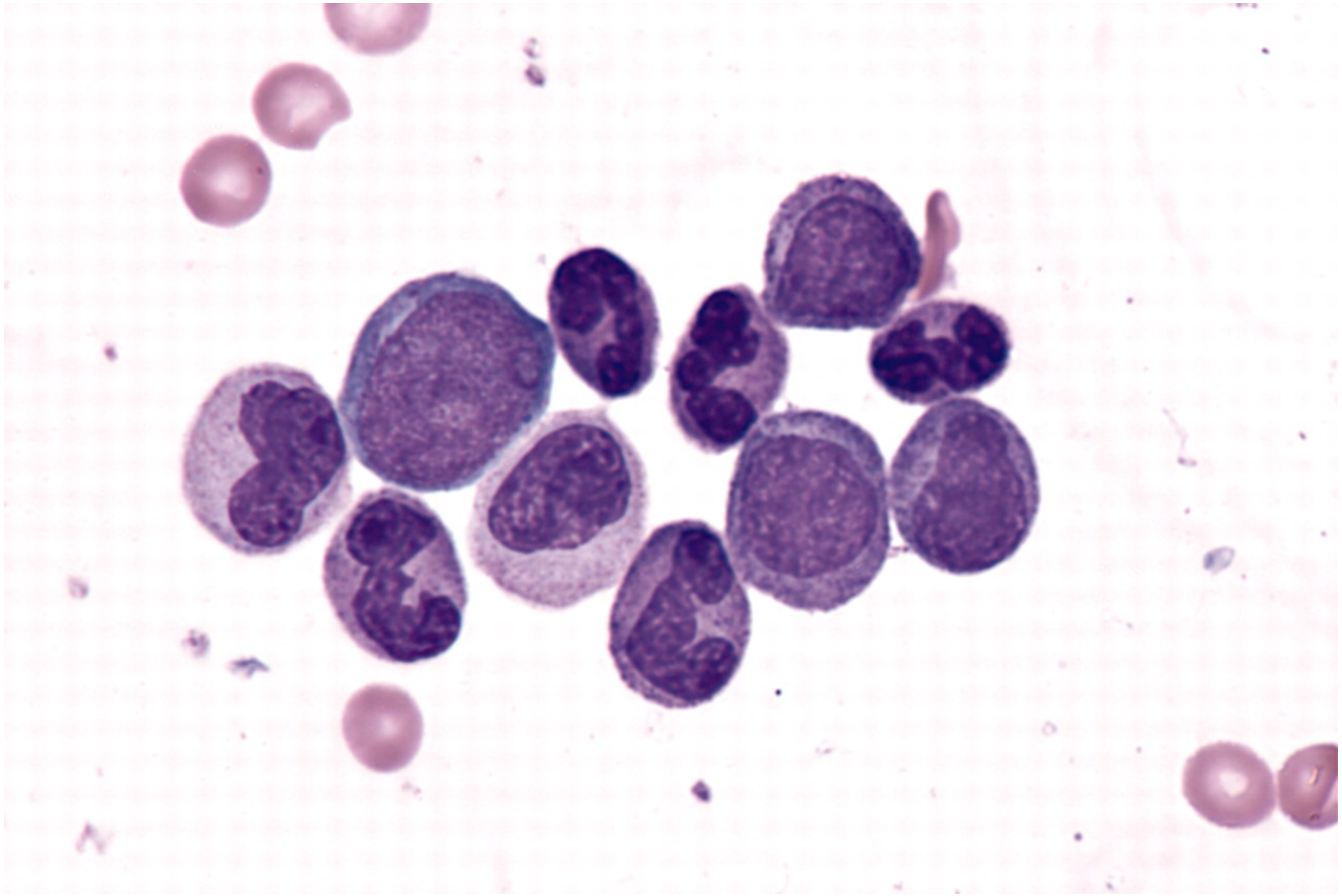
Peter Maslak, ASH Image Bank 2011; 2011-2394

Accelerated Phase CML - 3.



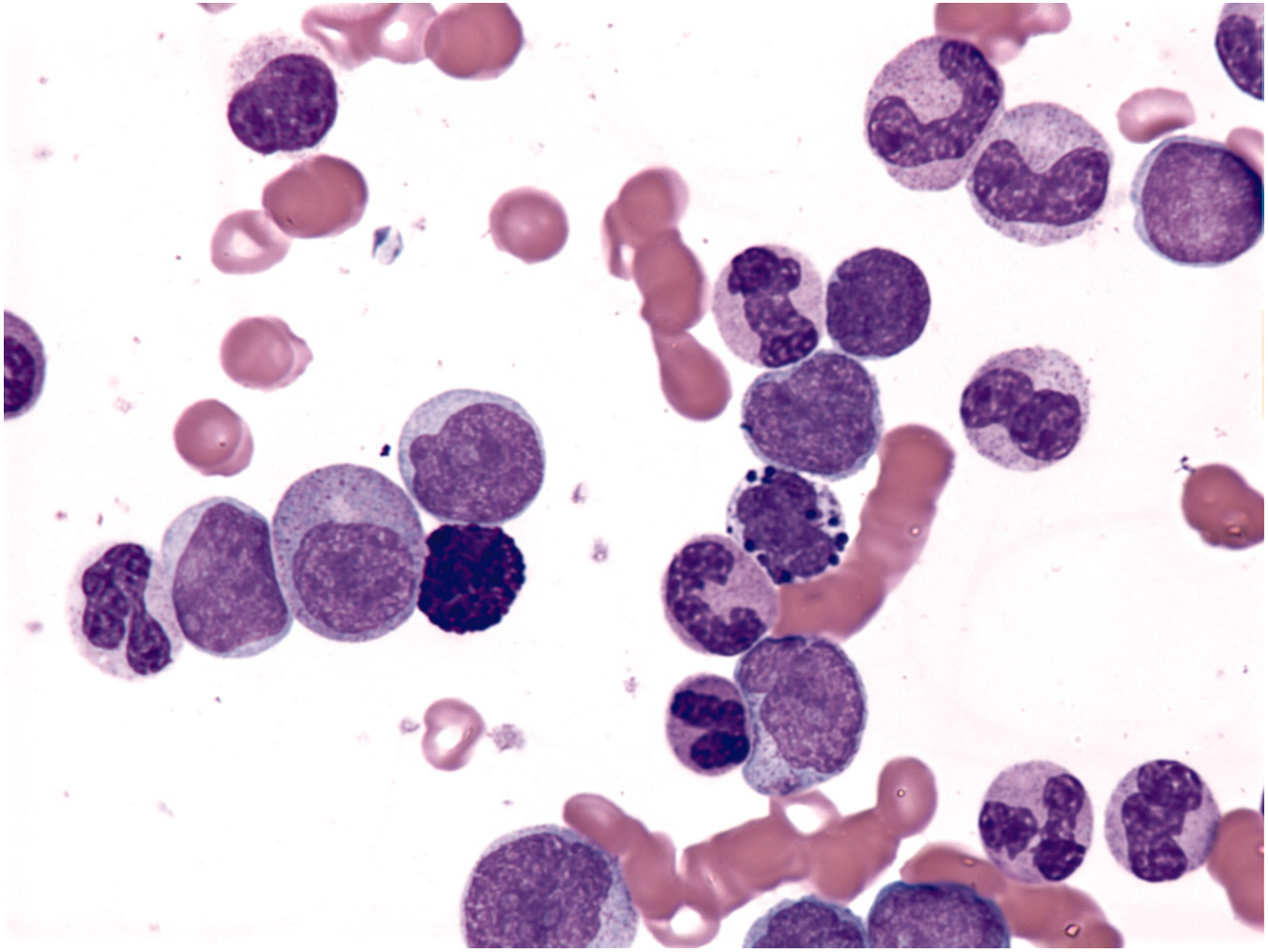
Peter Maslak, ASH Image Bank 2011; 2011-2395

Accelerated Phase of CML - 2.



Peter Maslak, ASH Image Bank 2011; 2011-2813

Accelerated Phase of CML - 3.



Peter Maslak, ASH Image Bank 2011; 2011-2814

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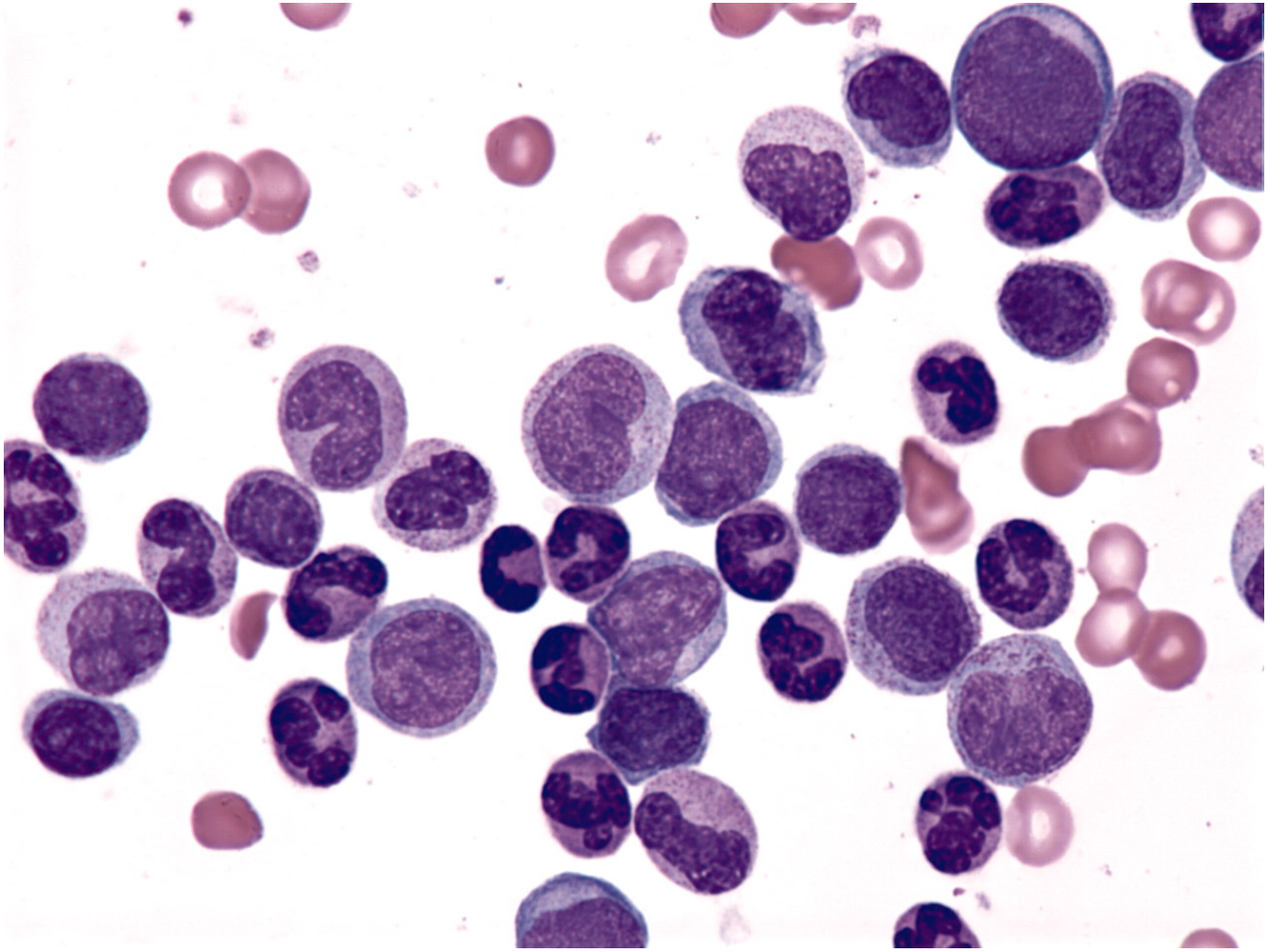
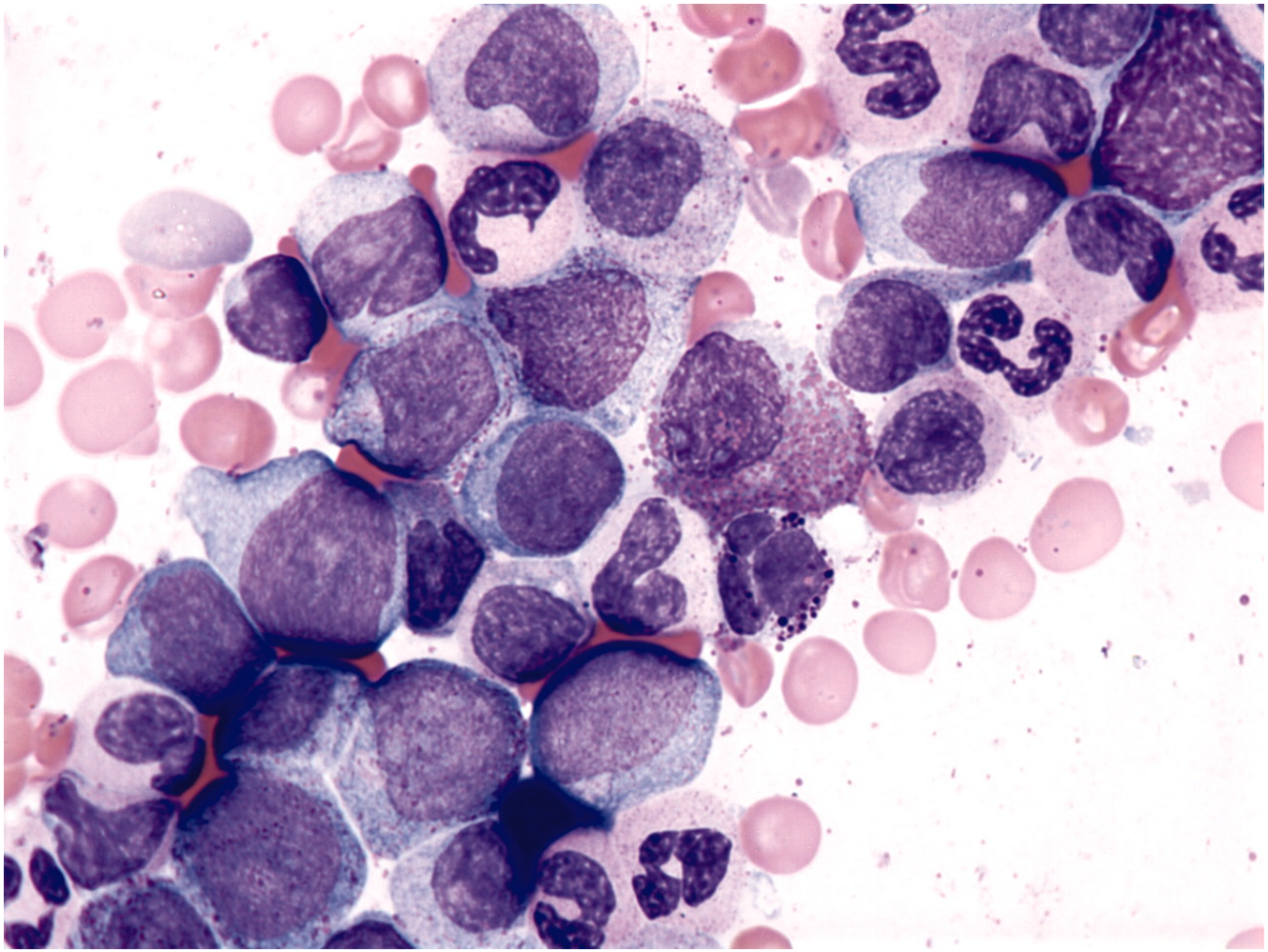


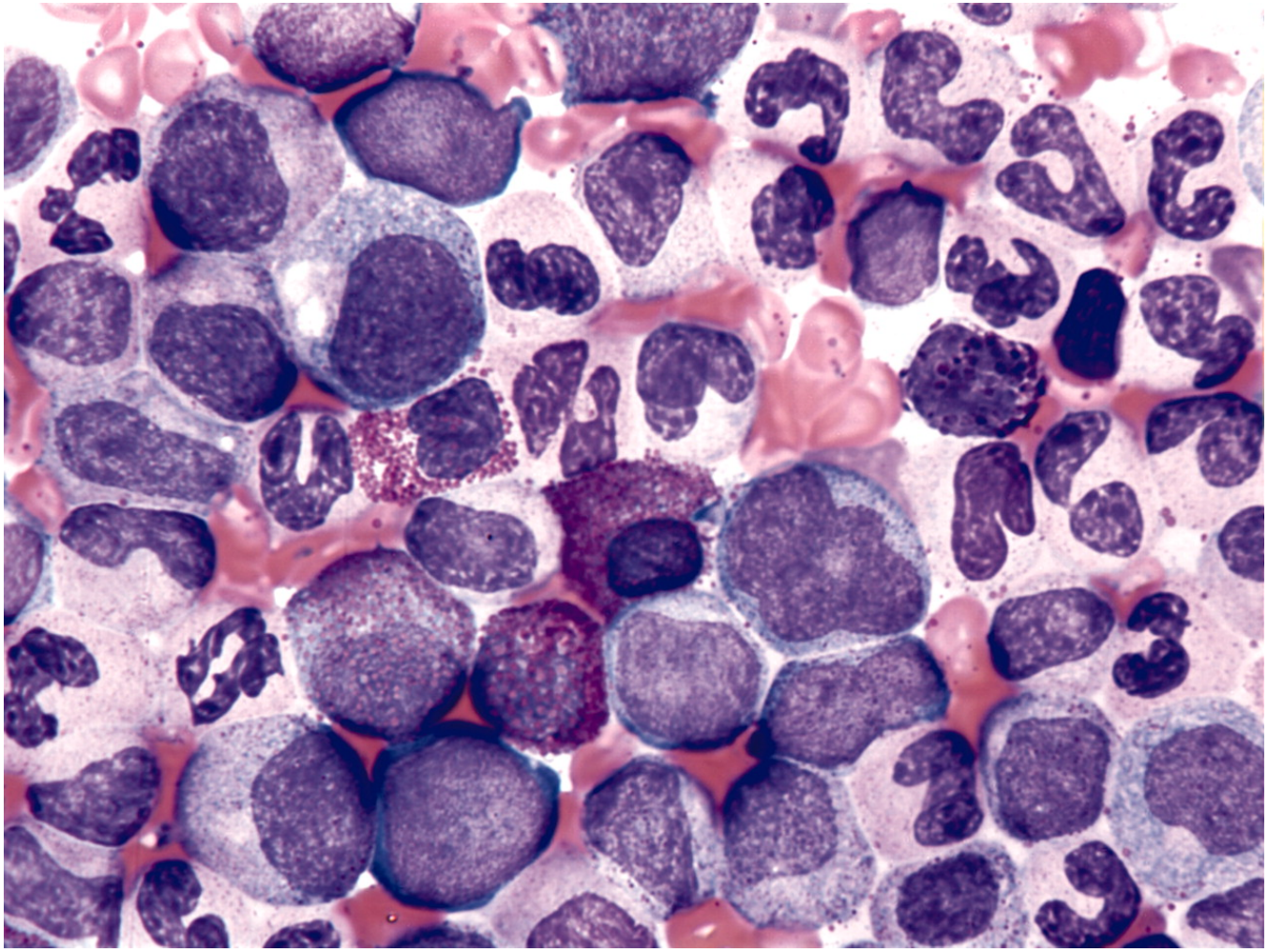
Peter Maslak, ASH Image Bank 2011; 2011-2815

Accelerated Phase of CML - 7.



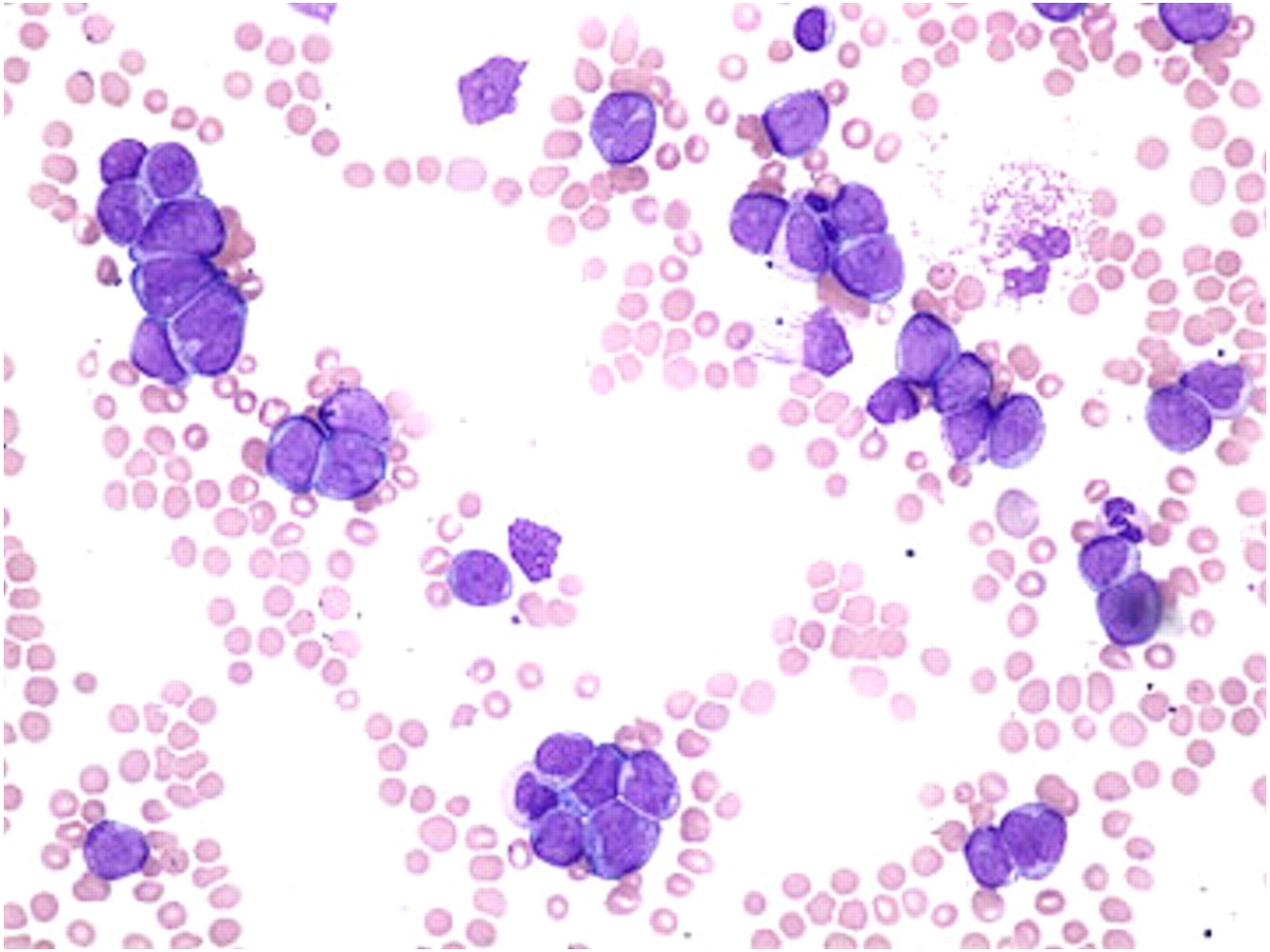
Peter Maslak, ASH Image Bank 2011; 2011-2818

Accelerated Phase of CML - 8.



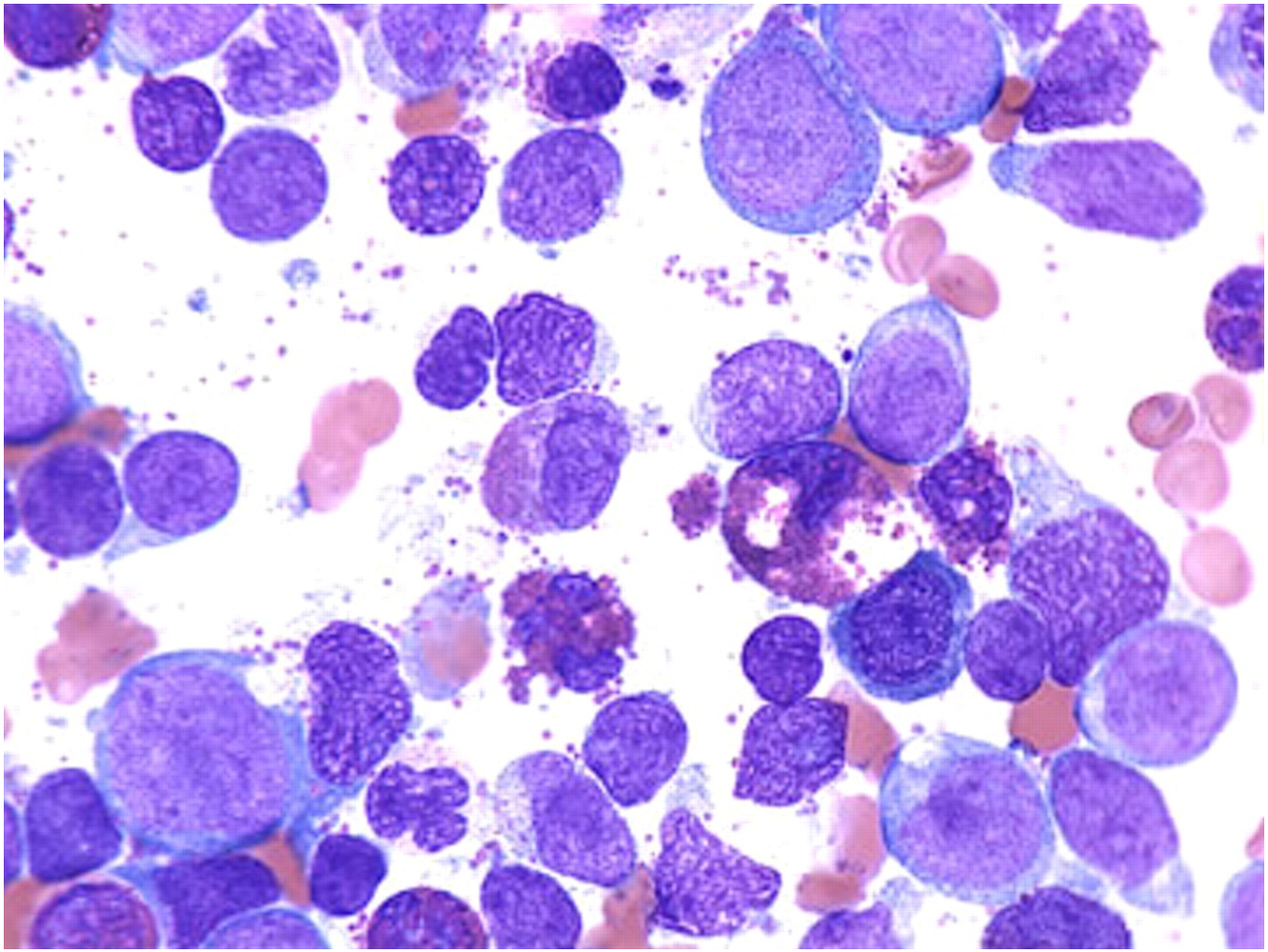
Peter Maslak, ASH Image Bank 2011; 2011-2819

Blast Crisis of CML - 1.



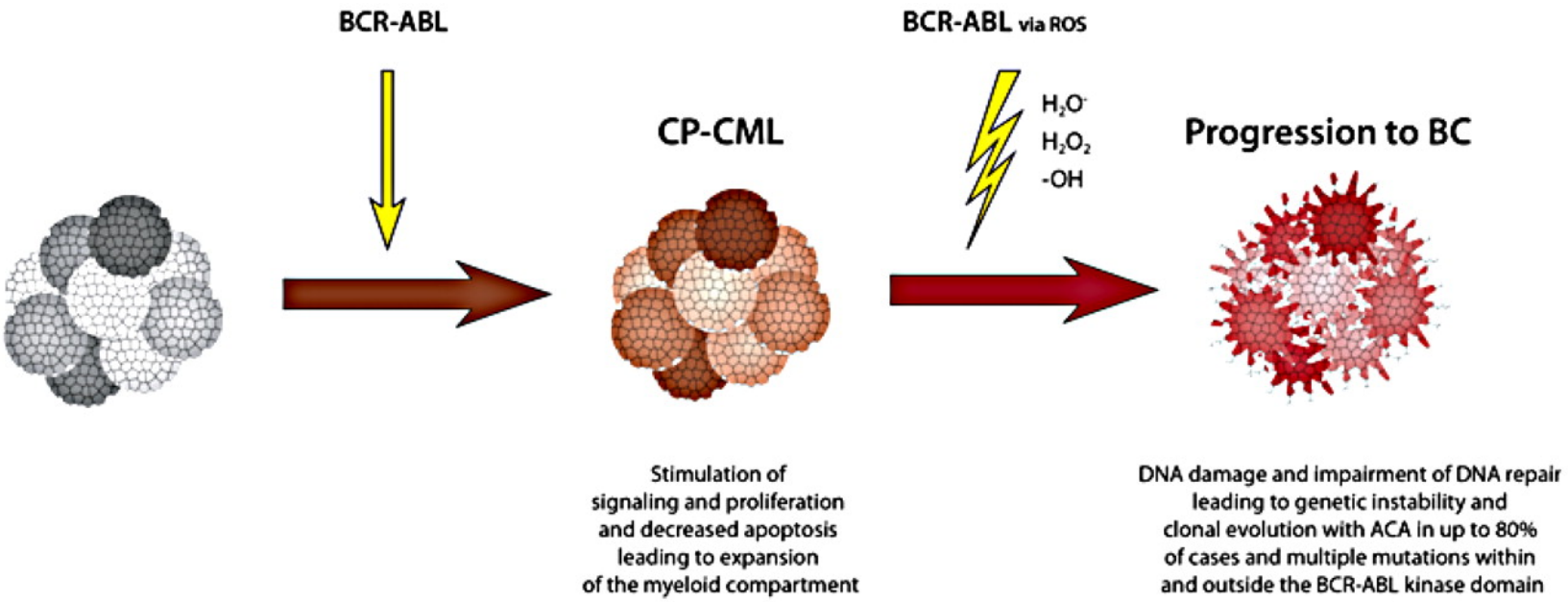
Peter Maslak, ASH Image Bank 2011; 2011-2312

Blast Crisis of CML - 10.



Peter Maslak, ASH Image Bank 2011; 2011-2313

Mechanisms of BCR-ABL activity in CML and blast crisis, leading to stimulation of proliferation and to induction of genetic instability, DNA damage, and impaired DNA repair.

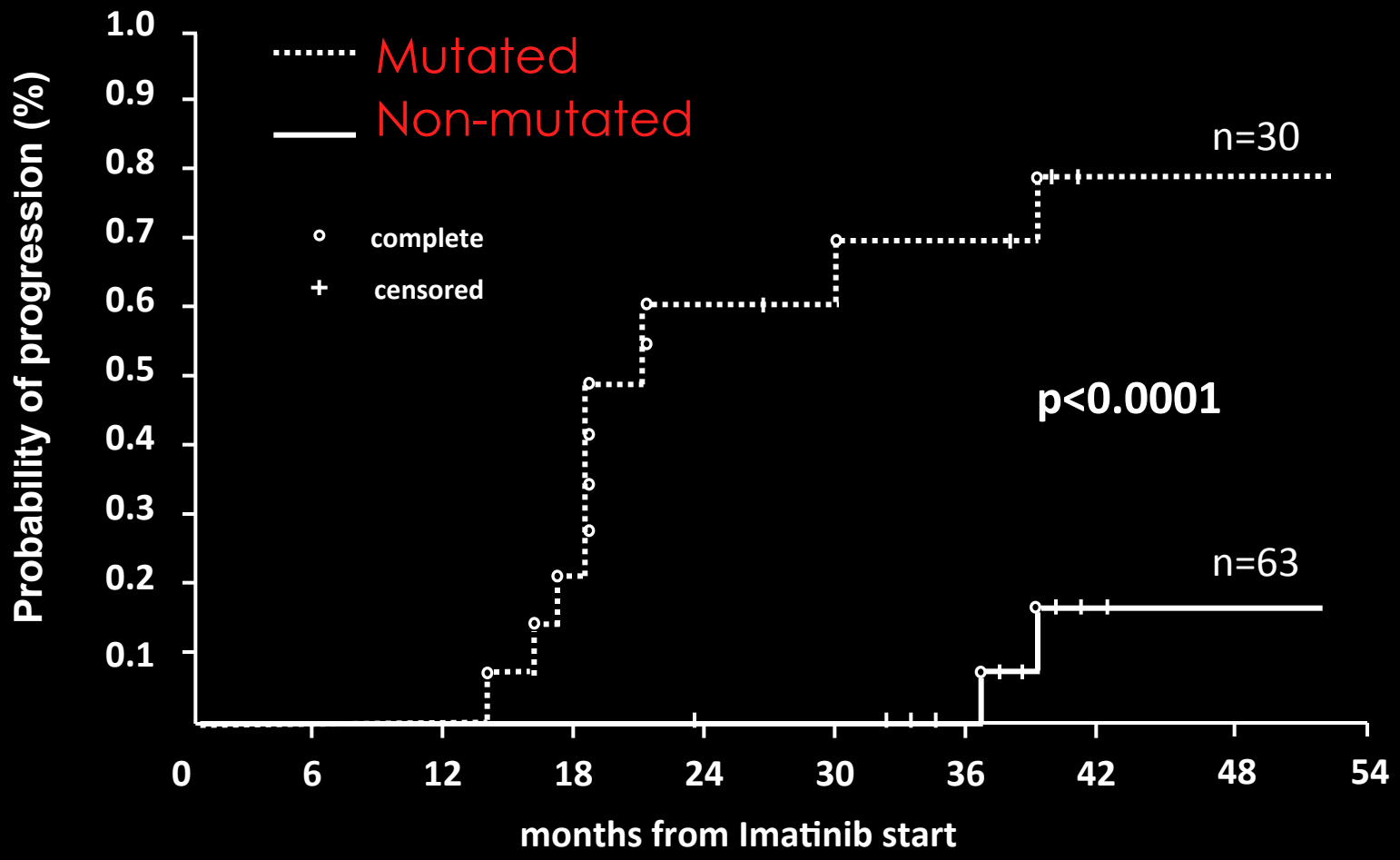


Rüdiger Hehlmann Blood 2012;120:737-747

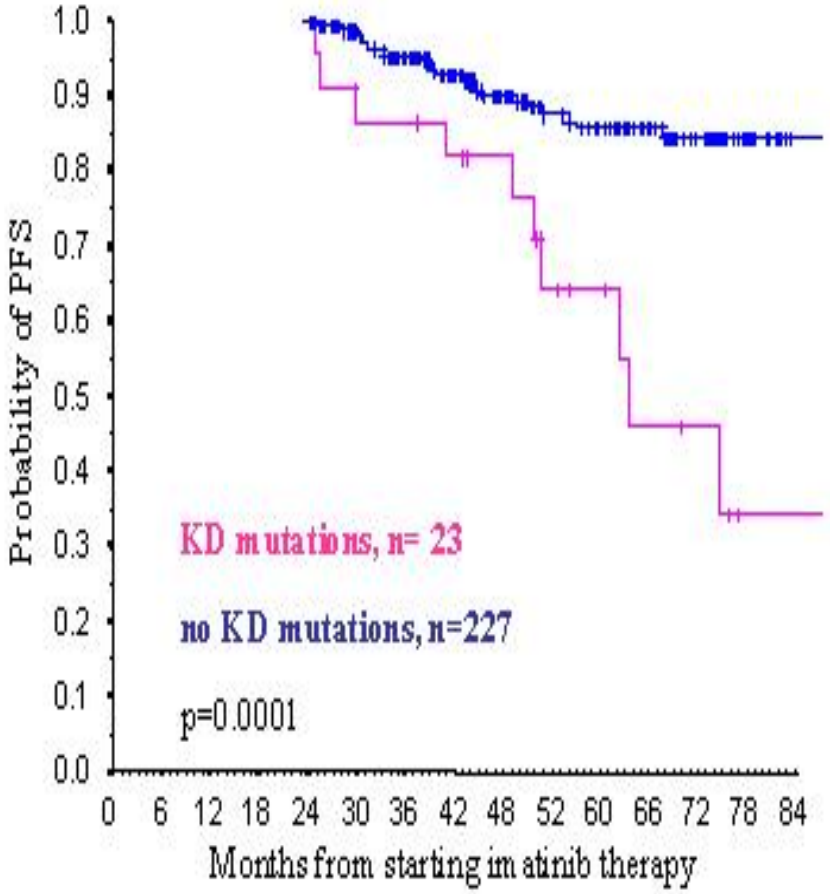
TIME TO PROGRESSION TO AP/BC

CML/002/STI571 trial (GIMEMA-CML WP)

93 late-CP CML pts who lost or never reached CCR



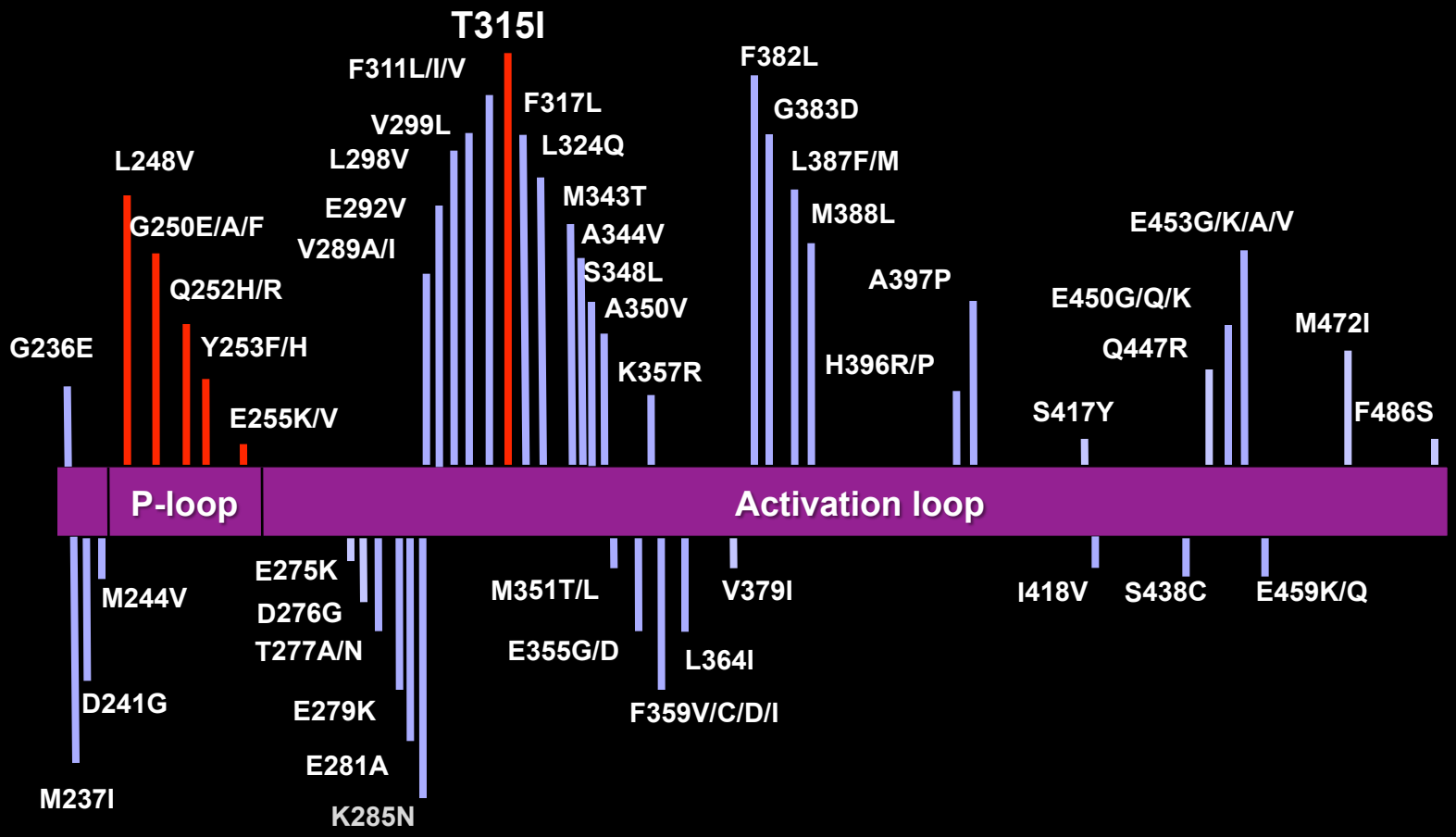
KD mutations w/o other signs of resistance



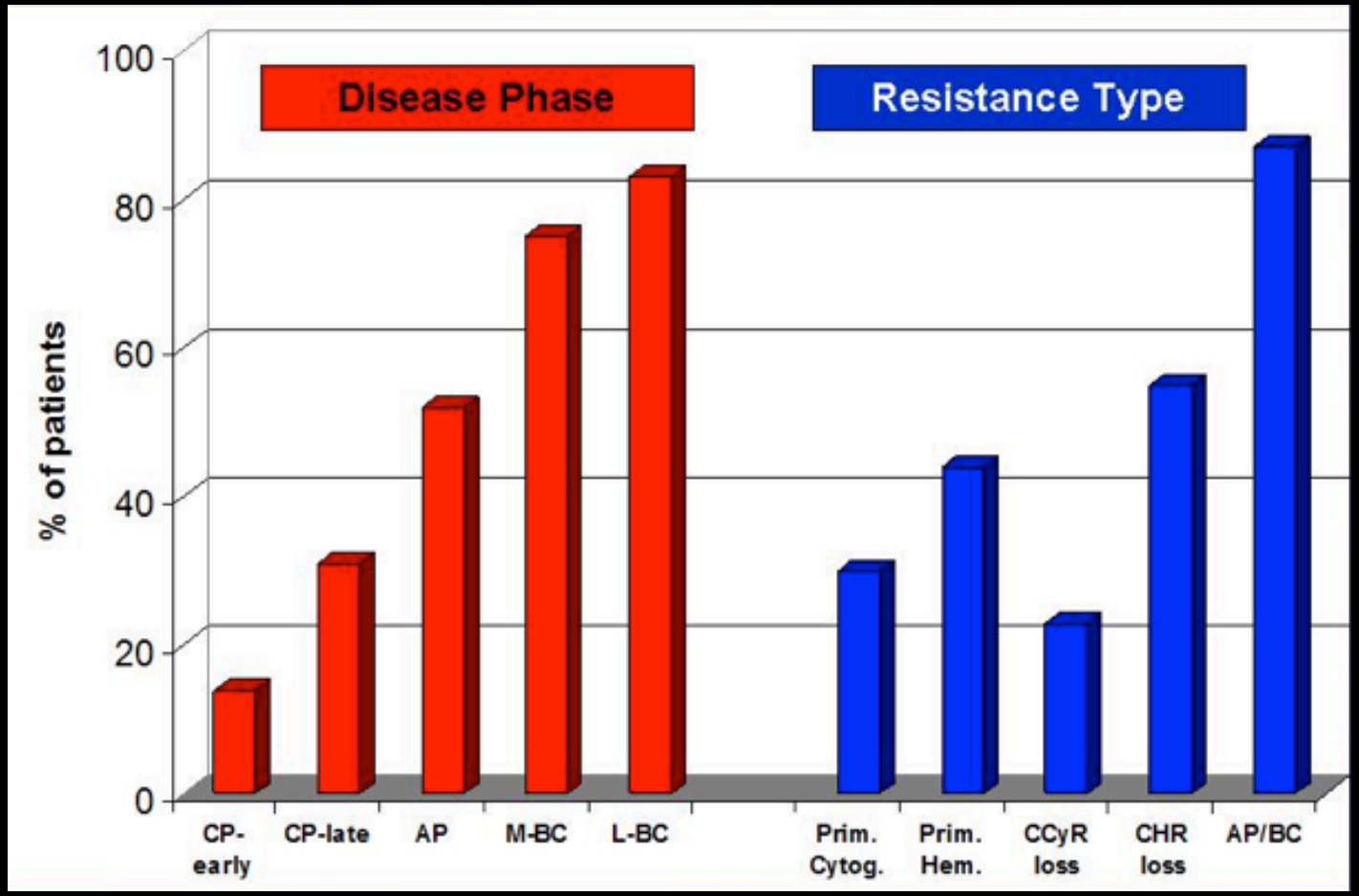
- The detection of mutation antedates any documented rise in the transcript level by a median time of 9 months
- TKD mutations were the only independent predictor for loss of CCyR in patients who receive imatinib as first line therapy (n=204, RR=13.4, p<0.0001)
- TKD mutations were an independent predictor for PFS in CP population (n= 319, RR=2.3, p=0.01)

Khorashad JCO 2008

BCR-ABL Imatinib-Resistance Mutations

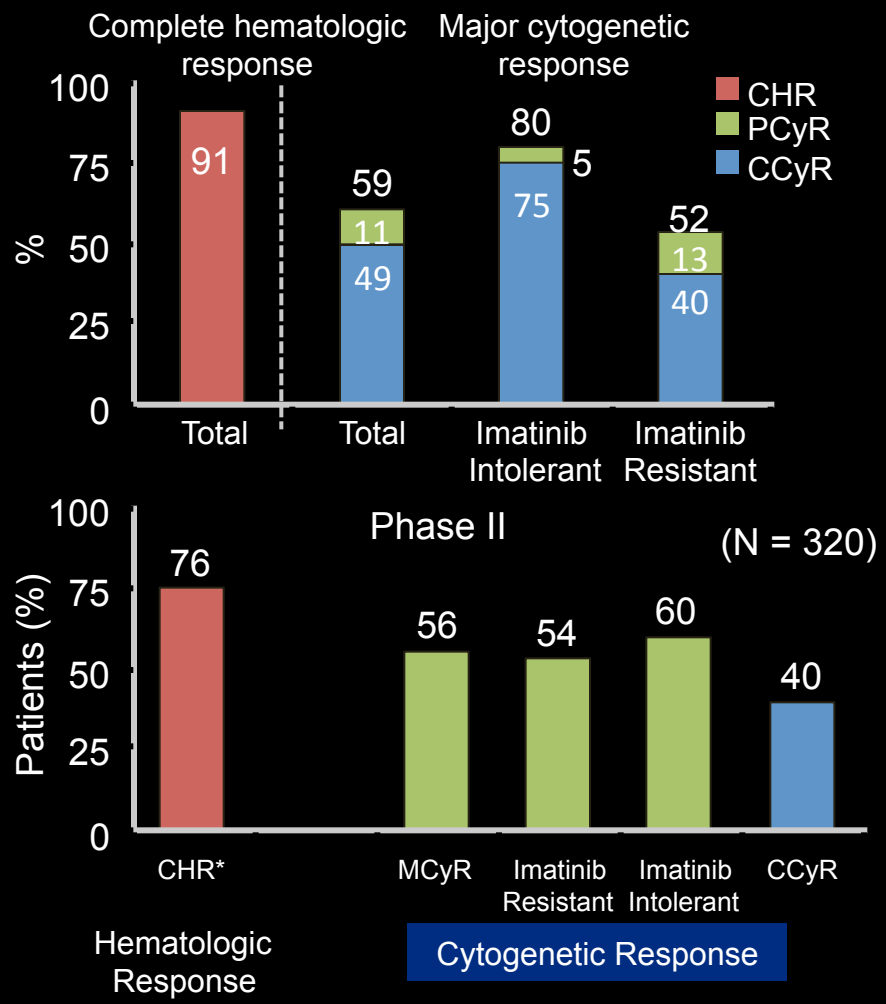


Abl mutations are associated with progression and resistance



Soverini Clin Cancer Res 2006

Dasatinib[1] (*Top*) and Nilotinib[2] (*Bottom*), CML-CP Post-Imatinib



- CHR in >75% of IM-resistant CP CML
- MCyR in ~ 50%
- CCyR in ~ 40%
- Somewhat higher rates of all responses in IM-intolerant cases
- Responses depend on type of mutation and *in vitro* sensitivity to the TKI

1. Hochhaus A, et al. Blood. 2007;109:2303-2309.
2. le Coutre P, et al. Blood. 2008;111:1834-1839.

Response and PFS with 2nd-Generation TKIs in Imatinib-Resistant CP-CML

	Dasatinib[1,2]	Nilotinib[3]	Bosutinib[4]
Number of pts	167*	226	200
Follow-up	Minimum 24 mo	Minimum 24 mo	Median 24 mo
MCyR	63% at 24 mo*	56% at 24 mo	33% at 6 mo
CCyR	50% at 24 mo*	41% at 24 mo	23% at 6 mo
PFS at 24 mo, %	80*	64*	73

*Includes imatinib-intolerant patients.

1. Sprycel® (dasatinib). Official prescribing information. November 2012.
2. Shah NP, et al. J Clin Oncol. 2010;28:15s (abstract 6512).
3. Kantarjian HM et al. *Blood*. 2011;117:1141-1145.
4. Cortes JE et al. *Blood* 2011;118:4567-4576.

TKI Activity Sensitivity Varies Among Agents

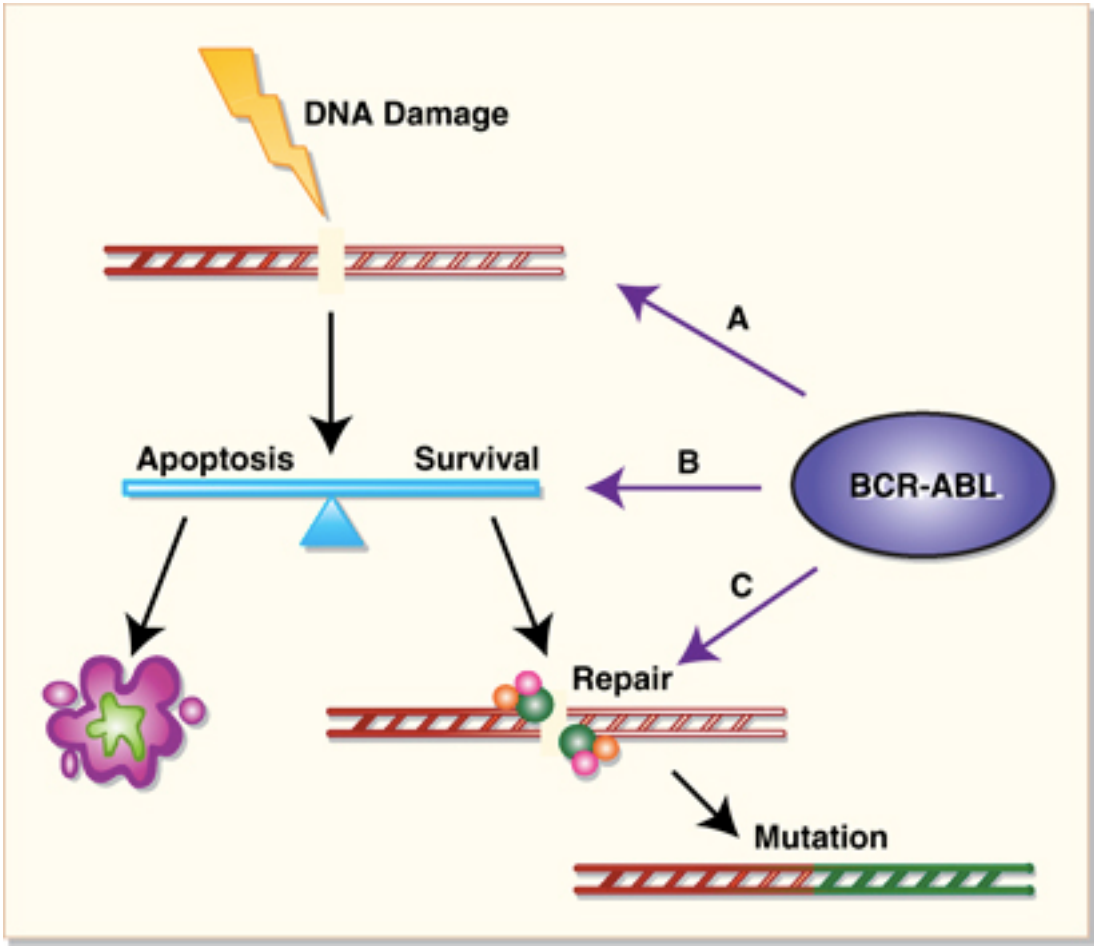
Sensitivity of 18 Imatinib-Resistant BCR/ABL Mutants

Sensitive	≤ 2
Moderately resistant	2.01–4
Resistant	4.01-10
Highly resistant	> 10

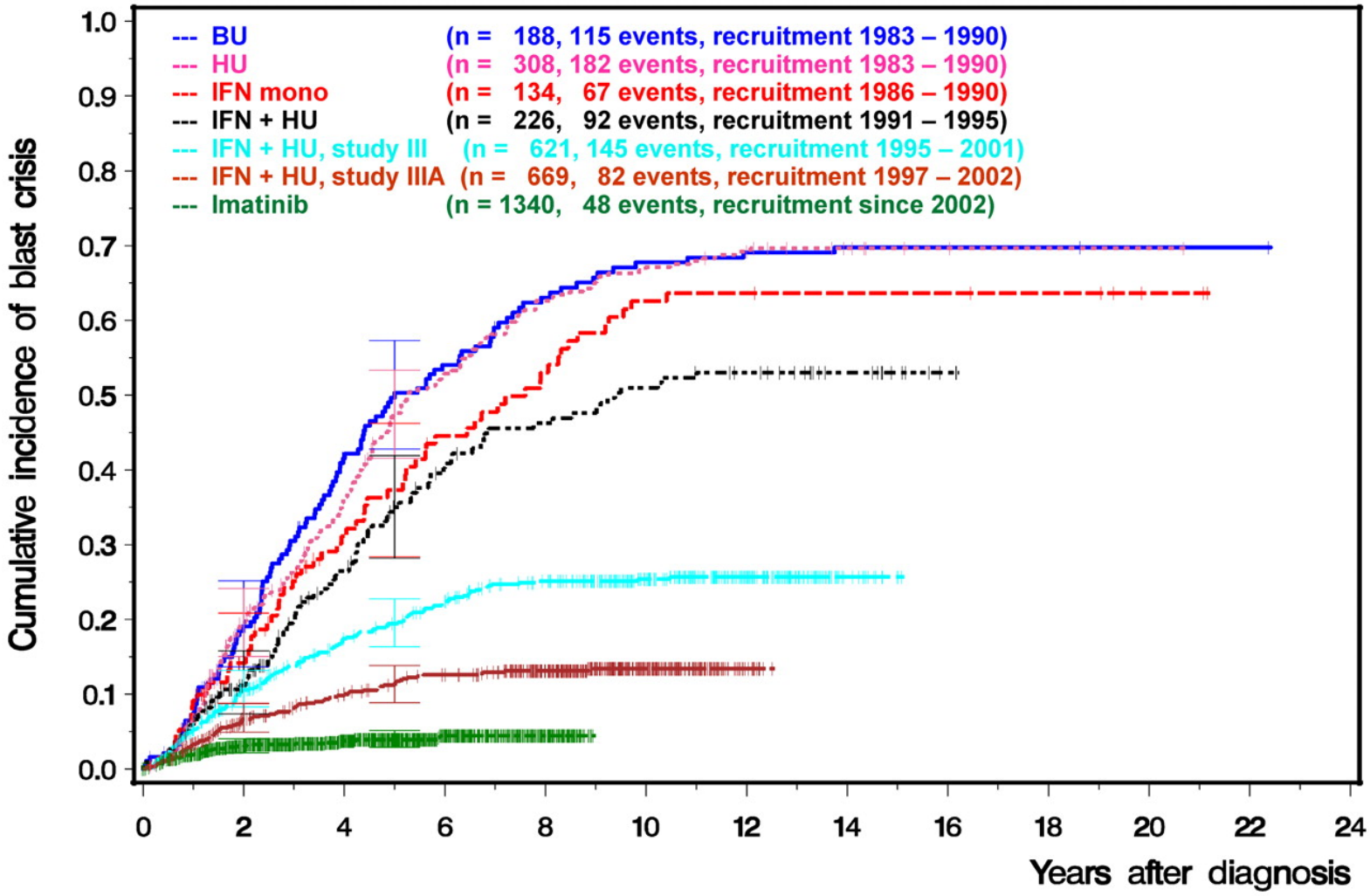
		IC_{50} fold increase (WT = 1)			
		Bosutinib	Imatinib	Dasatinib	Nilotinib
	Parental	38.31	10.78	> 50	38.43
	WT	1	1	1	1
P-LOOP	L248V	2.97	3.54	5.11	2.80
	G250E	4.31	6.86	4.45	4.56
	Q252H	0.81	1.39	3.05	2.64
	Y253F	0.96	3.58	1.58	3.23
	E255K	9.47	6.02	5.61	6.69
	E255V	5.53	16.99	3.44	10.31
C-Helix	D276G	0.60	2.18	1.44	2.00
	E279K	0.95	3.55	1.64	2.05
ATP binding region (drug contact sites)	V299L	26.10	1.54	8.65	1.34
	T315I	45.42	17.50	75.03	39.41
	F317L	2.42	2.60	4.46	2.22
SH2-contact	M351T	0.70	1.76	0.88	0.44
Substrate binding region (drug contact sites)	F359V	0.93	2.86	1.49	5.16
A-LOOP	L384M	0.47	1.28	2.21	2.33
	H396P	0.43	2.43	1.07	2.41
	H396R	0.81	3.91	1.63	3.10
	G398R	1.16	0.35	0.69	0.49
C terminal lobe	F486S	2.31	8.10	3.04	1.85

Redaelli S, et al. *J Clin Onc.* 2009;27(3):469-471.

BCR/ABL and DNA mutation

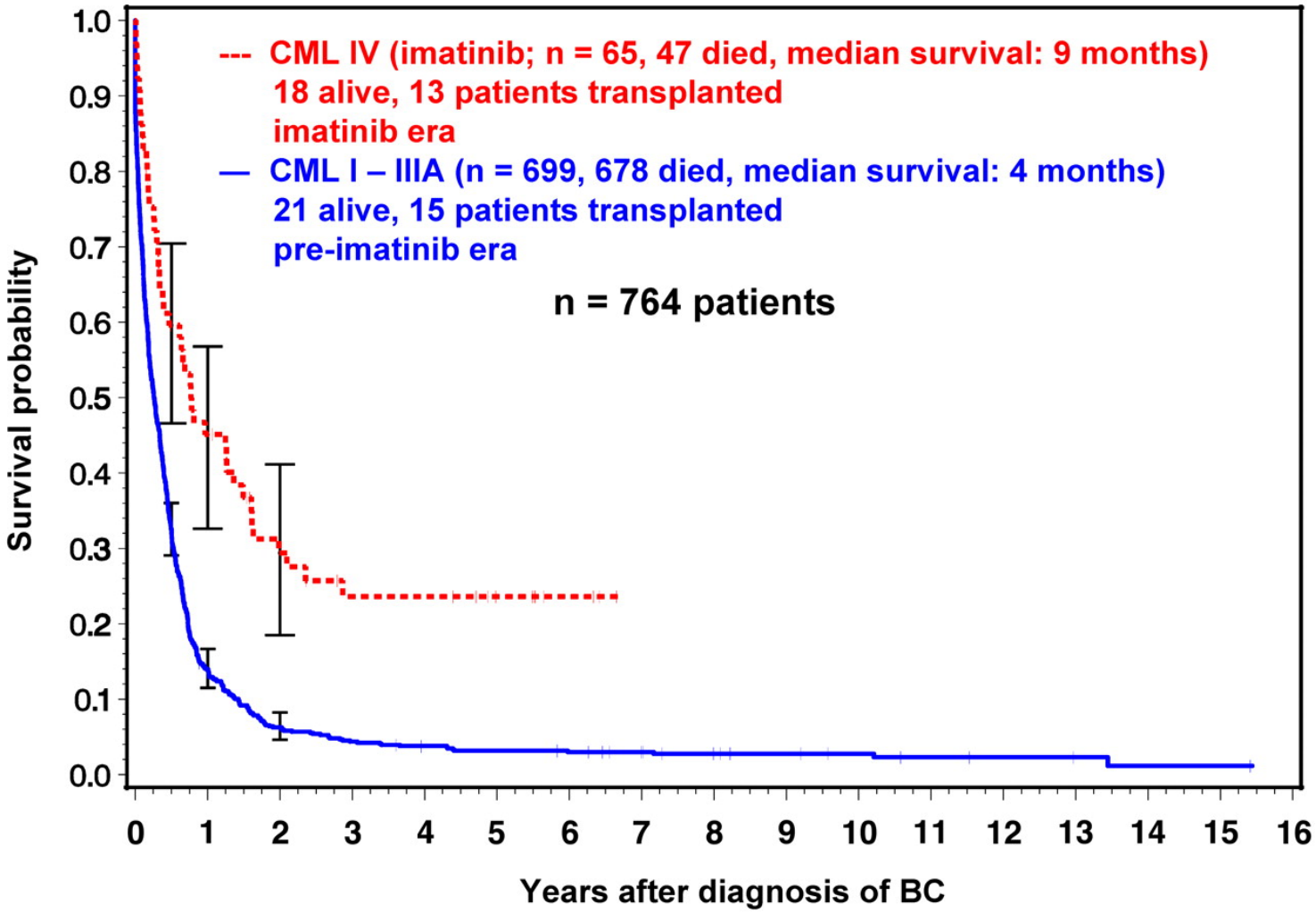


Prevention of BC by more effective treatment in early CP as shown by the cumulative incidence of blast crisis (German CML Study Group experience 1983-2011).



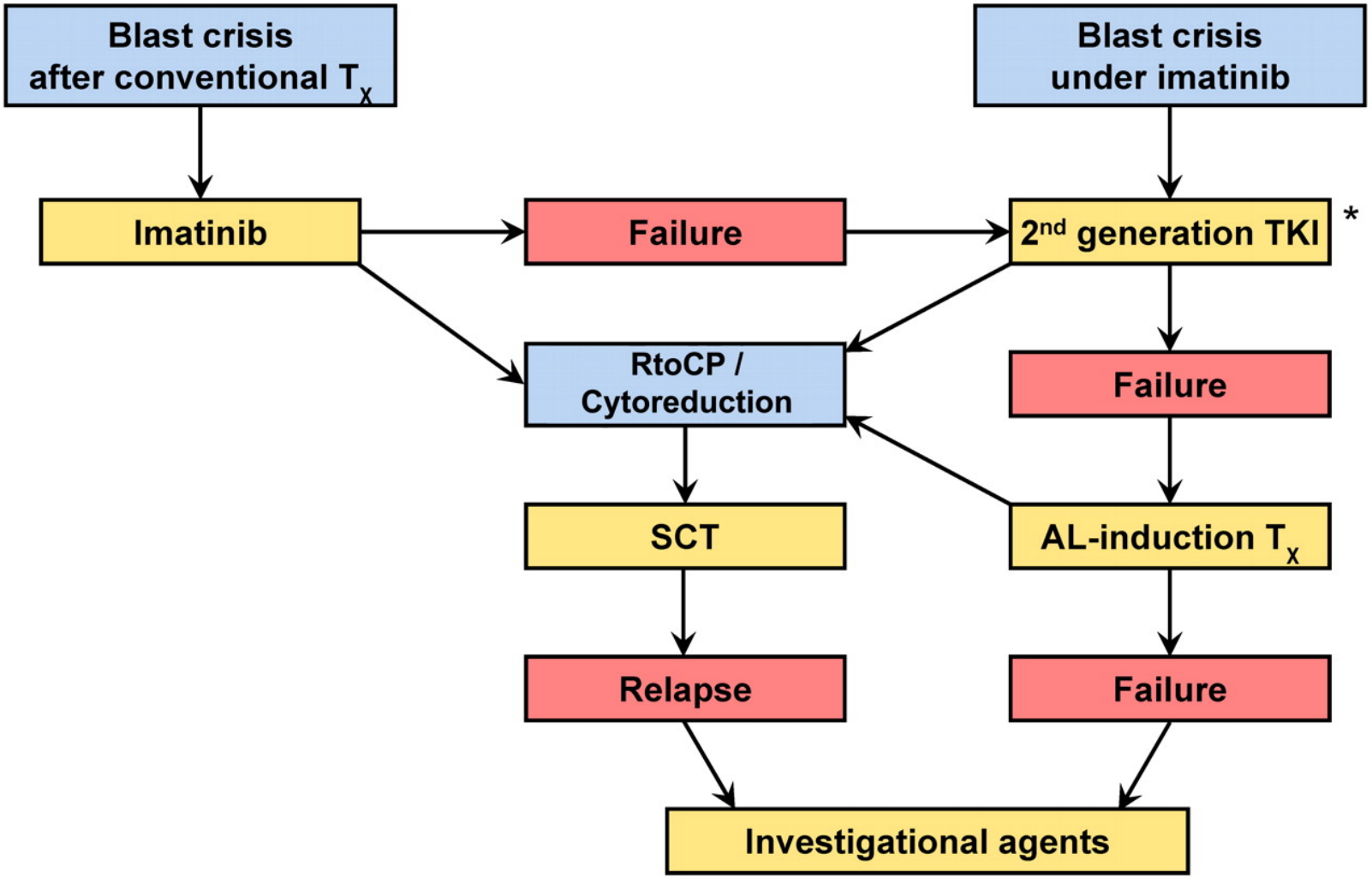
Rüdiger Hehlmann Blood 2012;120:737-747

Survival with BC in the preimatinib and imatinib eras.



Rüdiger Hehlmann Blood 2012;120:737-747

Management algorithm of CML-BC.



Rüdiger Hehlmann Blood 2012;120:737-747

Table 1

BC diagnostics

	Test rationale
Test at diagnosis of BC	
CBC with differential and bone marrow	Proportions of blasts, promyelocytes, and basophils?
Flow cytometry and/or cytochemistry	Myeloid or lymphoid phenotype?
Cytogenetics	Clonal evolution?
Molecular genetics	Mutation profile? Choice of TKI
Donor search (if applicable)	Allo-SCT
Follow-up under therapy	
Blood count and differential	Return to CP?
Bone marrow and cytogenetics	Ascertainment of second CP
Molecular genetics	Monitoring of BCR-ABL transcript levels under TKI and after allo-SCT
In lymphoid BC: CSF cytology	Intrathecal instillation for neuroprophylaxis

BC indicates blast crisis; CP, chronic phase; CSF, cerebrospinal fluid; CBC, complete blood count; and TKI, tyrosine kinase inhibitor.

Table 2

Treatment of BC by BCR-ABL TKI

Drug	Patients	CR, %	Survival	
		MBC/LBC	12 mo, %	Median, mo
Imatinib				
300-600 mg[28]	58 (20 LBC)	12	NA	NA
400-600 mg[49]	229 (MBC only)	16	30	6.9
300-1000 mg[50]	75 (10 LBC)	16	22	6.5
600 mg[51]	30	13	36	10
600 mg[52]	92 (20 LBC)	17	29	7
Dasatinib				
50-100 mg bid[54]	33 (10 LBC)	52/90	~ 22*	~ 6
70-100 mg bid[55]	157 (48 LBC)	35/56†	49/30	11.8 (5.3)
70 bid vs 140 mg qd[56]	210 (61 LBC)	25-28/40-50	34-39/39-46	8 (10)
Nilotinib				
Up to 1200 mg[58]	33 (9 LBC)	18	NA	NA
400-600 mg bid[59]	136 (31 LBC)	40	42	10

CR indicates cytogenetic response (includes complete, partial, minimal, and minor response when available); LBC, lymphoid blast crisis; NA, not available; MBC, myeloid blast crisis; bid, twice a day; and qd, daily.

* At 18 months.

† Only complete and major cytogenetic response listed. Updated from Hehlmann and Saussele.[5]

Table 3

Investigational approaches (selection)

Mode of action	Agent(s)	Phase	Target(s)
Third-generation TKI	Ponatinib[53]	II	Pan-BCR-ABL including T315I
	DCC-2036[72]	I	Abl-switch pocket
PP2A activation	Fingolimod (FTY720)[75]	Preclinical	PP2A
	SET antagonist OP449[76]	Preclinical	SET
	CIP2A inhibitor[74]	Preclinical	CIP2A
Survival of LSCs	BCL6 + TK inhibitors[78]	Preclinical	BCL6 + BCR-ABL
	HIF1α inhibitor[80]	Preclinical	HIF1α
	IL1 RAP antibodies[86]	Preclinical	IL1 RAP
	Smoothened inhibitors in combination with TKI[83] (dasatinib, nilotinib)	Preclinical	Smoothened (hedgehog pathway) + BCR-ABL
	Jak2 inhibitor + dasatinib[85]	Preclinical	Jak2 + BCR-ABL, LSC
Activation of apoptosis	BCL2-inhibitor ABT-737[88]	Preclinical	Antiapoptotic proteins
	Triptolide[87,88]	Preclinical	Antiapoptotic proteins
	Dual-kinase inhibitor ON044580[91]	Preclinical	BC, T315I
	MEK inhibitor PD184352 + farnesyltransferase inhibitor BMS-214662[89]	Preclinical	MEK1, MEK2, RAS
Others	Omacetaxine[92]	II / III	BCR-ABL, T315I, BC

LSC indicates leukemia stem cell; and MEK, mitogen-activated protein kinase kinase.

Table 4

Early prediction of progression

Study	n	Baseline	3 mo	6 mo	12 mo	End point
Historical						
Mahon et al (IFN)[121]	116	NA	CHR	NA	NA	MCR
Baccarani et al (imatinib, review)[8]	NA	NA	CHR	NA	CCR	OS
Baseline						
Hasford et al (EUTOS)[102]	2060	High risk	NA	NA	NA	CCR*
Fabarius et al[15]	1151	Major route ACA	NA	NA	NA	OS
Verma et al[103]	1292	$P190^{BCR-ABL}$	NA	NA	NA	PFS
Clonal evolution						
Baccarani et al (review)[8]	NA	NA	NA	Any time	NA	OS
Response						
Hanfstein et al[122]	692	NA	MR 10%, MCR	MR 1%, CCR	NA	OS
Hehlmann et al[42]	1014	NA	NA	NA	MMR (MR 0.1%)	OS
Marin et al[123]	282	NA	MR 9.84%	MR 1.67%	MR 0.53%	OS
Jabbour et al[124]	435	NA	MCR	CCR	NA	OS

Patients at increased risk of progression can be detected by baseline markers, clonal evolution, and early molecular or cytogenetic response indicators. Failure to reach the defined response landmarks at 3, 6, and 12 months identifies a group of high risk patients with higher progression risks (25%-33% of patients at 3 months[122,123]) who might benefit from an early change of therapy. Percentages are according to international scale.[130]

CHR indicates complete hematologic remission; MCR, major cytogenetic remission; NA, not applicable; OS, overall survival; ACA, additional cytogenetic aberrations; PFS, progression-free survival; and MR, molecular response.

* CCR at 18 months.