Long-term side effects of TKIs

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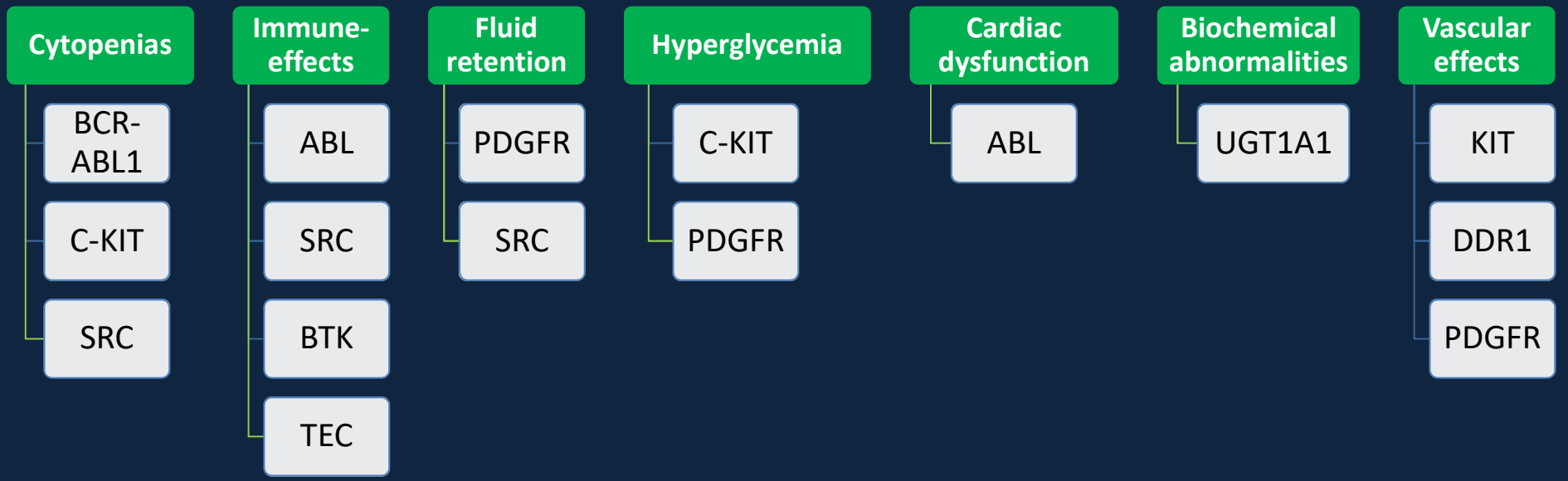
Targeted Strategy

Less Targeted Strategy

BCR-ABL1 Inhibitors: Putative Targets and Associated Adverse Events



“Targets” of Imatinib, Nilotinib, and Dasatinib

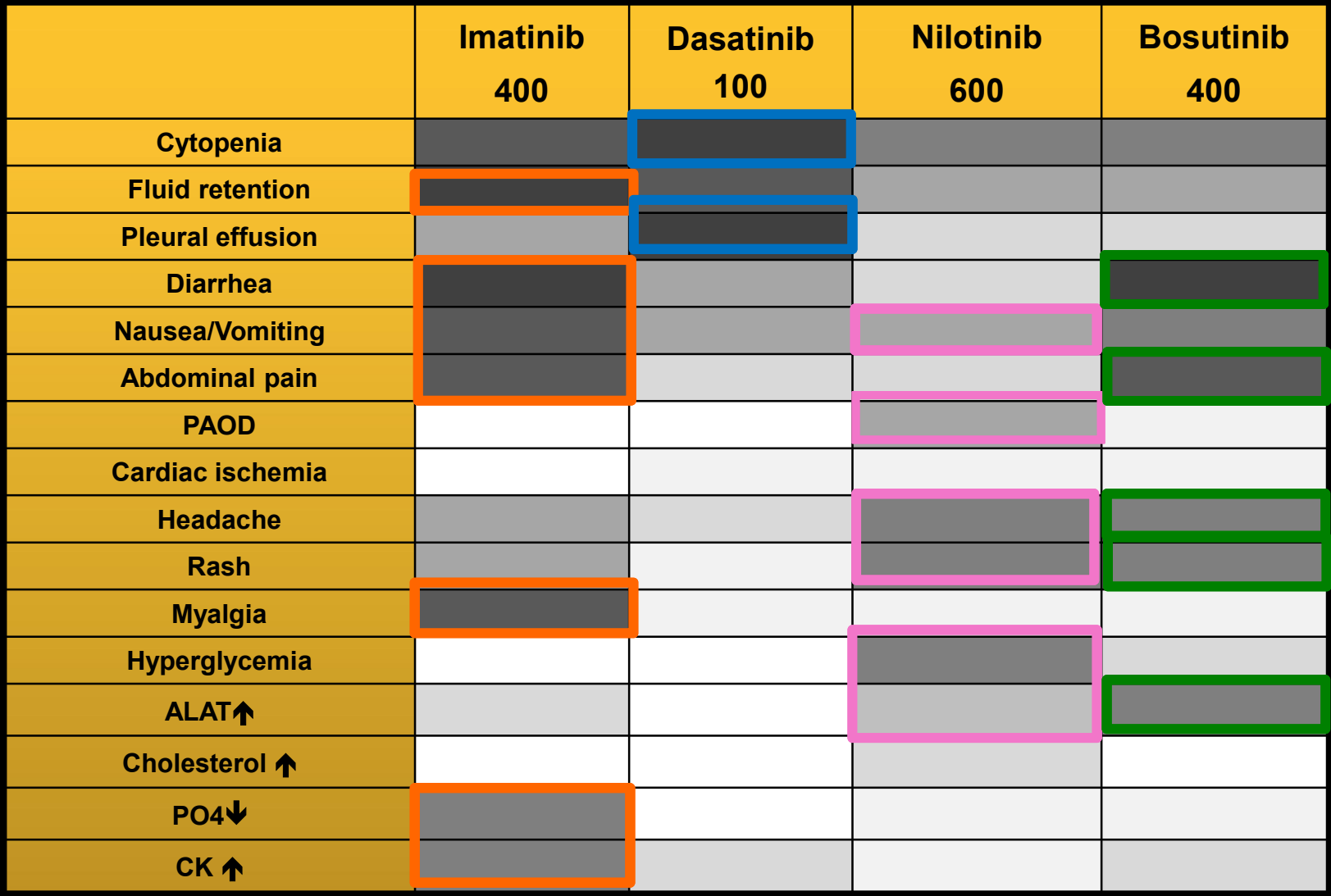
Imatinib	Nilotinib	Dasatinib		
ABL	ABL	ABL	DDR1	MYT1
ARG	ARG	ARG	DDR2	NLK
BCR-ABL	BCR-ABL	BCR-ABL	ACK	PTK6/Brk
KIT	KIT	KIT	ACTR2B	QIK
PDGFR	PDGFR	PDGFR	ACVR2	QSK
DDR1	DDR1	SRC	BRAF	RAF1
NQO2	NQO2	YES	EGFR/ERBB1	RET
		FYN	EPHA2	RIPK2
		LYN	EPHA3	SLK
		HCK	EPHA4	STK36/ULK
		LCK	EPHA5	SYK
		FGR	FAK	TAO3
		BLK	GAK	TESK2
		FRK	GCK	TYK2
		CSK	HH498/TNNI3K	ZAK
		BTK	ILK	
		TEC	LIMK1	
		BMX	LIMK2	
		TXK		

Hantschel et al. Leuk Lymphoma 49; 615, 2008.

Early adverse events

Late (long-term) adverse events

It is clear that every TKI has its own Achiles' heel (first-line drugs)



Shading based in actual frequences (relative in each row) in first-line trial

Leukemia (2016) **30**, 1648–1671

www.nature.com/leu

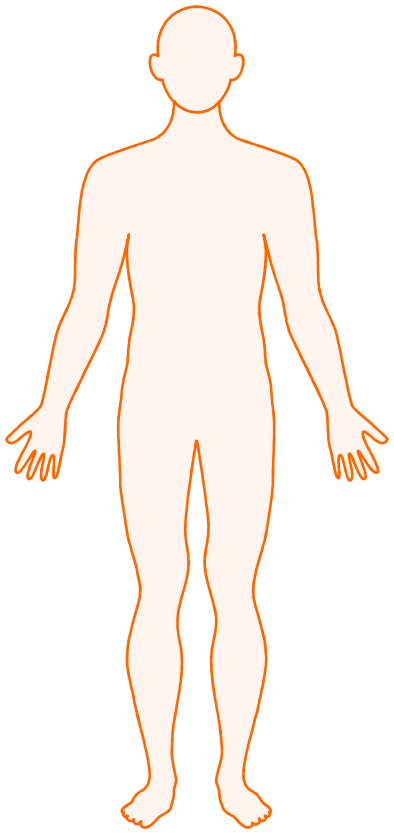
OPEN

REVIEW

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

JL Steegmann[1], M Baccarani[2], M Breccia[3], LF Casado[4], V García-Gutiérrez[5], A Hochhaus[6], D-W Kim[7], TD Kim[8], HJ Khoury[9], P Le Coutre[8], J Mayer[10], D Milojkovic[11], K Porkka[12,13], D Rea[14], G Rosti[2], S Saussele[15], R Hehlmann[16] and RE Clark[17]

Potential long-term effects of TKIs



- Cardiovascular toxicity
- Pulmonary toxicity
- Other malignancies
- Immune-modulatory effects
- Bone homeostasis
- Renal toxicity

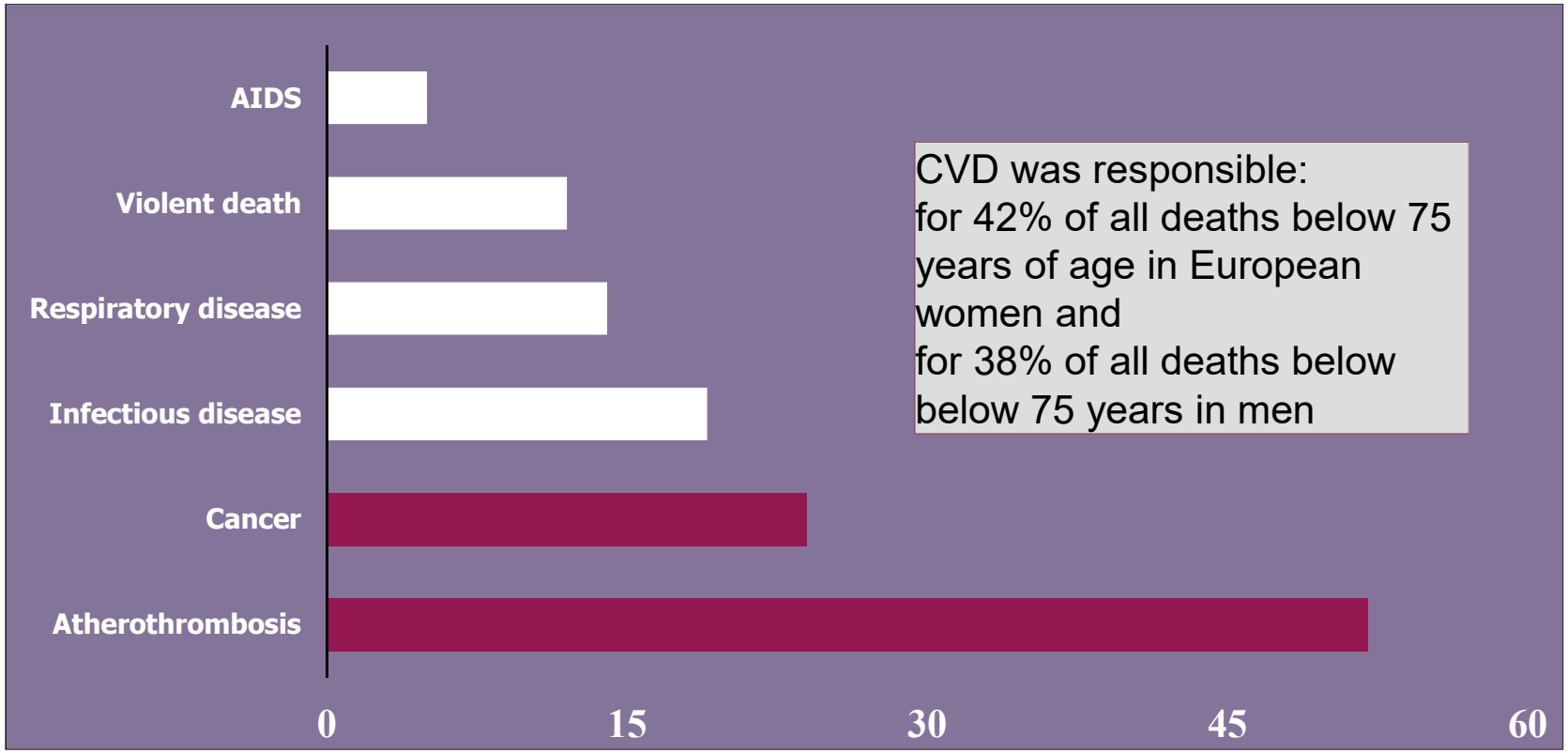
CML Study IV – Causes of death

N= 1536 pts, median follow-up ≈ 10 aa

	N (%)
Progression to AP/BC	67 (24)
Transplantation related	31 (11)
Secondary malignancy	**44 (16)**
Cardiopulmonary	**40 (15)**
Infection in CP	**20 (7)**
Thromboembolic/ischemic (not cardiac)	**8 (3)**
Renal insufficiency	**7 (3)**
Bleeding	4 (1)
Others	14 (5)
Unknown	40 (15)
Total	**275 (18)**

Hehlmann R et al., Leukemia 2017

Atherosclerosis is the leading cause of deaths in the world



The World Health Report, WHO Geneva, 2010

Why this topic is very important and actual?

Attention must be given to comorbidities and drug interactions, **and to new events unrelated to TKIs that are inevitable during such a prolonged treatment.**

Some TKI-related adverse events have emerged which were not predicted or detected in earlier studies, maybe because of suboptimal attention to, or absence from, the preclinical data.

Evaluation of Second Primary Malignancies risk

- Comparison with the general population:
  - Standardized Incidence Ratio (SIR) and Standardized Mortality Ratio (SMR)

Cases observed in the cohort under evaluation\ cases expected in the reference population

- Stratified according to:
  - Sex
  - Age
  - Region
- For an appropriate estimation of SPM risk:
  - **large cohorts of patients**
  - **long-follow-up**
  - accurate and comprehensive data collection
  - proper reference population

Epidemiologic Studies
Clinical trials

Risk of Second Malignancies before the introduction of TKIs

Country	Sweden (1)	Denmark (2)	US (3)	US (4)
Patients	2753	569	8005	4252
Years	1970-1995	1977-1994	1973-2000	1992-2000
SIR	**1.82 (1.53-2.14)**	**1.6 (1.3 – 2)**	**1.16 (1.04 – 1.29)**	1.06

- It is still debated if CML patients per se, regardless of the treatment used, might be at higher risk of SPM

1. Rebora P et al. Am J Epidemiol. 2010; 2. Frederiksen H et al. Blood. 2011. 3. Curtis RE et al. National Cancer Institute, 2006. 4. Shah BK et al. Indian J Hematol Blood Transfus. 2014

Imatinib

- Imatinib is the first TKI developed in CML and the most extensively studied. However, it is still unclear if its **immune-modulatory properties** (1-8) may affect the anti-cancer immune-surveillance in the long-term, or if its off-target activity may **influence onco-suppressive pathways.**

- Of note, regardless of the underlying mechanisms, neoplastic alterations have been described in multiple tissues of rats exposed to imatinib (9).

1. Steegmann JL et al. Leukemia. 2016; 2. Cwynarski K et al. Leukemia. 2004; 3. Dietz AB et al. Blood. 2004; 4. Gao H et al. Leukemia. 2005; 5. Steegmann JL et al. Haematologica. 2003; 6. Appel S et al. Stem Cells. 2005; 7. Leder C et al. Exp Hematol. 2007; 8. EMA. Glivec: EPAR - Product Information. 2015; 9. Rappa G et al. Cancer Chemother Pharmacol. 2011.

Risk of secondary primary malignancies in patients treated with TKIs

- Several studies, mainly referring to imatinib-treated patients, have investigated the risk of second primary malignancy (SPM) in CML compared to the general population (1-9). However, results are sometimes contrasting:
  - **higher incidence** of SPM in some **epidemiologic studies** of unselected CML patients (6, 9, 10)
  - **similar incidence** in three large analyses of patients enrolled in **clinical trials** (2, 5, 8).

1. Roy L et al. Leukemia 2005; 2. Pilot PR et al. Leukemia 2006; 3. Roy L et al. Leukemia 2006; 4. Voglova J et al. Neoplasma 2011; 5. Verma D et al. Blood 2011; 6. Gunnarsson N et al. Br J Haematol. 2015; 7. Gambacorti-Passerini C et al. J Natl Cancer Inst. 2011; 8. Miranda MB et al. Leukemia 2016; 9. Shah BK et al. Indian J Hematol Blood Transfus. 2014; 10. Frederiksen H et al. Blood. 2011.

Secondary primary malignancies – Summary and perspectives

- The prevalence of CML is increasing steadily, and, together with the aging of patients, several of them will be at risk of developing SPM
- Among CML-unrelated deaths, other malignancies are the most common cause of death
- In the majority of the analyzed cohorts so far, chronic TKI therapy, and particularly imatinib, was not associated with an increased risk of SPM compared to the general population

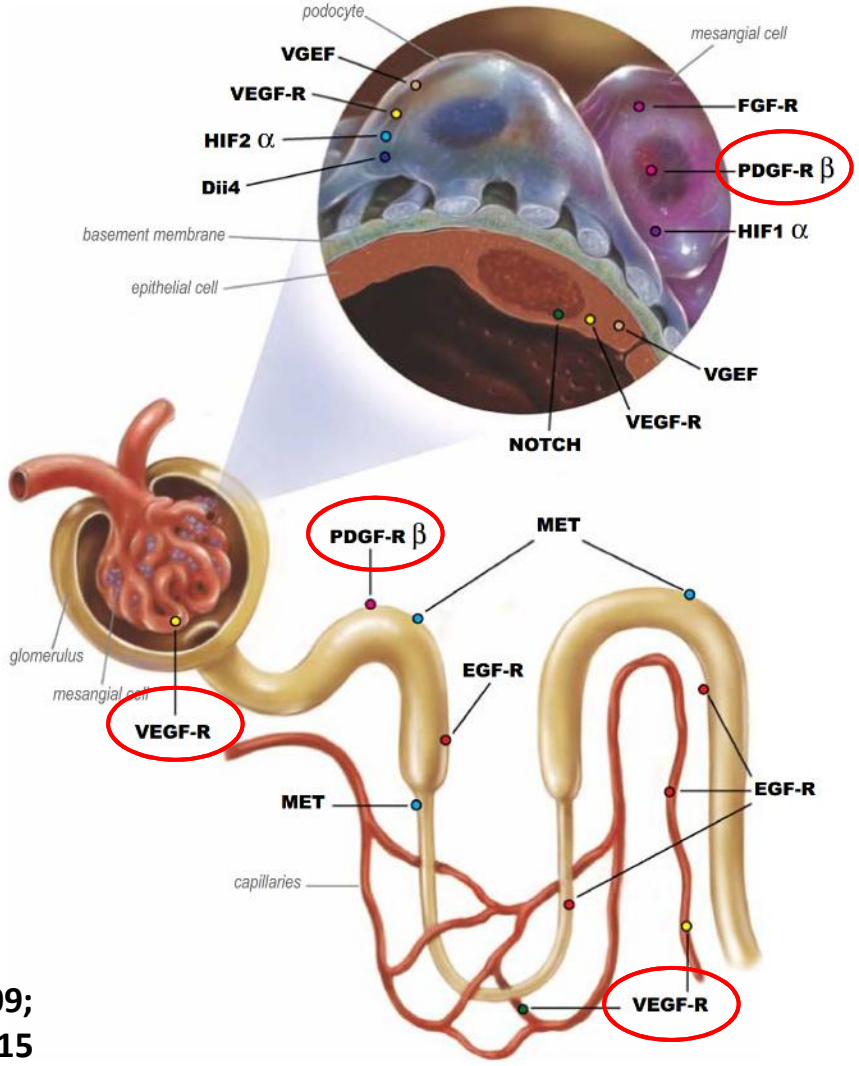
Immunological alterations and infections

- **In vitro** studies have shown that imatinib, dasatinib and nilotinib have inhibitory effects on T-cell proliferation and activation. The in vitro effects of dasatinib have been found to be more profound.

- **In patients:**
  - With imatinib, infection by opportunistic agents and viruses does not appear to be a major problem.
  - HBV reactivation has been reported in few cases, regardless of the TKI used
  - No significant incidence of severe infections in first line (CP), although the incidence with dasatinib appears to be higher, also at 100 mg once daily

Steegmann et al, Leukemia 2016

Renal toxicity of TKIs

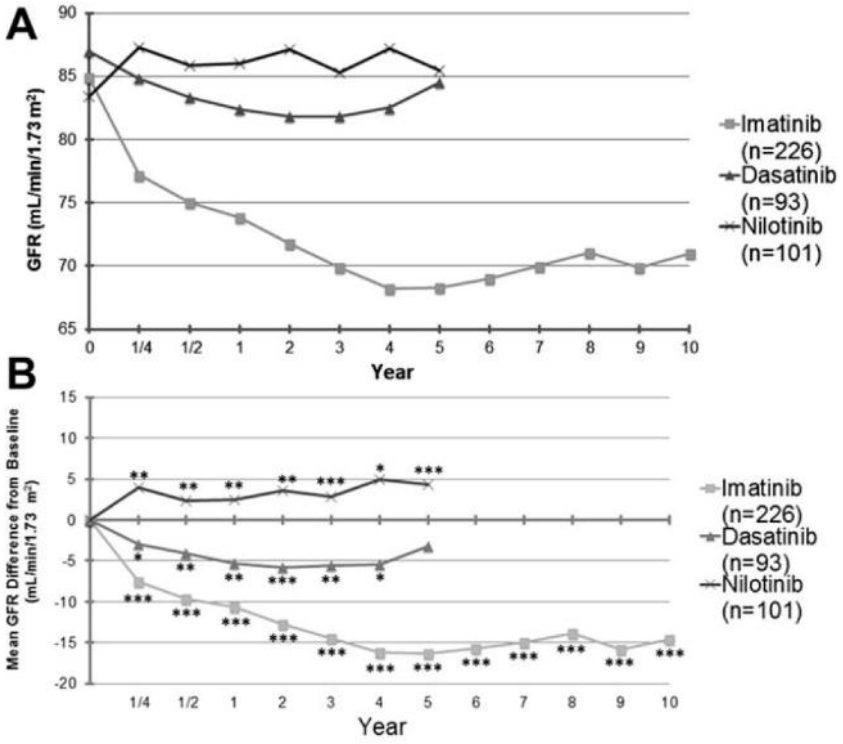


Kelly JR et al., Targ Oncol 2009;
Abbas A et al., Targ Oncol 2015

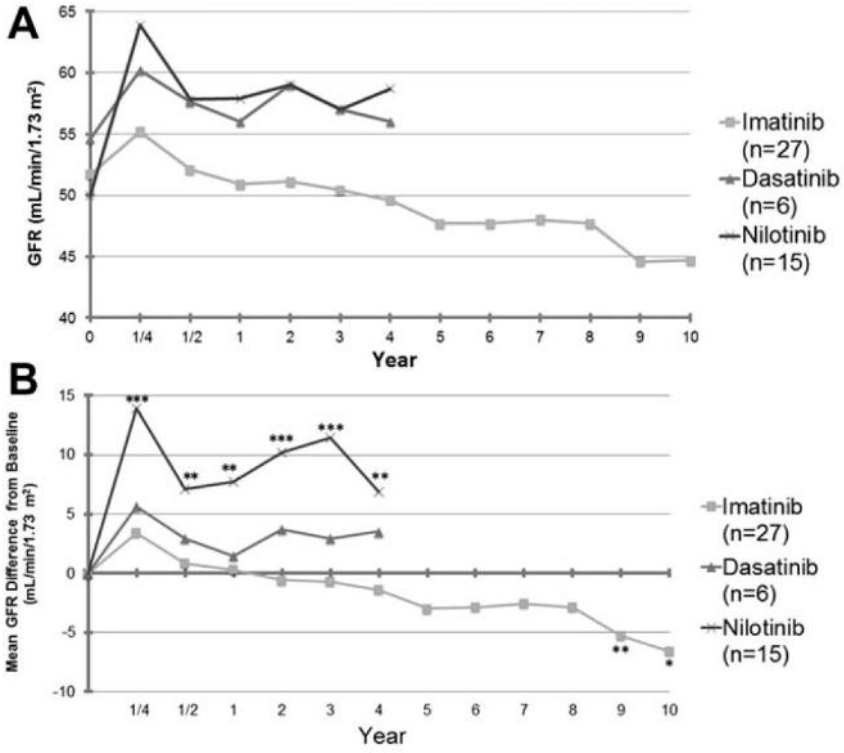
Evolution of glomerular filtration rates

- **≥ Grade 3 (GFR 30-59 ml/min/1.73 m^2) CKD: IM: 22%; DAS 5%, NIL 4%**

WITHOUT Chronic kidney disease (CKD)



WITH Chronic kidney disease (CKD)

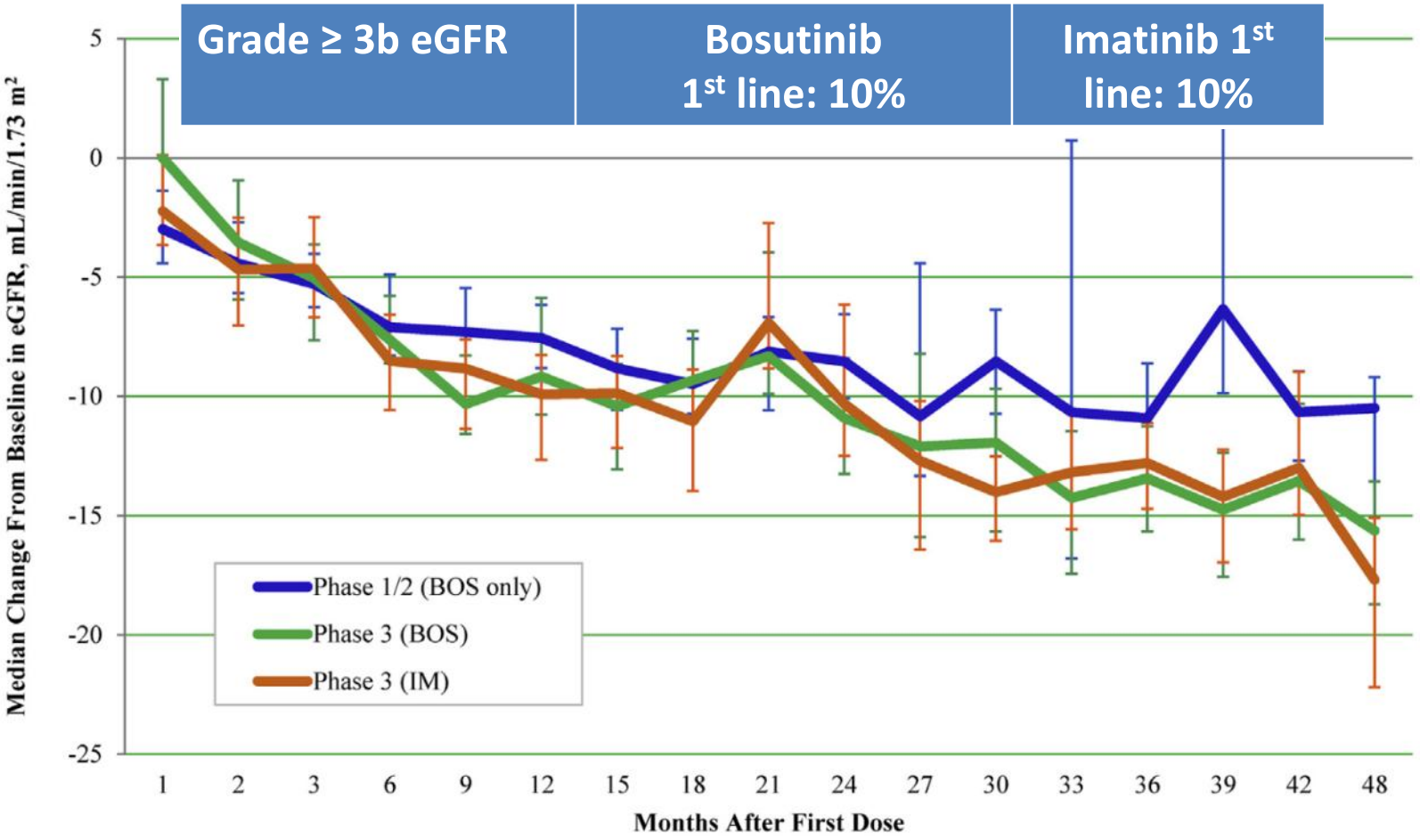


- In the multivariate analysis, age, treatment with imatinib (OR 8.3), and the coexistence of DM or HTN were found to be associated with the development of CKD ($P < .01$).

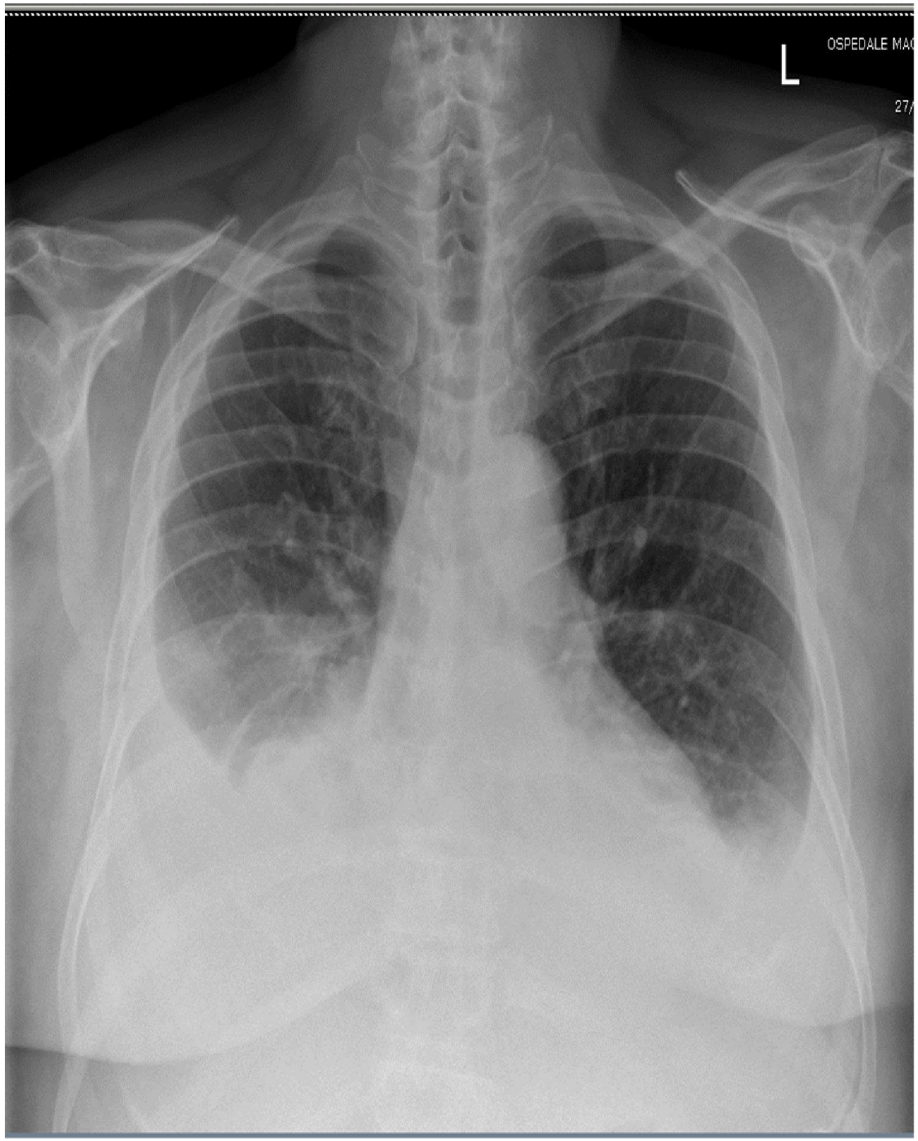
Yilmaz et al. Cancer 2015

Renal function – Bosutinib and Imatinib

Bosutinib 1st line: 248 pts; Imatinib 1st line 251 pts; Bosutinib ≥ 2nd line: 570 pts



Cortes J et al., Clin Lymphoma Myeloma Leuk 2017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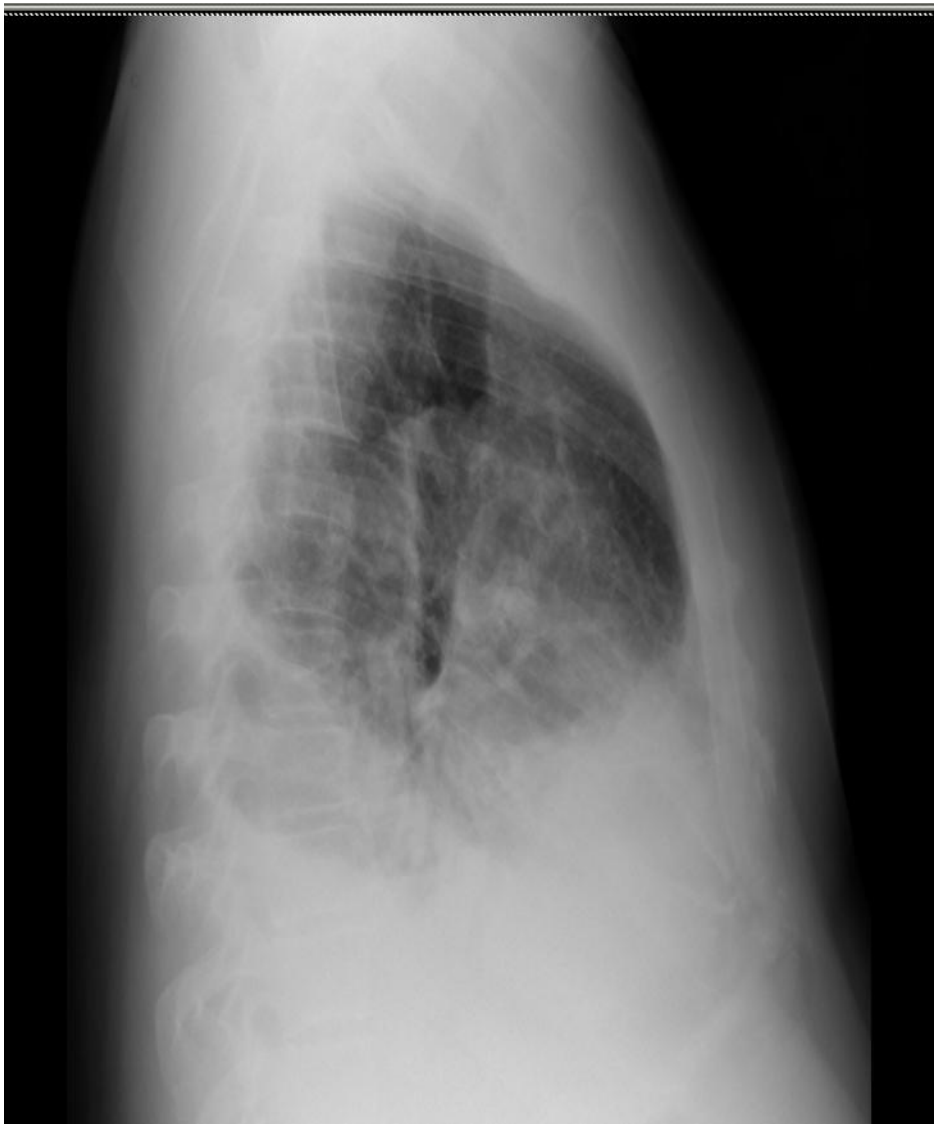
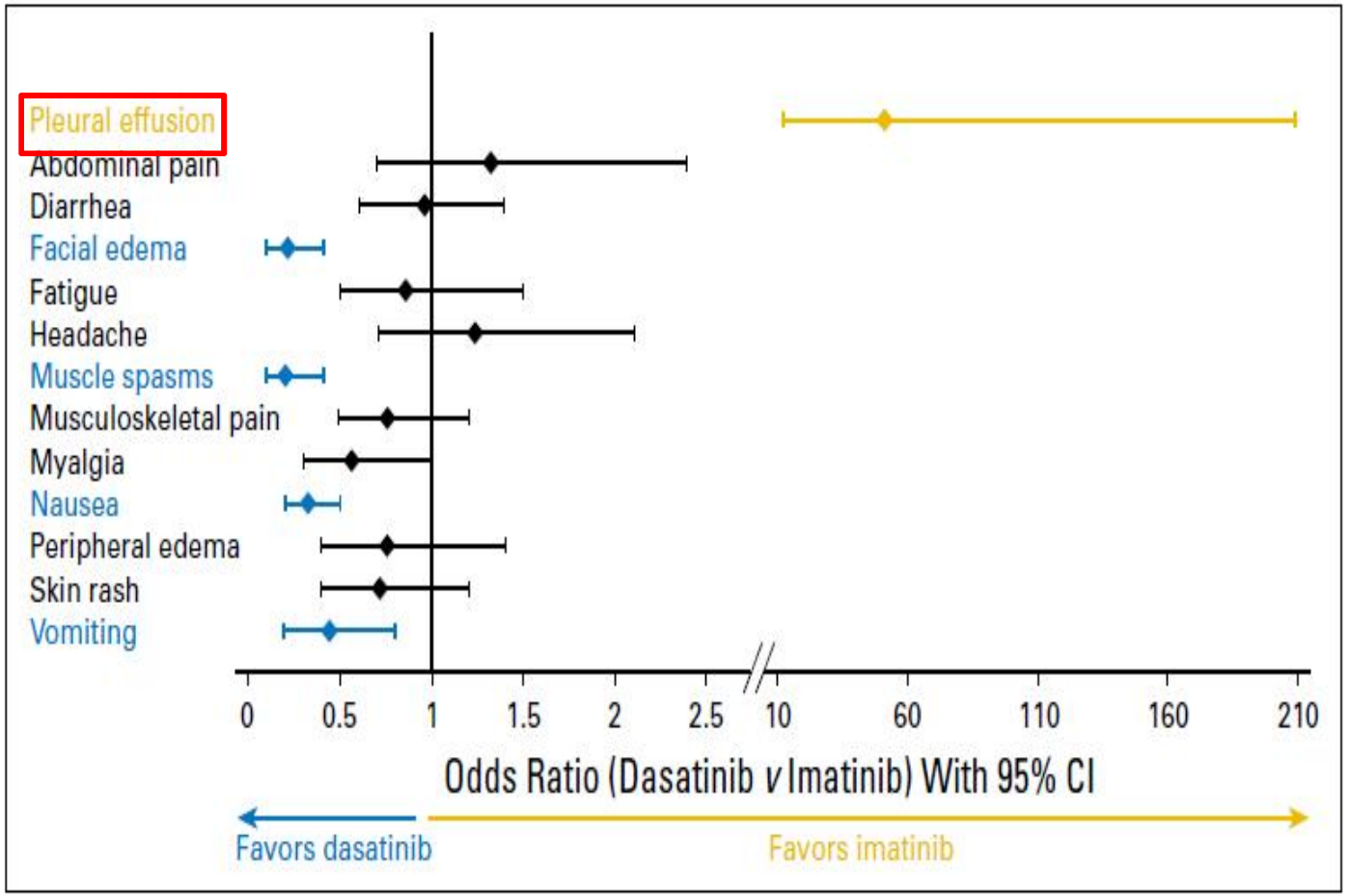
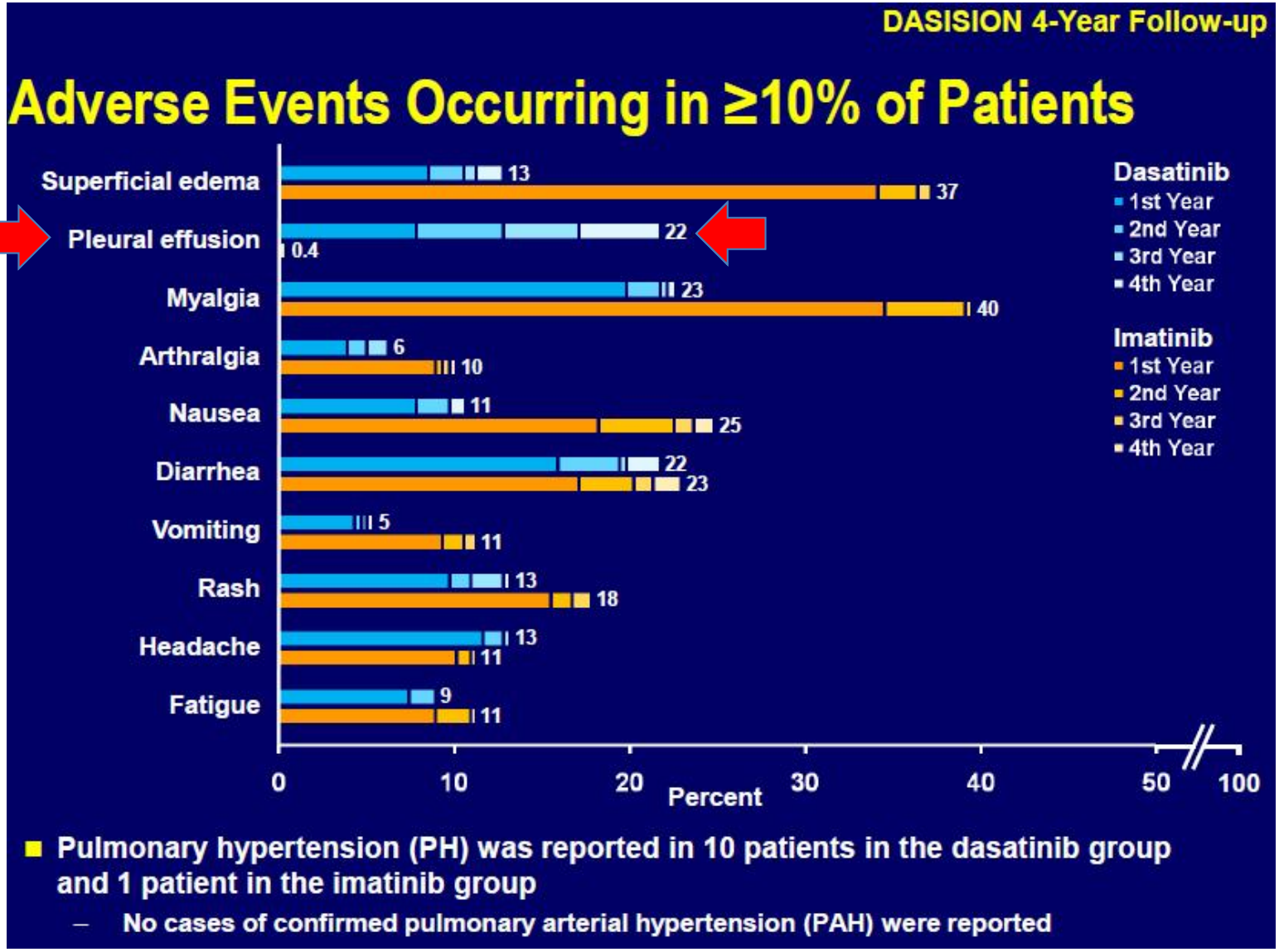


Forest plot comparing differences in rates of drug-related non-hematologic and grade 3/4 hematologic adverse events for patients treated with dasatinib or imatinib



Cortes JE et al. J Clin Oncol 2016

Adverse events (any grade)



Pathogenesis of pleural effusion: immune dysfunction?

"Immunologic" risk factors

Autoimmune disease

Prior rash on dasatinib

Clinical/biological features

Exudate

Increased lymphocyte count in PE

Lymphocitosis

Response to steroids treatment

Other autoimmune disease

Panniculitis

Lupus

Possible mechanisms

Inhibition of TECK and BTK involved in signalling pathway of T and B cell receptor, endotehlial, pulmonary and mast cells

Inhibition of SRC kinases, including LCK and LYN, expressed in B and T lymphocytes

Brixey et al. Curr Opin Pulm Med 2010
Kelly et al. Targ Oncol 2009
Mustjoki et al. Leukemia 2009
Rea et al. Lancet 2008
Rix et al. Blood 2007
Bergeron et al. Am J Resp Crit Care Med 2007
Punnialingam et al. ASH 2007
Quintas-Cardama et al. JCO 2007
Assouline et al. NEJM 2006

Pleural Effusion: risk factors

- Older age
- Cardiac disease
- Hypertension
- Hypercholesterolemia
- Auto-immune disease

- Advanced phase
- Dose > 100 mg
- Twice daily administration
- Prior rash on dasatinib

Porkka et al. Cancer 2010
Shah et al. JCO 2008
de Lavallade et al. Br J Hematol 2008
Quintas-Cardama et al. JCO 2007

Guidelines for the management of pleural effusions during dasatinib treatment in chronic myeloid leukemia

Massimo Breccia[1], Luigiana Luciano[2], Alessandra Iurlo[3], Fabio Stagno[4], Matteo Molica[1], Antonella Gozzini[5], Giuseppe Saglio[6], Giuliana Alimena[1]

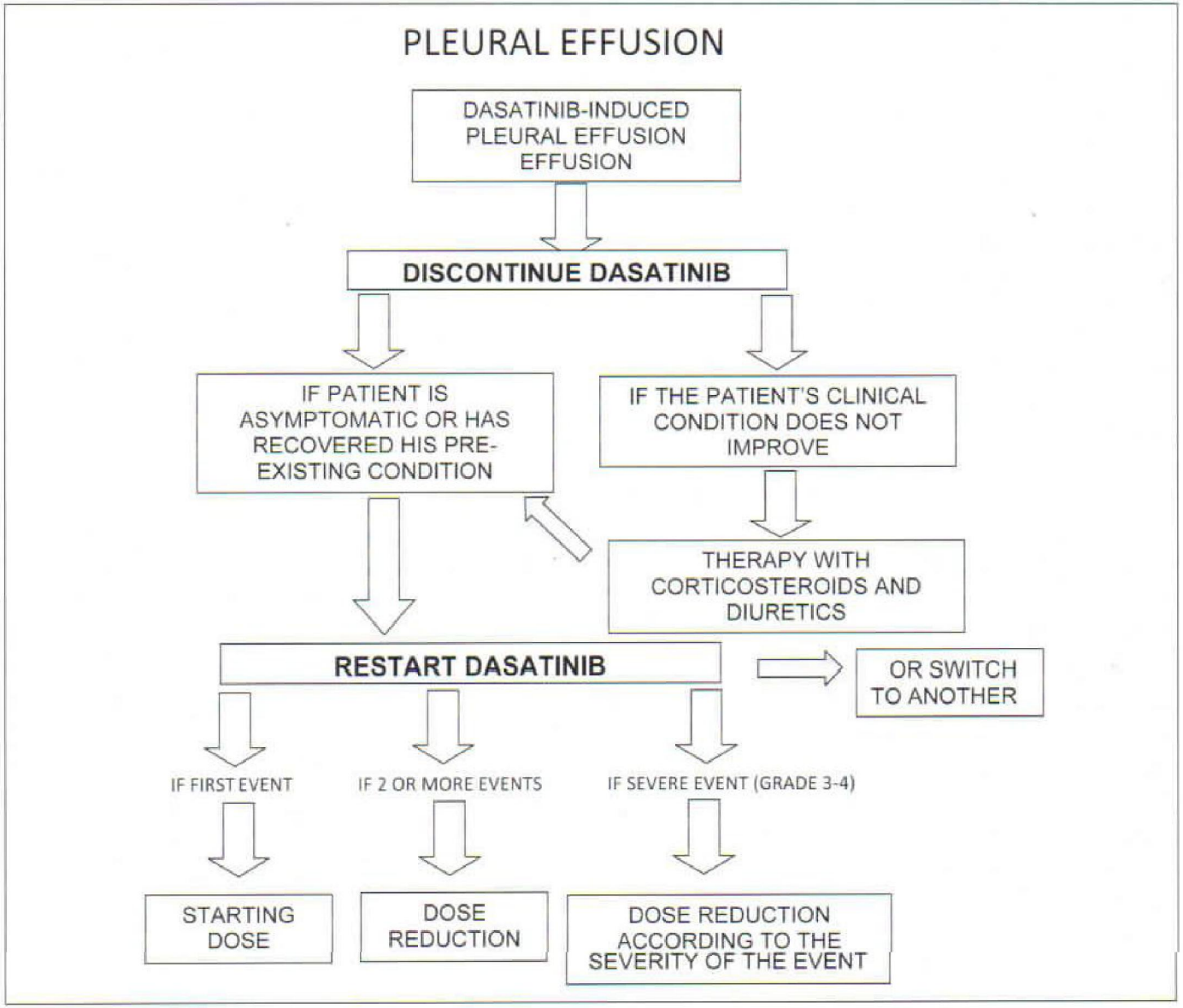


Figure 1. Algorithm for the managment of adverse events

Eur J Oncol 2015

Long-term follow-up CA180-034 study

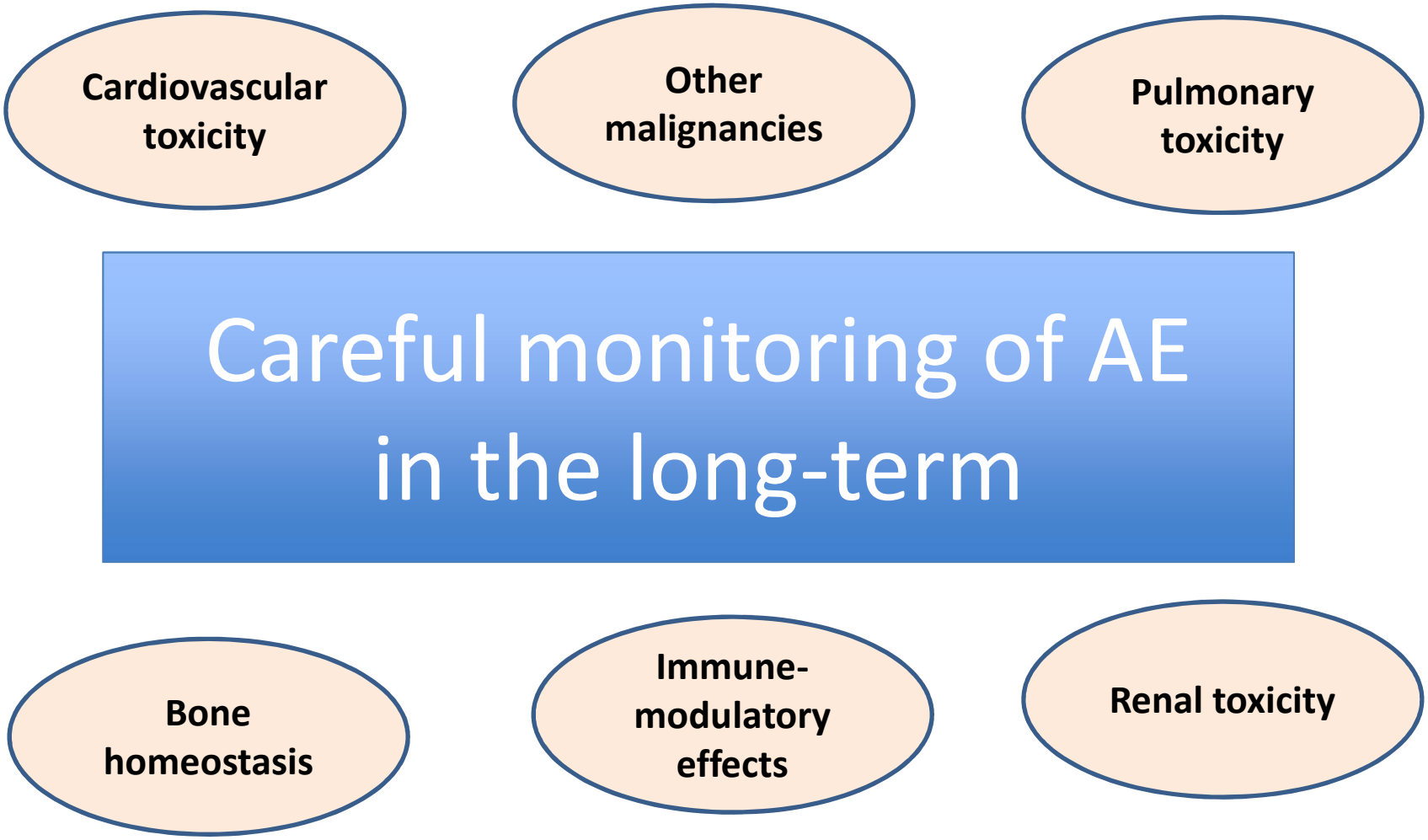
Supplemental Table 6. Discontinuation due to pleural effusion

	Patients who discontinued dasatinib because of pleural effusion				
	Between 0 and 2 years	**Between 2 and 4 years**	**Between 4 and 5 years**	**Between 5 and 6 years**	**Between 0 and 6 years**
100 mg once daily arm	0/165 (0%)	6/105 (6%)	3/69 (4%)	2/58 (3%)	11/165 (7%)
All arms	16/662 (2%)	32/385 (8%)	10/247 (4%)	4/205 (2%)	62/662 (9%)

n = 165 treated patients in the 100 mg once daily arm; n = 662 treated patients in all arms.

Jabbour et al. Blood 2014

Potential long-term effects of TKIs



Long-term side effects of TKIs

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BACK-UP

Glomerular filtration rates – Imatinib dose

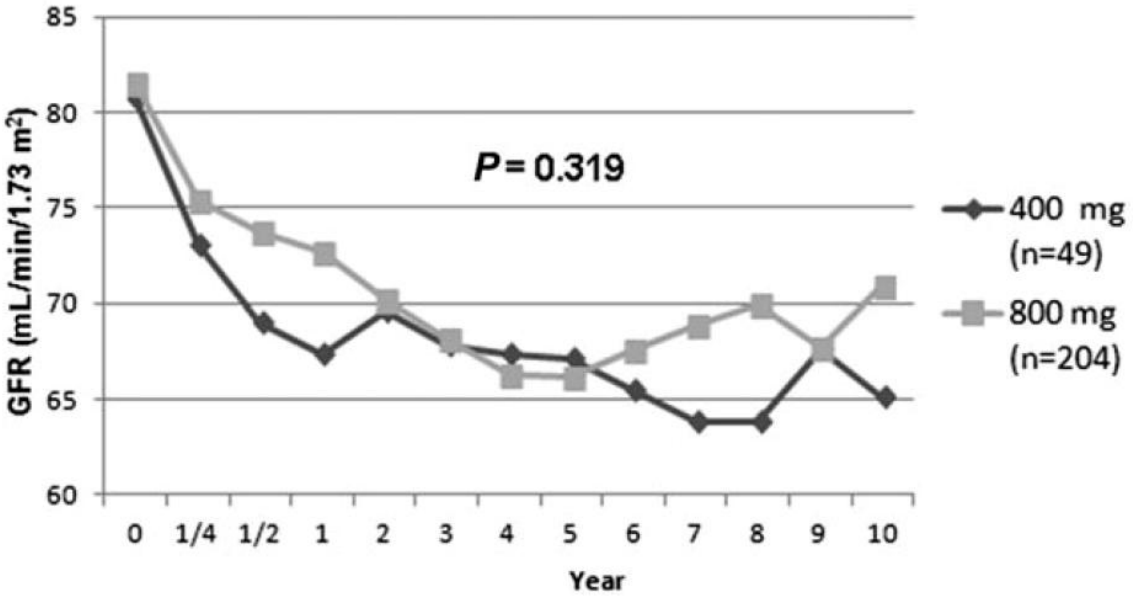
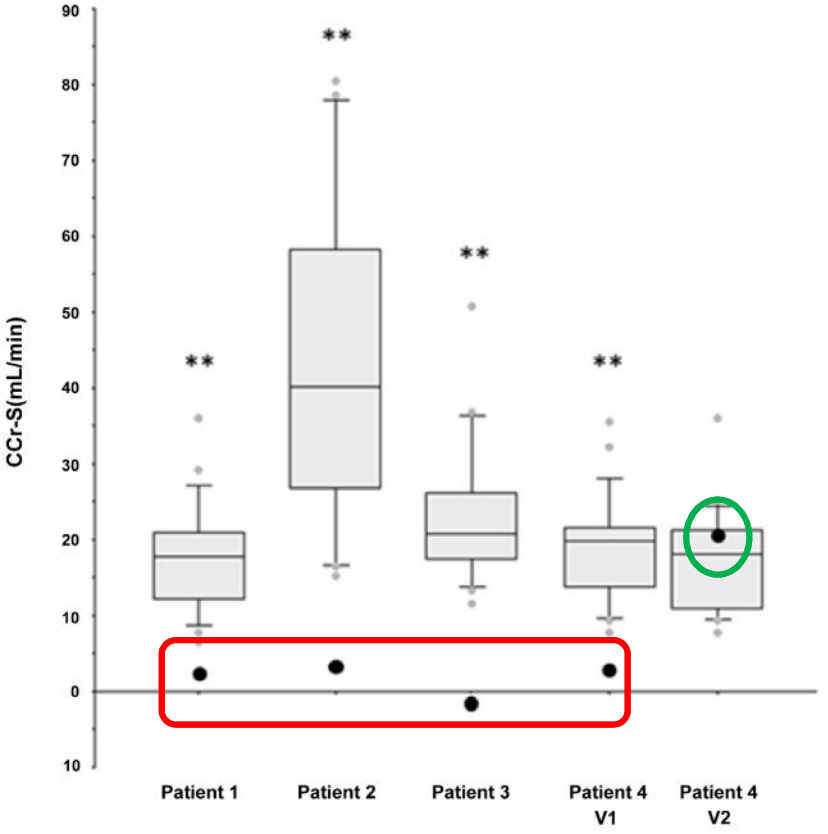


Figure 3. GFR changes in chronic myeloid leukemia patients treated with a high or standard dose of imatinib. The n values are the numbers of patients at the start of treatment. The *P* value was calculated with a repeated measures analysis of variance. GFR indicates glomerular filtration fate.

Yilmaz et al. Cancer 2015

Imatinib Increases Serum Creatinine by Inhibiting Its Tubular Secretion in a Reversible Fashion

- Part of Creatinine Clearance due to Tubular Secretion (CCr-S) in the 4 Patients and the Control Matched Populations.
- Data From the Imatinib-Treated Patients Are Indicated With the Black Dots.
- For Patient 4, V1 is the Visit During Imatinib Therapy and V2 is the Visit After Discontinuation of Imatinib.
- Box Plots Represent Data From the Control Populations. P < .001 Versus the Matched Control Population



Visal-Pietot E et al., Clin Lymphoma Myeloma Leuk 2017

Phosphate and calcium metabolism

Incidence and severity:

- Hypophosphataemia was first described with imatinib, with an early onset in younger patients treated with higher doses
- As a consequence of hypophosphataemia, a reduced serum calcium level and increased renal phosphate excretion with increased serum levels of parathyroid hormone have been reported.
- In the long-term, 50% of adults developed decreased bone mineral density.

First line studies	Imatinib[1,2]	Nilotinib[1,2]	Dasatinib[2]
Hypophospatemia (all grades)	**25 – 49%**	**33%**	**7%**

1. ENESTnd; 2. DASISION

Steegmann L et al, Leukemia 2016

TKIs and second malignancies – Epidemiologic studies

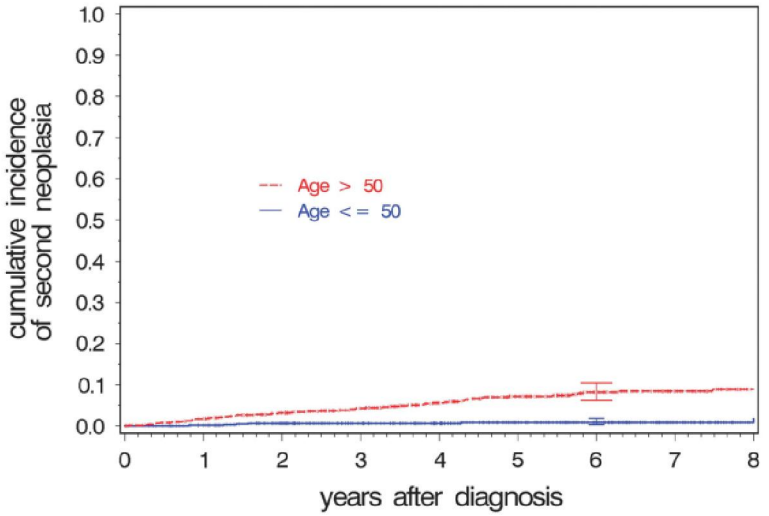
- 868 patients diagnosed with CML between 2002 and 2011
- Swedish CML register, cross-linked to the Swedish Cancer register
- Median follow-up of 3.7 (range 0–9.9) years; 3293 pt-years

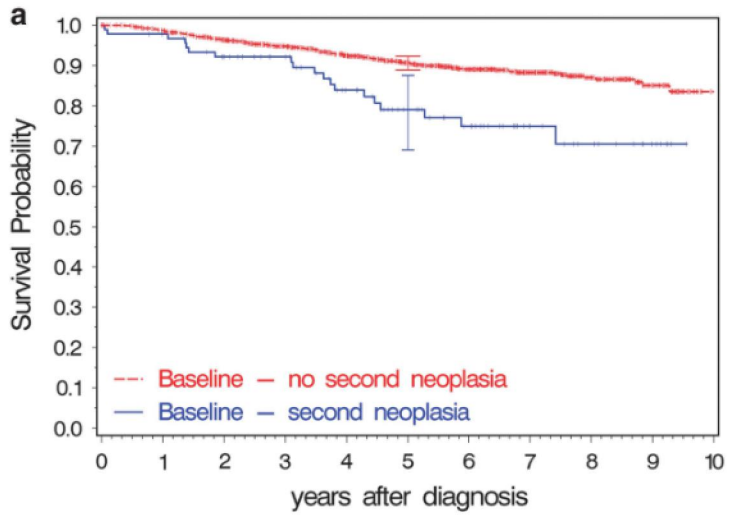
Variable	Observed	Expected	SIR (observed/ expected)	95% CI for SIR
Overall	52	34	1·52	1·13–1·99
Male	26	20	1·30	0·85–1·91
Female	26	14	1·81	1·18–2·66
Age < 60 years	10	5	1·86	0·89–3·42
Age ≥ 60 years	42	29	1·45	1·05–1·96
Second cancer type				
Prostate	14	8	1·80	0·98–3·02
Gastrointestinal	13	4	3·02	1·61–5·17
Gynaecological	4	1	3·63	0·98–9·30
Nose and throat	3	0·1	37·12	7·46–108·46
Lung	2	3	0·74	0·08–2·67
Breast	4	4	0·96	0·26–2·45

Gunnarsson et al. Br J Haematol 2015

TKIs and second malignancies – Clinical trials

- **1525 pts, median follow-up 67 months**
- **64 (4.2%) patients had a SPM**
- **No overall increased SIRs:**
  - Men: 0.88 (0.63-1.2)
  - Women: 1.06 (0.69-1.55)
- **Increased SIRs for NHL:**
  - Men: 3.33 (1.06-8.04)
  - Women: 4.29 (1.09-11.66)





Miranda MB et al. Leukemia 2016

GIMEMA analysis – Imatinib frontline – Observed Malignancies

559 patients → survey → 514 (92%) patients

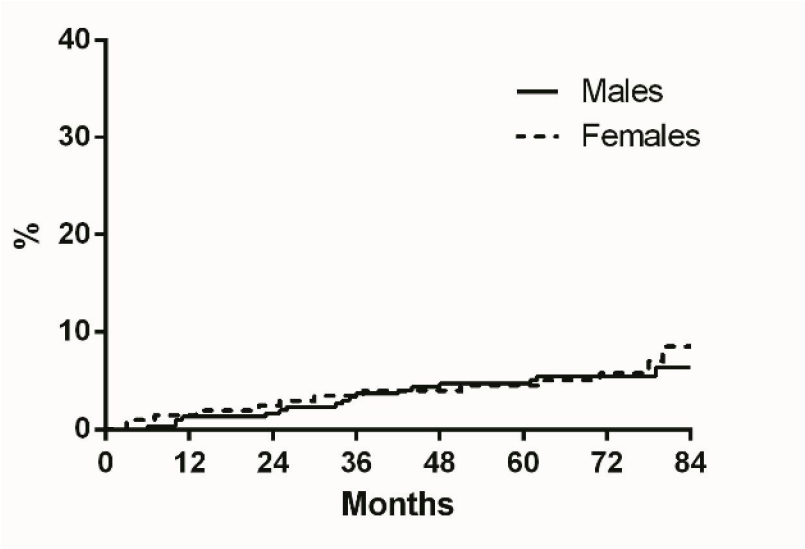
Median follow-up: 74 (3 – 99) months

Malignancy Type	All Malignancies Observed / Deaths, N	Second Primary Malignancies Observed / Deaths, N
Colon	4 / 4	4 / 4
Prostate	3 / 0	3 / 0
Breast	3 / 0	2 / 0
….	….	….
TOTAL, n	**35 / 19**	**30 / 16**
% of all patients (N=514)	**6.8 / 3.7**	**5.8 / 3.1**

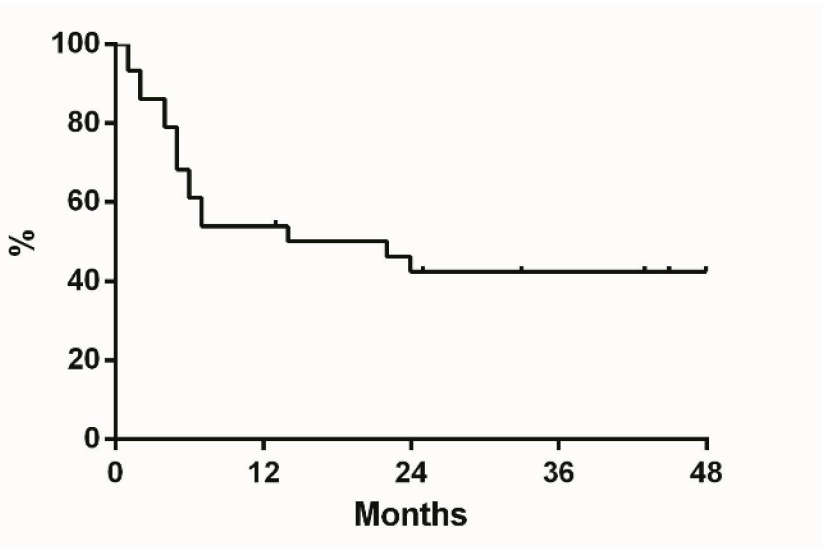
Gugliotta G et al., Haematologica 2017

GIMEMA analysis – Imatinib frontline

INCIDENCE



SURVIVAL AFTER SPM



Sex	Pt-Years	SIR	95% CI
M	1806.3	1.06	(0.57; 1.54)
F	1204.8	1.61	(0.92; 2.31)

Sex	Pt-Years	SMR	95% CI
M	1849.4	1.26	(0.53; 1.99)
F	1228.3	**2.41**	**(1.26; 3.56)**

Gugliotta G et al., Haematologica 2017

Why this topic is very important and actual?

Adverse events (AEs) are often reported as infrequent, minor, tolerable and manageable, but they are increasingly important as therapy is **potentially lifelong** and multiple TKIs are available.

Why this topic is very important and actual?

The main purpose of CML treatment is the antileukemic effect. Suboptimal management of AEs must not compromise this first objective.

Most patients will have AEs, usually early, mostly mild to moderate, and which will resolve spontaneously or are easily controlled by simple means.

Why this topic is very important and actual?

Reduction or interruption of treatment must only be done if optimal management of the AE cannot be accomplished in other ways, and frequent monitoring is needed to detect resolution of the AE as early as possible.

Why this topic is very important and actual?

Attention must be given to comorbidities and drug interactions, and to new events unrelated to TKIs that are inevitable during such a prolonged treatment.

Some TKI-related AEs have emerged which were not predicted or detected in earlier studies, maybe because of suboptimal attention to or absence from the preclinical data.