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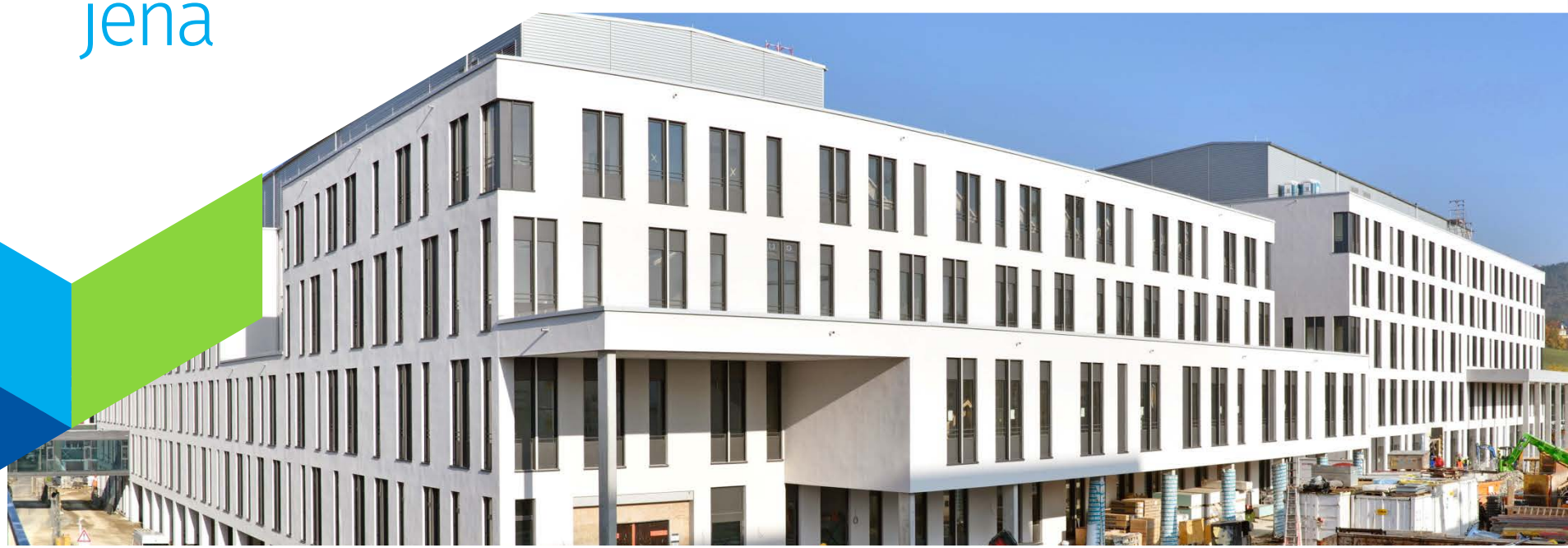


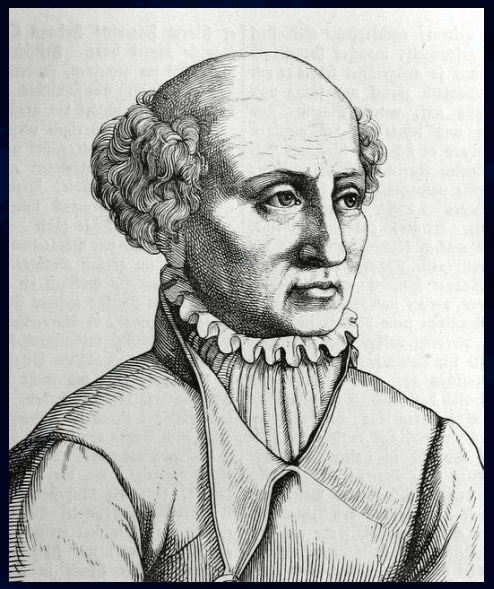
Long-term side effects, comorbidities & their impact on choice of treatment CML management and quality of life

Andreas Hochhaus

Frankfurt I 27.5.2017

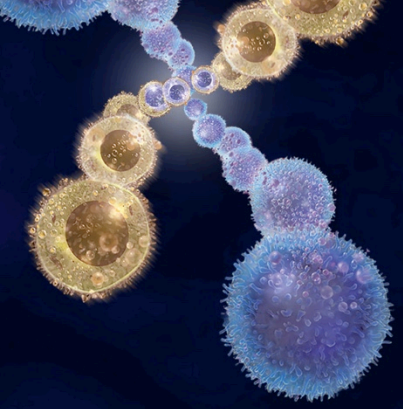
„sola dosis facit venenum“

Paracelsus 1493-1541
Swiss philosopher and botanist



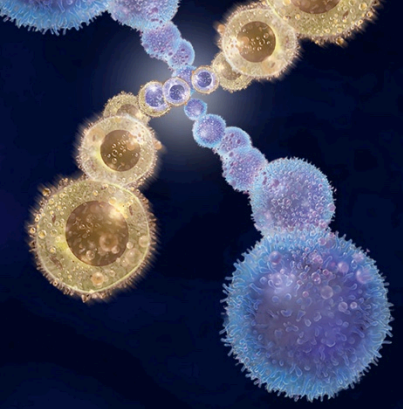
Basic principle of toxicology.

Meaning:
All things are poison and nothing is without poison;
only the dose makes a thing not a poison.



Main messages to doctors treating CML patients

- First, think about the antileukemic effect
- Second, know the toxicity profile of all the drugs you could use
- Third, think about previous comorbidities
- Any adverse event adds up on comorbidity



Aim of the adverse event management

- Awareness of adverse event profil enables selection of the most appropriate inhibitor
- Knowledge of potential adverse events guide correct follow up to uncover such events early
- Treatment of adverse events increases quality of life, improves adherance and therefore improves efficacy and outcome

Now Available

ICLUSIG™
(ponatinib) tablets

SPRYCEL™
dasatinib

Bosulif™
bosutinib 500mg tablets

Generics

CML: Treatment goals

- ✓ Survival
- ✓ Progression free survival
- ✓ Quality of life
- ✓ Good tolerability
- ✓ Avoid long term toxicity
- ✓ Chance to achieve treatment free remission
- ✓ Costs

IRIS Study: >10 year update of imatinib therapy (n=553)

- 10 year survival: 83%

- 49% of patients discontinued imatinib therapy, but only 6.9% due to adverse events

Hochhaus et al., NEJM 2017

Background of side effects

- ✓ Inhibition of normal ABL1
- ✓ Inhibition of other tyrosine kinases ("off target inhibition")
- ✓ Caused by the pharmacologic formulation

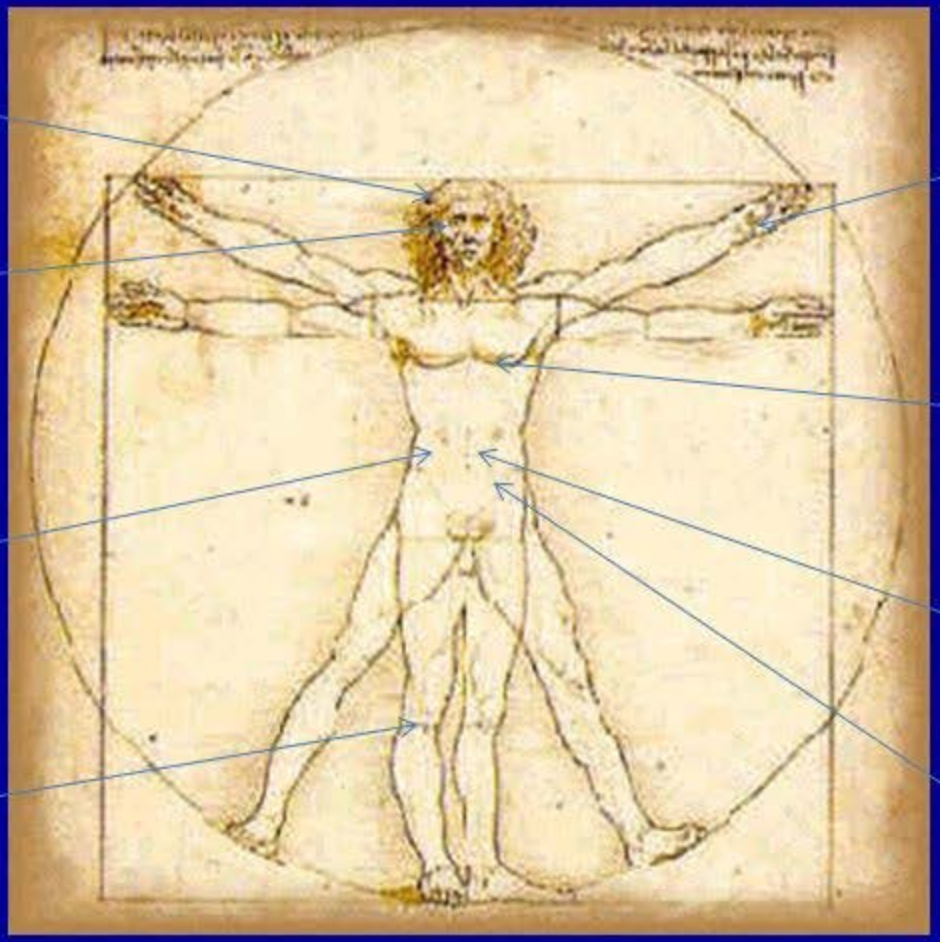
Side-effects of imatinib therapy

GENERAL
Fatigue

EYES
Dryness
Peri-orbital oedema

LIVER
Transaminitis

MUSCULOSKELETAL
Arthalgia
Myalgia
CPK↑



SKIN
Dermatitis
Hypopigmentation
Stevens-Johnson
Alopecia

CARDIAC
CCF
Fluid retention

GI TRACT
Nausea/Vomiting
Diarrhoea

RENAL
Impairment

risk
benefit

Comorbidities are common in CML at diagnosis

- Frequency:
  - EUTOS population study[1]: 2903 patients
    - 1 comorbidity : 29%
    - 2 comorbidities : 15.3%
    - >2 comorbidities : 11.5%
    - Most common:
      - » Hypertension: 26%,
      - » Other cardiovascular disorders: 17.2%
      - » Diabetes mellitus: 9.5%

1 Hoffmann V et al. Leukemia 2017

Imatinib treated patients, 1st line
German CML study IV:

- **1,524 patients, median age 52 years**
- **521 comorbidities**
- Median Charlson Comorbidity Index (CCI): 3 (2-12)
- **Most common: diabetes mellitus (n=106), chronic lung disease (n=74), kidney insufficiency (n=47), and myocardial infarction (n=38)**
- No significant differences in remission rates, time to CCyR or time to MMR
- No differences were observed between the CCI groups for the probability of progression
- Significant differences in survival according to CCI at diagnosis

Saussele S, et al. Blood 2013;122:91.

Common Terminology Criteria for Adverse Events (CTCAE)

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

Common side-effects from TKIs in CML

	Imatinib		Dasatinib		Nilotinib	
	All grades	Gr 3&4	All grades	Gr 3&4	All grades	Gr 3&4
Fatigue	4+	+	3+	+	4+	+
Skin rash	4+	2+	3+	+	4+	+
Nausea	4+		4+		3+	+
Diarrhea	4+	2+	4+	+	3+	+
Myalgia	5+		4+			
Headache	3+		4+		4+	
Edema	4+	2+	4+	2+	3+	
Pl. Effusion	2+	+	4+	2+	2+	+
Hyperglycemia					4+	3+
Elevated Lipase	4+	2+			4+	3+
Elevated ALT	4+	2+		+	5+	3+

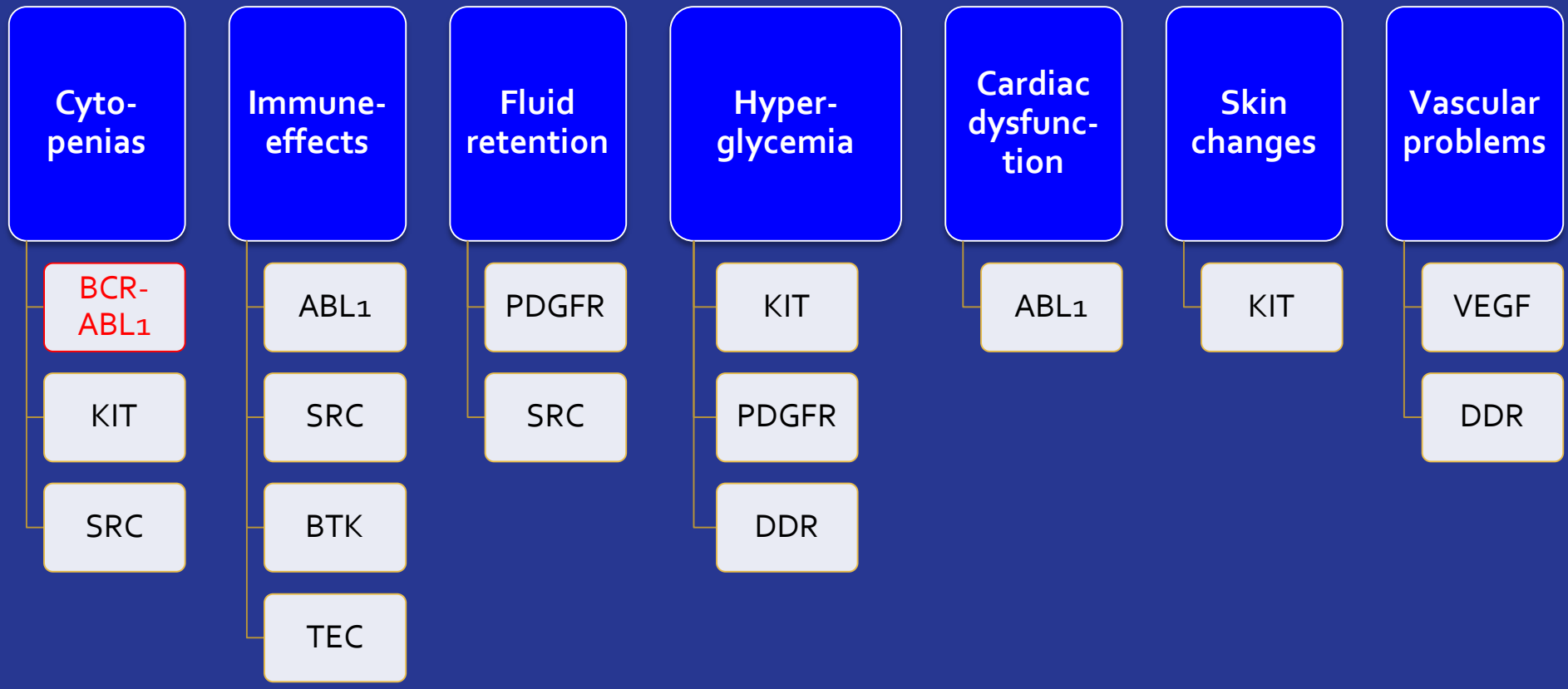
2+, 1-5%; 3+, 5-10%; 4+, 10-50%; 5+, >50%

Apperley. Lancet, 2014;
Steegmann et al. Leuk Lymph 2012; 53:2351.

Clinical Relevance of Side Effects

- A trivial adverse events, if sustained, is not trivial at all
- The sum of trivial effects is non-trivial at all
- Chronic fatigue is the variable most strongly associated with a lower quality of life in patients treated with imatinib

Off-target effects of BCR-ABL1 inhibitors and putative targets

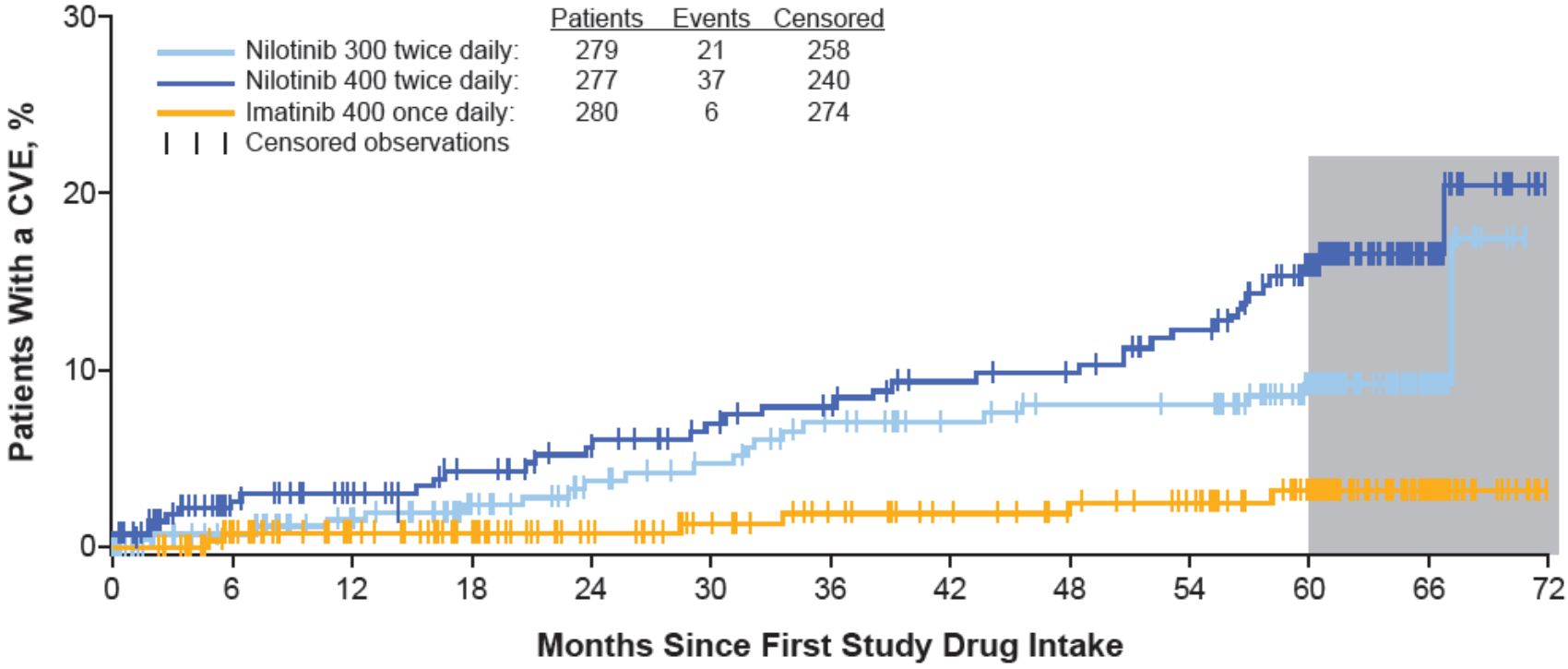


: Steegmann JL, Cervantes F, le Coutre P, Porkka K, Saglio G Leuk Lymphoma 2012, 53:2351-2361.

Adverse Events: Management Issues

Imatinib	Nilotinib	Dasatinib
Initial Grade 3/4 Myelosuppression		
GI Toxicity Edema Rash Myalgia Diarrhea	Rash QTc prolongation Hepatotoxicity Lipase elevation Peripheral artery occlusion	Bleeding Pleural effusions Pulmonary artery hypertension
Once/day. Take with food.	Take on an empty stomach q 12 hrs. Avoid PPIs. Monitor ECG, glucose and lipase levels.	Once/day. Take with or without food. Avoid PPIs.

Incidence of Cardiovascular Events on ENESTnd (Imatinib vs. Nilotinib)



Hochhaus et al. ENESTnd. LEUKEMIA 2016

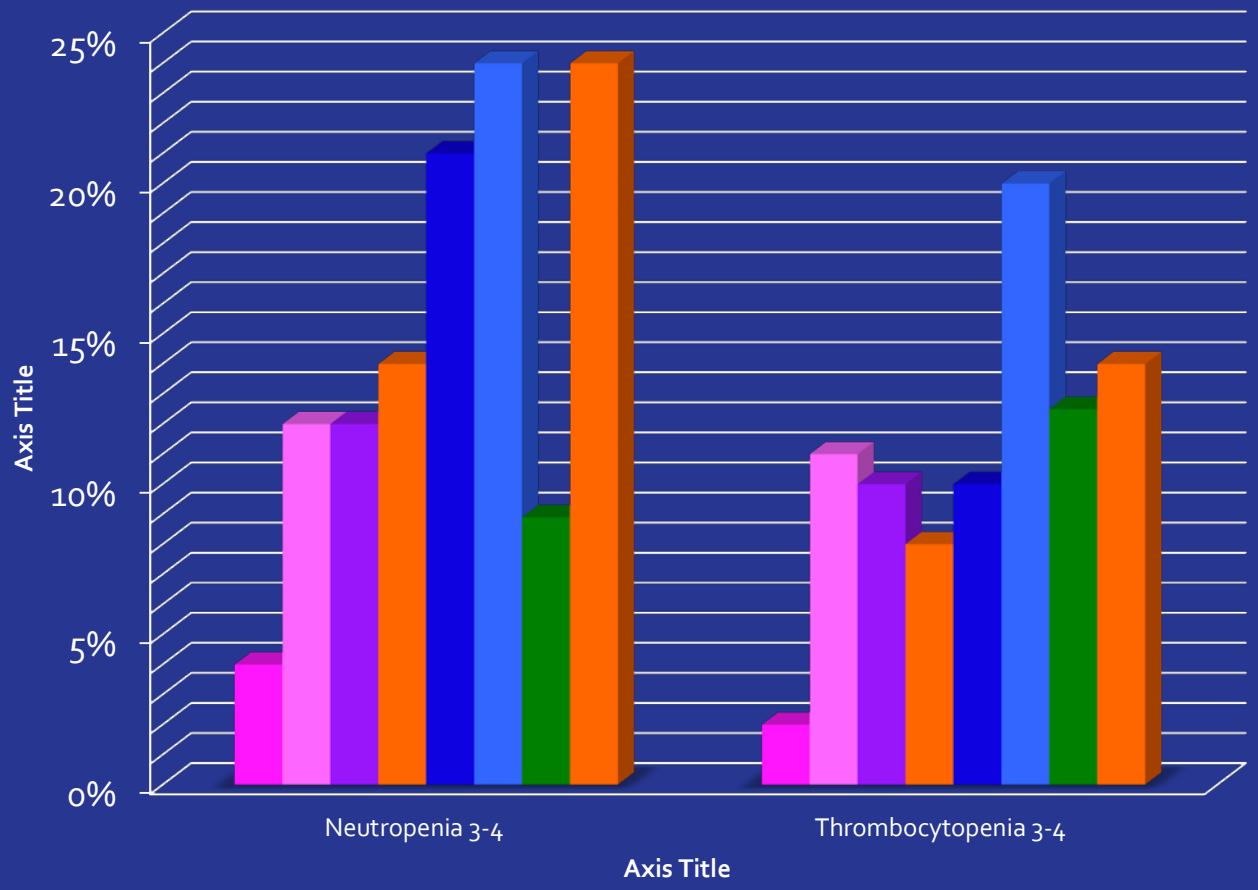
Modifiable Risk Factors and Cardiovascular Disease

- Smoking
  - 2- to 3- fold increased risk of Cardivascular disease
- Dyslipidemia
  - serum LDL level
- Hypertension
  - 7 mm Hg increase increases risk of CVD by 27%
- Diabetes mellitus
  - Increases risk 2- to 4- fold in men and 3- to 7- fold in women

Summary of Cardiovascular Risk Reduction

- Medicines and strategies that lower vascular risk:
  - Statins
  - Blood Pressure Reduction
  - ACE inhibitors
- Medications *may* lower vascular risk:
  - Aspirin
  - Metformin
- Treatments that do not lower vascular risk:
  - Glucose lowering below glycosylated hemoglobin (HbA1c) of <7%

Cytopenias and BCR-ABL1 Inhibitors



These data are from separate studies.

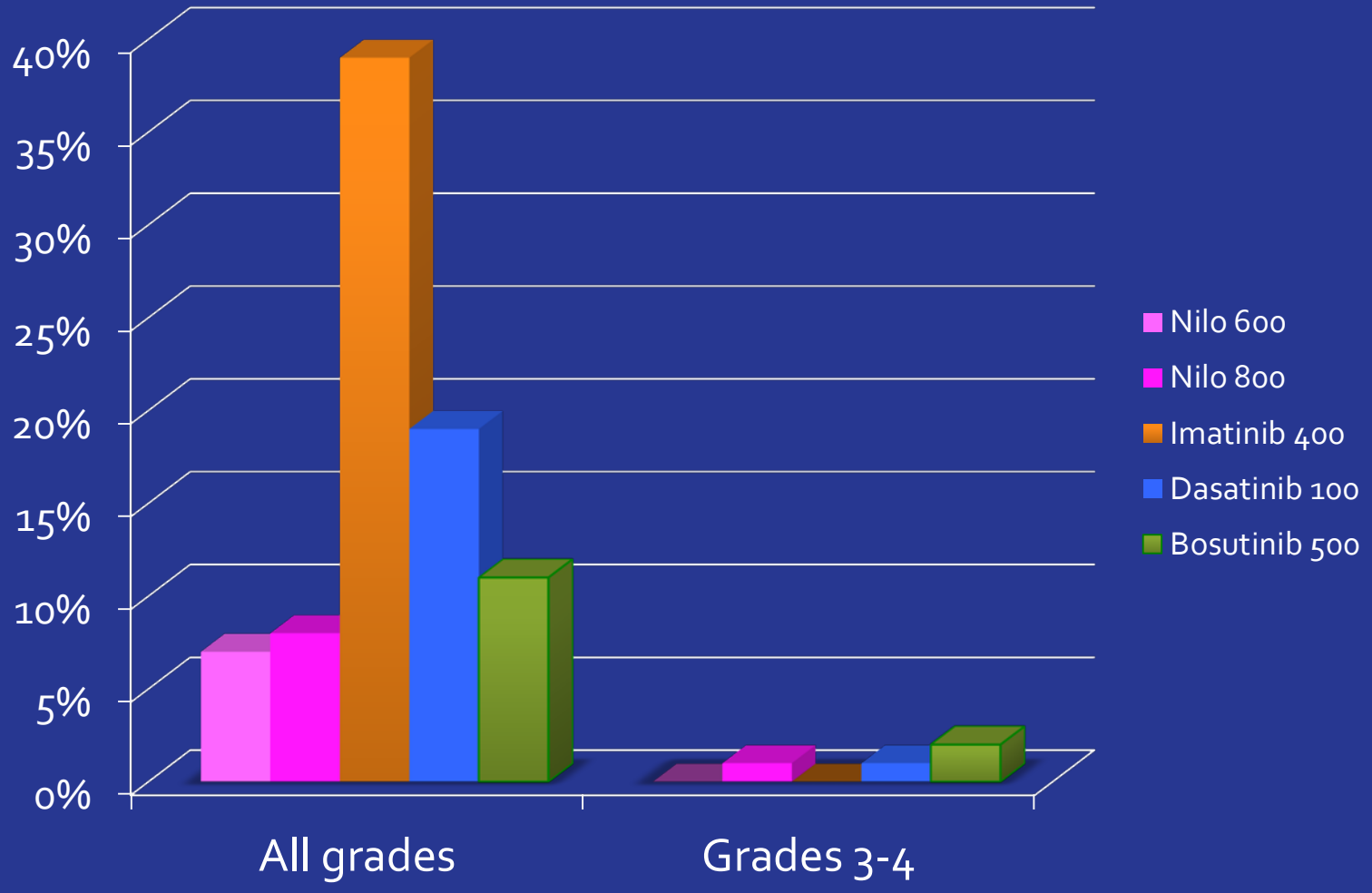
- GIMEMA NILO — 15 mo follow up[1]
- MDACC NILO — 17.3 mo follow up[2]
- ENEST NILO — 24 mo follow up[3]
- IRIS IMAT — 24 mo follow up[4]
- MDACC DASA — 24 mo follow up[5]
- DASISION DASA — 24 mo follow up[6]
- BELA BOSU — >12 mo follow up[7]
- BELA IMA — >12 mo follow up[7]

Cytopenias are more frequent with dasatinib (and imatinib, in some trials)

Rosti G, et al. Blood. 2009;114(24):4933-8.
Cortes JE, et al. JCO. 2010;28(3):392-7.
Hochhaus A, et al. Haematologica. 2011;96(s2):203-4 [abs 484, oral].
Druker BJ, et al. NEJM. 2006;355(23):2408-17.
Cortes JE, et al. JCO. 2010;28(3):398-404.
Hochhaus A, et al. Haematologica. 2011;96(s2):422 [abs 1011, oral]
Cortes J , et alJCO 2012. 10.1200/JCO.2011.38.7522

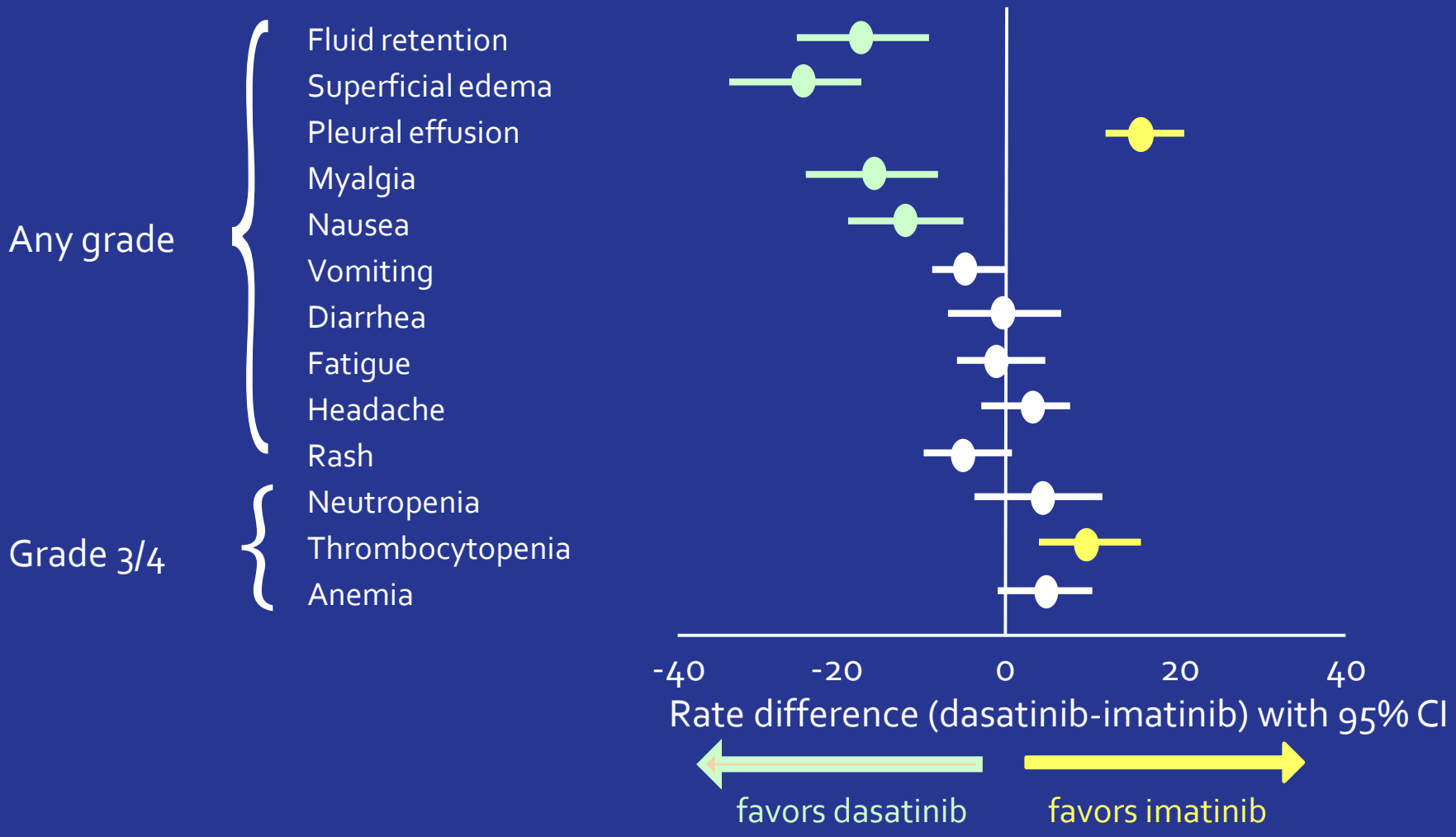
Edema

Imatinib is associated with more peripheral edema than nilotinib, bosutinib or dasatinib



1. Larson, R. A., et al. (2012) Leukemia **26**(10): 2197-2203.
2. Kantarjian, H. M., et al. (2012). Blood **119**(5): 1123-1129.
3. Cortes, J. E., et al. (2012). J Clin Oncol **30**(28): 3486-3492.

DASISION Trial: Differences In Adverse Event Rates



Hochhaus A, et al. Haematologica. 2011; 96(s2):422 [abstract 1011], adapted.

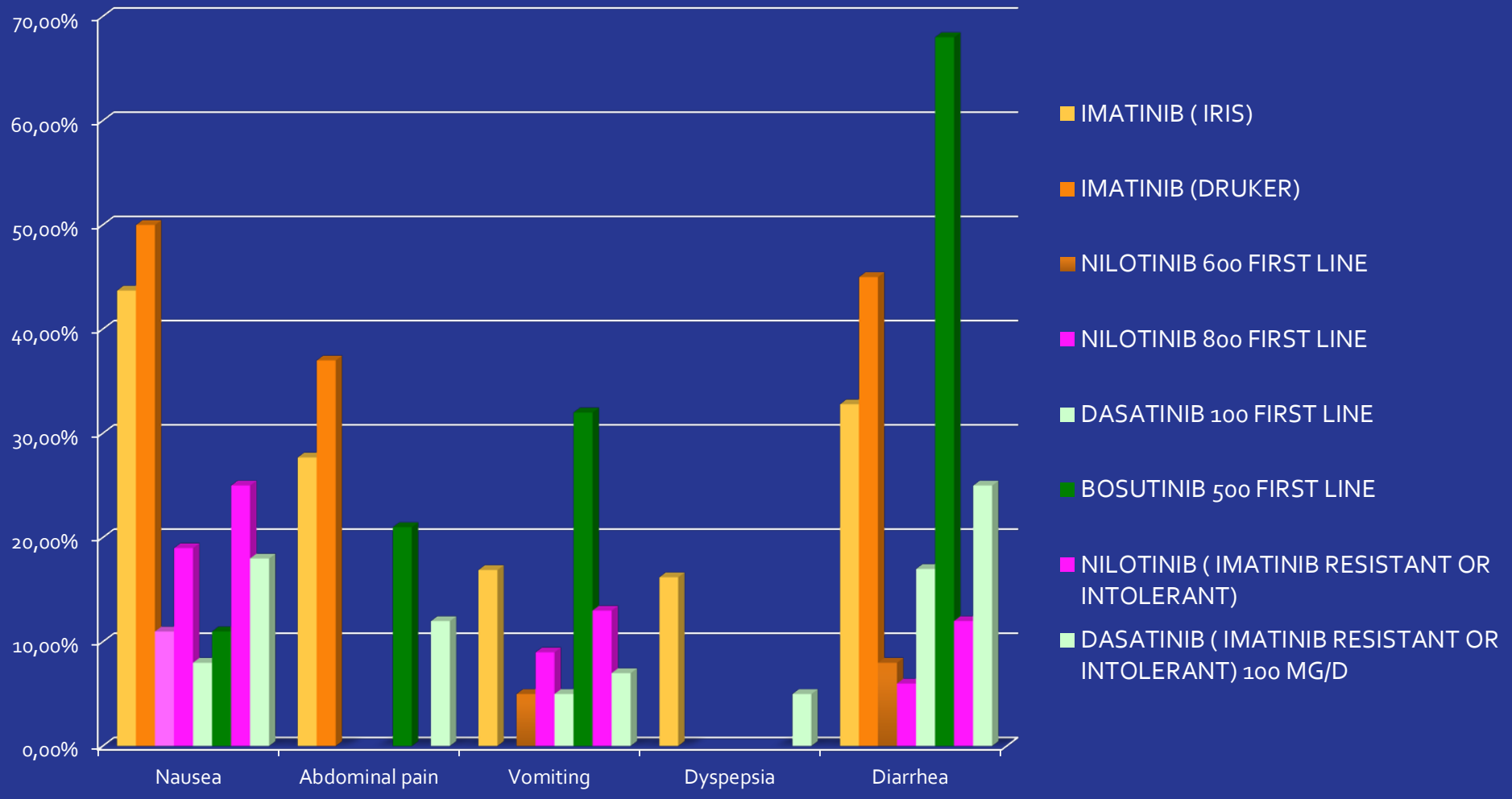
Preventing Pleural Effusion

- Negligible in nilotinib-treated patients
- In dasatinib-treated patients
  - ➢ Higher risk of pleural effusions if
    - Age >66 y
    - Prior autoimmune disease
    - Higher dose
    - Previous rash
    - Others
      - Prior cardiac problems
      - Hypertension
      - Hypercholesterolemia
      - More concomitant medications
      - Higher Charlson Comorbidity Index in patients > 60 y

Phase III study
5 days per week
Interruption over the weekend

1. Reviewed in : Steegmann JL, et al Leuk Lymphoma 2012, 53:2351-2361.
2. Reviewed in : Breccia, M. and G. Alimena (2013). Leuk Res **37**(6): 713-720.
3. Breccia, M., et al. (2011). Haematologica **96**(10): 1457-1461.

Gastrointestinal Adverse Events and BCR-ABL1 Inhibitors



These data are from separate studies.

Larson R. A. et al.JCO 28:7s ASCO 2010 (suppl; abs 6501, Oral);
Shah et al. Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 206;
Gambacorti-Passerini et al. Blood ASH 2010 (suppl; abs 208, Oral).

Hyperglycemia and Nilotinib

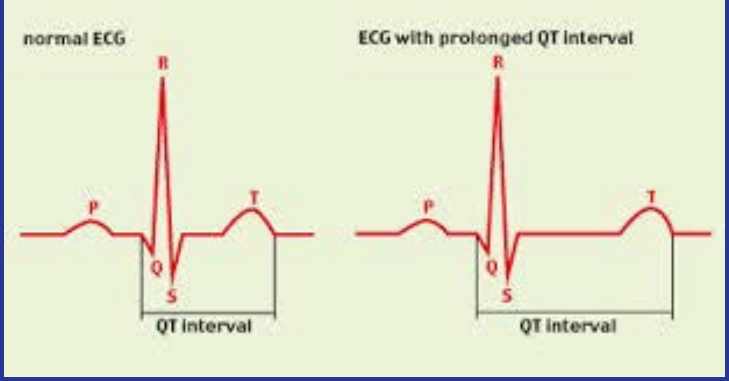
- Cause unknown
- Incidence of glucose elevation
  - All grades: 38-42% (Grade 3-4: 4-6%)
- In non-diabetic patients
  - Median variation: +0.4 mmol/L
- In diabetic patients
  - Median variation: +0.8 mmol/L
  - 69% did not change diabetes therapy
  - CML response not affected (rate of MMR)

Saglio G, et al. Blood 2010;116 [abs 3430].
Saglio G, et al. NEJM 2010;362(24):2251-2259.

Cardiac effects of TKIs and QT Prolongation: Recommendations

Use with caution in patients with

- Uncontrolled or significant cardiac disease
- Patients who have or may develop prolongation of the QTc interval
  - Hypomagnesemia, hypokalemia
  - Congenital long QT syndrome
  - Medications known to cause QTc prolongation
  - Correct hypokalemia and hypomagnesemia prior to TKI administration



Coagulation Problems

- **Thrombocytopenia**
  - Common to all inhibitors
    - KIT, SRC
  - Specific
    - Dasatinib interferes with proplatelet formation
- **Platelet dysfunction**
  - Dasatinib inhibits aggregation
- **Bleeding** mostly restricted to
  - Patients with TKIs and oral anticoagulants
  - Patients with advanced disease treated with dasatinib and having thrombocytopenia

Quintas-Cardama, A., H. Kantarjian, et al. (2009). Cancer 115(11): 2482-2490.

DRUGS WHICH INCREASE TKI EXPOSURE

JL Steegmann, elaborated from Haouala A. et al, Blood. 2011 Feb 24;117(8):e75-87.

Conclusions: Minimizing Adverse Events

- **Knowledge**
  - Different drugs, different spectrum of AEs
- **Prevention**
  - Taking into account comorbidities and medications
- **Treatment of adverse effects**
  - Follow the guidelines
- Attention to interactions
  - Ask your doctor
  - Communication between doctors
  - Web consultation

Reference

Leukemia (2016) **30**, 1648–1671
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www.nature.com/leu

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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]