Old and New Drugs: Side Effects

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Baggers can’t be choosers

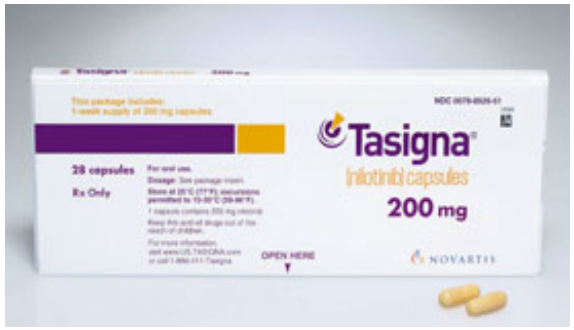
We are not baggers anymore

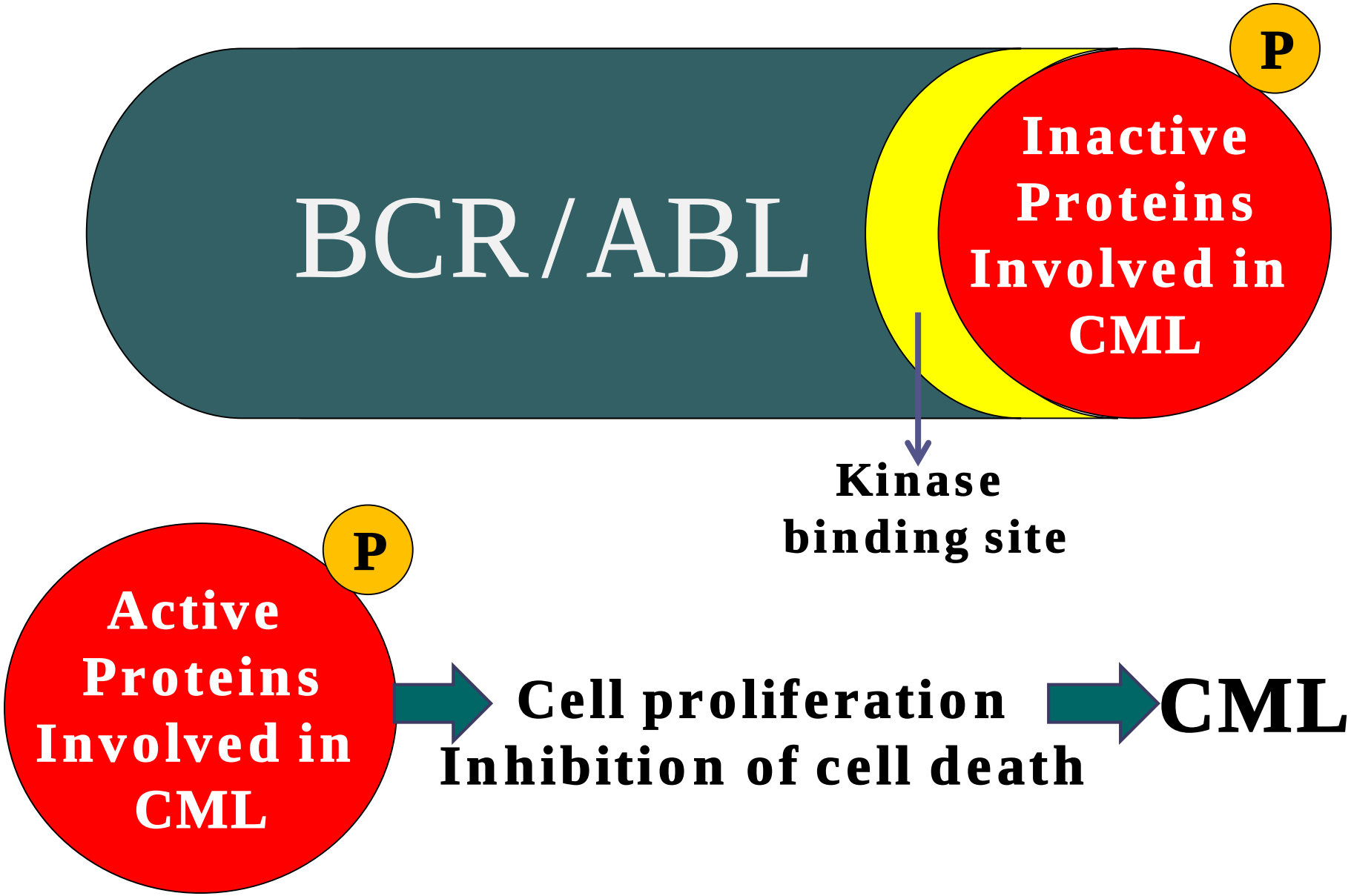
3173/nrc10.1038) | doi:2011(December 832-833 , 11*Nature Reviews Cancer*

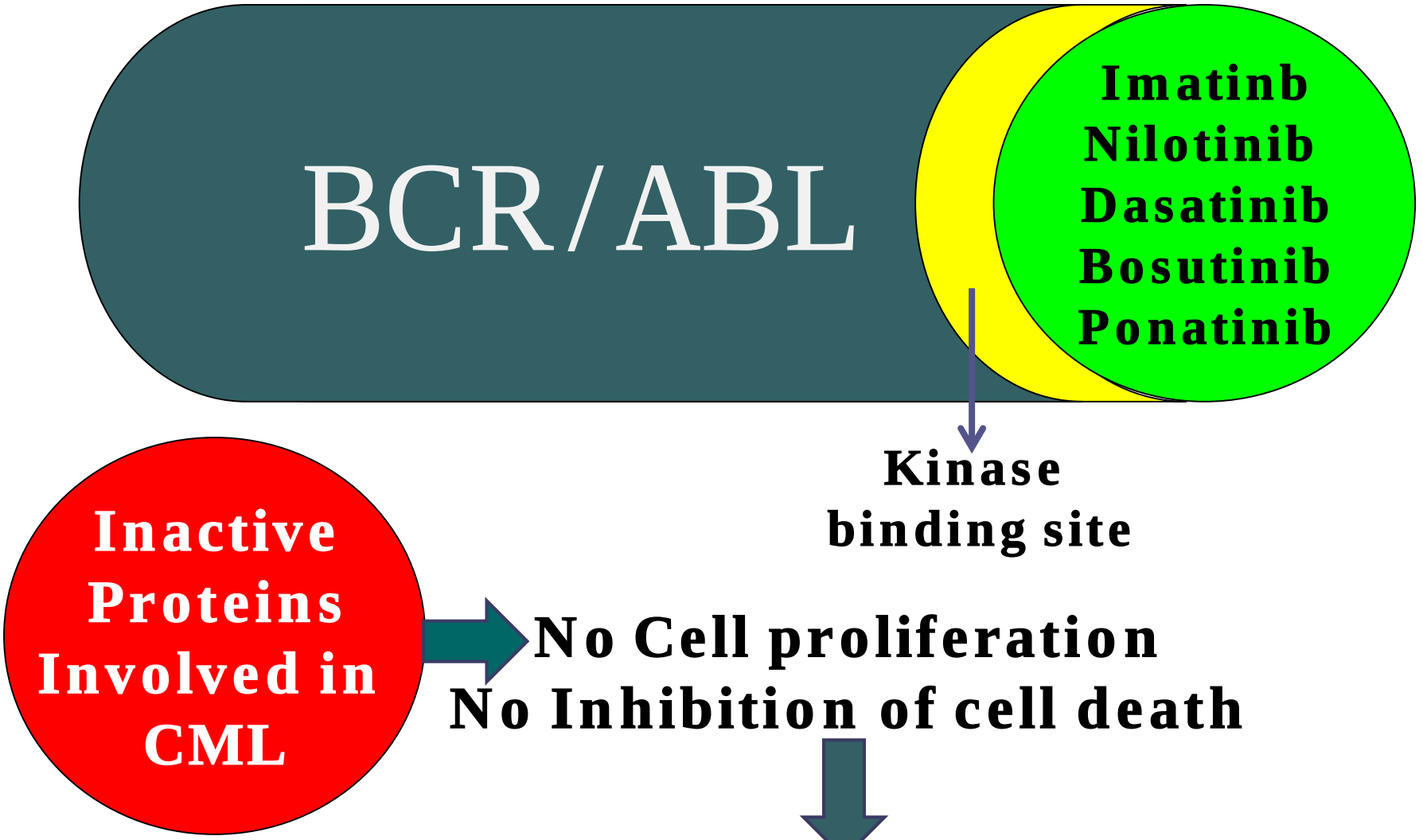
THERAPEUTICS:

Another tool in the BCR-ABL kit?

Sarah Seton-Rogers




P
BCR/ABL
Inactive Proteins Involved in CML
Kinase binding site
P
Active Proteins Involved in CML
Cell proliferation
Inhibition of cell death
CML


BCR/ABL
Imatinb
Nilotinib
Dasatinib
Bosutinib
Ponatinib
Kinase
binding site
Inactive
Proteins
Involved in
CML
No Cell proliferation
No Inhibition of cell death
No CML

The Drugs are not Specific for BCR/ABL Only

In vitro Kinase Targets of the TKIs

Imatinib Nilotinib Bosutinib*	Dasatinib	Ponatinib
BCR–ABL	BCR–ABL	BCR/ABL
C-KIT	C-KIT	C-KIT
DDR1, DDR2	DDR1, DDR2	PDFGRA
CSF-1R	EPHB4	FGFR1-4
PDGFRα/β	PDGFRβ	FLT-3
WT-ABL	WT-ABL	
ETV6–ABL	ETV6–ABL	
NUP214–ABL	NUP214–ABL	
TEL–PDGFRβ	FAK and FYN	
FIP1L1–PDGFRα	HCK	
	LYN	
*SRC	SRC	

Adapted from: Steegmann et al Leukemia&Lymphoma 2012

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*SRC	SRC	

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The Drugs are not Specific for BCR/ABL Only

C-KIT= Factor responsible for blood formation (Stem Cell Factor)

Off Target effects of BCR/ABL Inhibitors Adverse Event (AE) Profiles

- **Hematologic AE**
- **Non-Hematologic AE**
- **Laboratory abnormalities**

Hematologic Adverse Events (%) in Newly Diagnosed Pts with CML on Imatinib, Nilotinib or Dasatinib

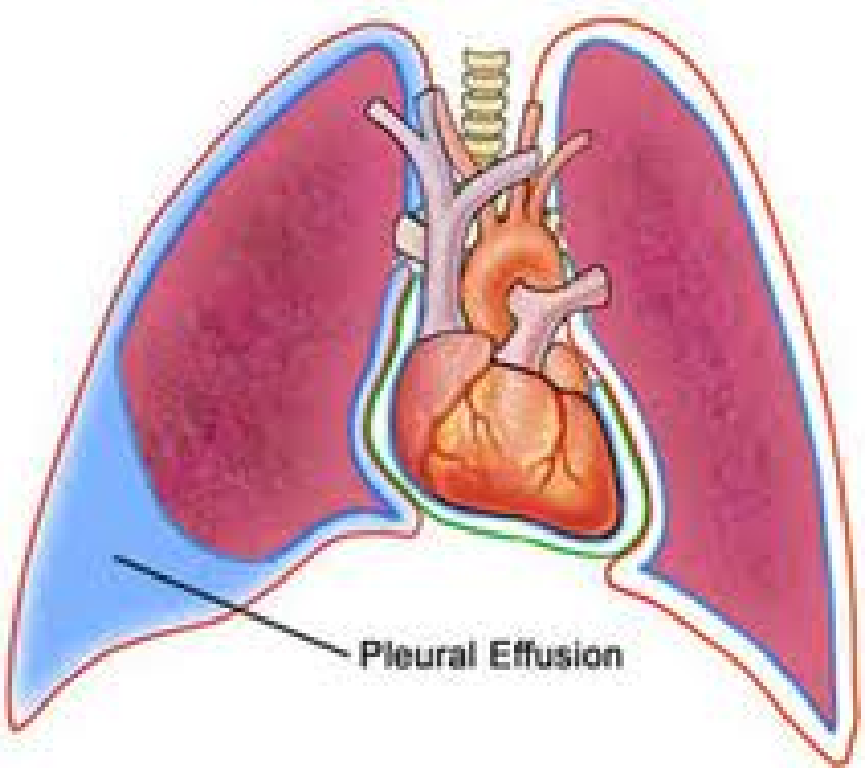
	ENESTnd		DASISION	
	Nilotinib 300 mg bid (n = 279)	Imatinib 400 mg (n = 280)	Dasatinib 100 mg (n = 258)	Imatinib 400 mg (n = 258)
Neutropenia	12	20	21	20
Thrombocytopenia Low platelets	10	9	19	10
Anemia	3	5	10	7

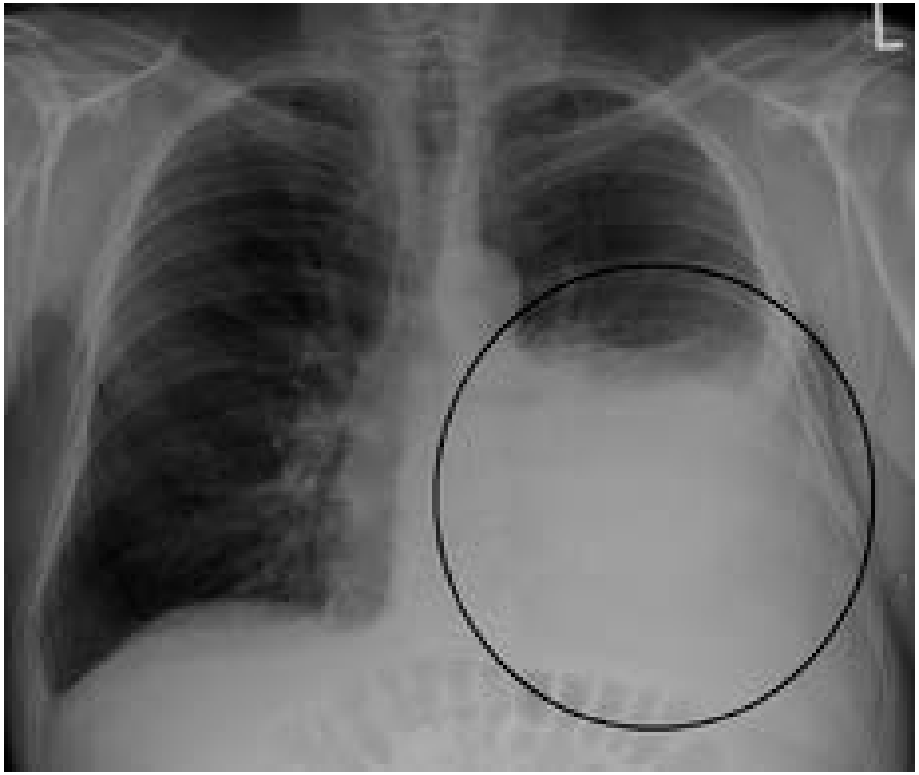
Dasatinib more toxic for the bone marrow

Non Hematologic Adverse Events (%) in Newly Diagnosed Pts on Imatinib, Nilotinib or Dasatinib

	ENESTnd		DASISION	
	Nilotinib 300 mgX2 (n = 279)	Imatinib 400 mg (n = 280)	Dasatinib 100 mg (n = 258)	Imatinib 400 mg (n = 258)
Diarrhea	**Nilotinib and Imatinib more edema, skin problems**			
Fatigue				
Headache				
Nausea/Vomiting				
Peripheral edema				
Superficial edema				
Pruritus				
Rash				
Pleural effusion	**Dasatinib more pleural effusion**			

Pleural Effusion





Fluid retention and TKIs

- Imatinib: peripheral edema (legs) and superficial edema (around the eyes)
- Dasatinib10–20% of patients pleural effusion
  - **Variability in the time to development (5-28 weeks)**
  - **Predictors for the development: Advanced age and twice-daily Dasatinib**

Laboratory abnormalities in Newly Diagnosed Pts on Imatinib, Nilotinib or Dasatinib

	ENESTnd		DASISION	
	Nilotinib 300 mgX2 (n = 279)	Imatinib 400 mg (n = 280)	Dasatinib 100 mg (n = 258)	Imatinib 400 mg (n = 258)
Elevated lipase	++	-	-	-
Hyperglycemia	++	-	-	-
Hypo-phosphatemia Kidney and bones	++	+-	-	+-
Disturbed liver function tests	++	++	+-	+

Long Term Adverse Events: Facts and Myths

- **Cardiovascular effects**
- **Effects on the immune system**
- **Renal Failure**
- **Secondary malignancies**
- **Memory loss**
- **Fertility and sexuality**
- **Overall QOL**

Cardiovascular Effects-Facts

- ***ABL1* has a key role in cardiac development**
- **Imatinib, Nilotinib, dasatinib, Bosutinib Ponatinib are ABL1 inhibitors**
- **ABL1 inhibitors Cardiomyocyte damage induced by continuous treatment *in vitro* with different TKIs**
- **There have been concerns regarding cardiac side effects following treatment with these drugs**

Cardiovascular Effects

- **In a review of serious AEs reported in 1276 pts treated with Imatinib**
- **1.7% (22 pts) had heart failure-related symptoms**
  - **18 had predisposing cardiac risk factors or symptoms**
  - **11 who remained on treatment underwent dose reductions and had no further symptoms**

QT-Interval

- QT interval represents electrical changes in the heart during heart beat
- A lengthened QT interval is a biomarker for

❖**Despite isolated reports of QTc increases, these events are rare (0.4-1.7%) but important!**

❖**More likely to occur in pts with a history of cardiac disease or those who have underlying cardiac risk factors**

Effects on the Immune System

- Preclinical data suggest that Nilotinib, Imatinib and Dasatinib have effects on the immune system
- However, the preclinical immunosuppressive effects observed with most TKIs correlate poorly with the effects observed in patients
- 3000 CML patients treated at MD Anderson with TKIs>10 years - No higher incidence of infectious diseases compared to the general population

Renal Failure

- Acute renal failure has been reported in several patients, including Imatinib-resistant patients receiving second-line Nilotinib or Dasatinib
- The true incidence is unknown
- In a 5-year study of 105 patients with CML, imatinib treatment was associated with chronic renal failure in 12% of patients
- Renal effects may be related to altered phosphorus/calcium processing in the kidney

Secondary Malignancies

- The incidence of secondary cancers in patients treated with any TKI, appears to be similar to the incidence in the general population
- 3000 CML patients treated at MD Anderson with TKIs>10 years - No higher incidence of malignant diseases compared to the general population

On Apr, 5, 2013: 19,753 people who reported to have side effects when taking Imatinib
125 people (0.63%)-Memory Loss

Imatinib do not cross the Blood Brain Barrier

Fertility and Sexuality

- **Men: On Imatinib OK, Nilotinib and Dasatinb probably OK unknown yet**
- **Women: Teratogenic**
- **On Apr, 3, 2013: 19,753 people reported to have side effects when taking Imatinib Among them, 19 people (0.10%) have Erectile Dysfunction**

Most Common Adverse Events With Ponatinib (449 pts) Cortes JE, et al. ASH 2012

Nonhematologic	GRADE 3/4
Rash/Dry skin	6
Abdominal pain	9
Headache	2
Constipation	2
Hypertension	7
Lipase increased	12
Pancreatitis	5

Hematologic	
Low Platelets	34
Neutropenia	21
Anemia	14

Bosutinib The Bela Trial

- **Gastrointestinal and liver-related events were more frequent with Bosutinib**
- **Neutropenia, musculoskeletal disorders, and edema were more frequent with Imatinib.**

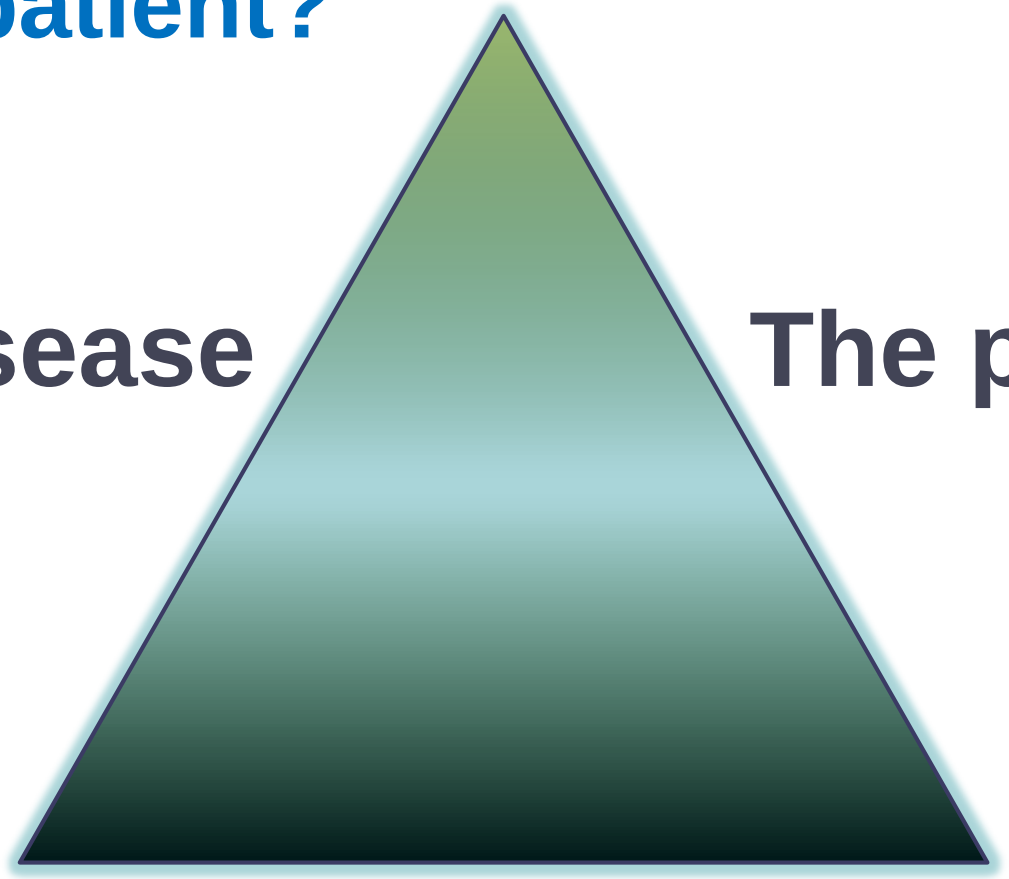
Overall Quality Of Life

- **Constant awareness of having leukemia (Older vs Younger)**
- Compared to controls (*n* = 62), CML patients (*n* = 62) taking a TKI (Imatinib 55 % Nilotinib 31 % Dasatinib 14 %) reported:
  - **Significantly worse fatigue**
  - **More depression**

Phillips et al Support Care Cancer 2013

How to select the appropriate Drug to my patient?

The disease



The patient

The X factor

Considerations Regarding the Patient

- **Co morbidities**
- **Compliance**

Choosing Between Nilotinib and Dasatinib

Problematic with Nilotinib	Problematic with both	Problematic with Dasatinib
Liver or pancreatic disease	Myelosupression	Heart and lung disease
Hyperlipidemia	Gastrointestinal tract	Anticoagulat Rx
Uncontrolled diabetes	Prolonged QT	
Skin problems		

Compliance

- **Once daily versus twice daily with food restriction**
- **No difference in clinical trials**
- **What about real life?**

The X Factor
The physician the Companies & National Reimbursement

- The physicians filling more secure with a drug used for over 12 years (Imatinib)
- The drug companies and the prices
- Imatinib being Generic: The insurance companies and the national health basket

Conclusions

- The tyrosine kinase inhibitors has greatly improved patients' survival and prolonged disease remission
- The TKIs are well tolerated in most patients
- The TKIs are not entirely BCR–ABL specific, leading to off-target side effects
- Understanding the side effects is a powerful tool in choosing the appropriate drug to a given patient and dictates the tests for early detection and intervention

Thank You

Peripheral Arterial Occlusive Disease

- 11 of 179 patients (6%) developed severe PAOD while on nilotinib. All but one had known risk factors for PAOD
- The 2-year follow-up of the ENESTnd trial revealed a total of six cases of PAOD in both nilotinib arms, with no cases observed on imatinib
- All six cases occurred in patients with preexisting risk factors for PAOD: older age, history of smoking, hypertension, diabetes and hypercholesterolemia