Chronic myeloid leukaemia

Nilotinib in the front line setting: Update on efficacy and safety

Chronic myeloid leukaemia

- Myeloproliferative neoplasm that originates in an abnormal pluripotent bone marrow (BM) stem cell and is consistently asssociated with the BCR-ABL fusion gene located in the Philadelphia (Ph) cromosome

CML - Incidence

- CML occurs more often in men than in women, the ratio being 1.3-1.8/100,000♂; 1/100,000♀.
- In caucasians, CML occurs more often in senior patients with a median age of about 60 years.
- In the Asia-Pacific Region the mean age is only 45 years.
- The median age of CML patients in clinical trials is about 50 years.

Little is known about regional and social variability, and about the stage of CML at diagnosis in the population.

IBE
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Etiology of CML

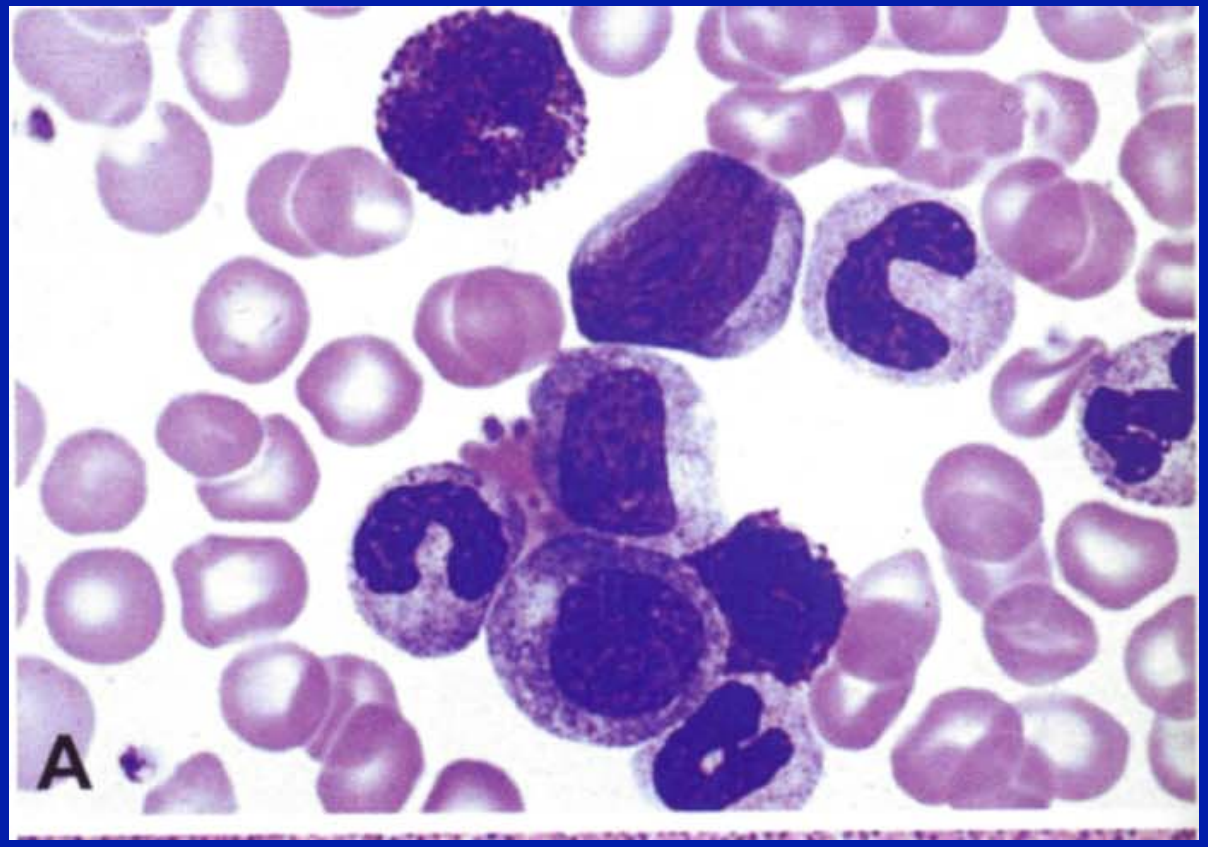
- CML most probably an acquired disease, very few familial cases only
- High dose ionising radiation (e.g. Hiroshima)
- Chemical exposures to benzene, organic solvents, alkylating agents and topoisomerase II inhibitors

Very little is known about the etiology of CML

Morphology

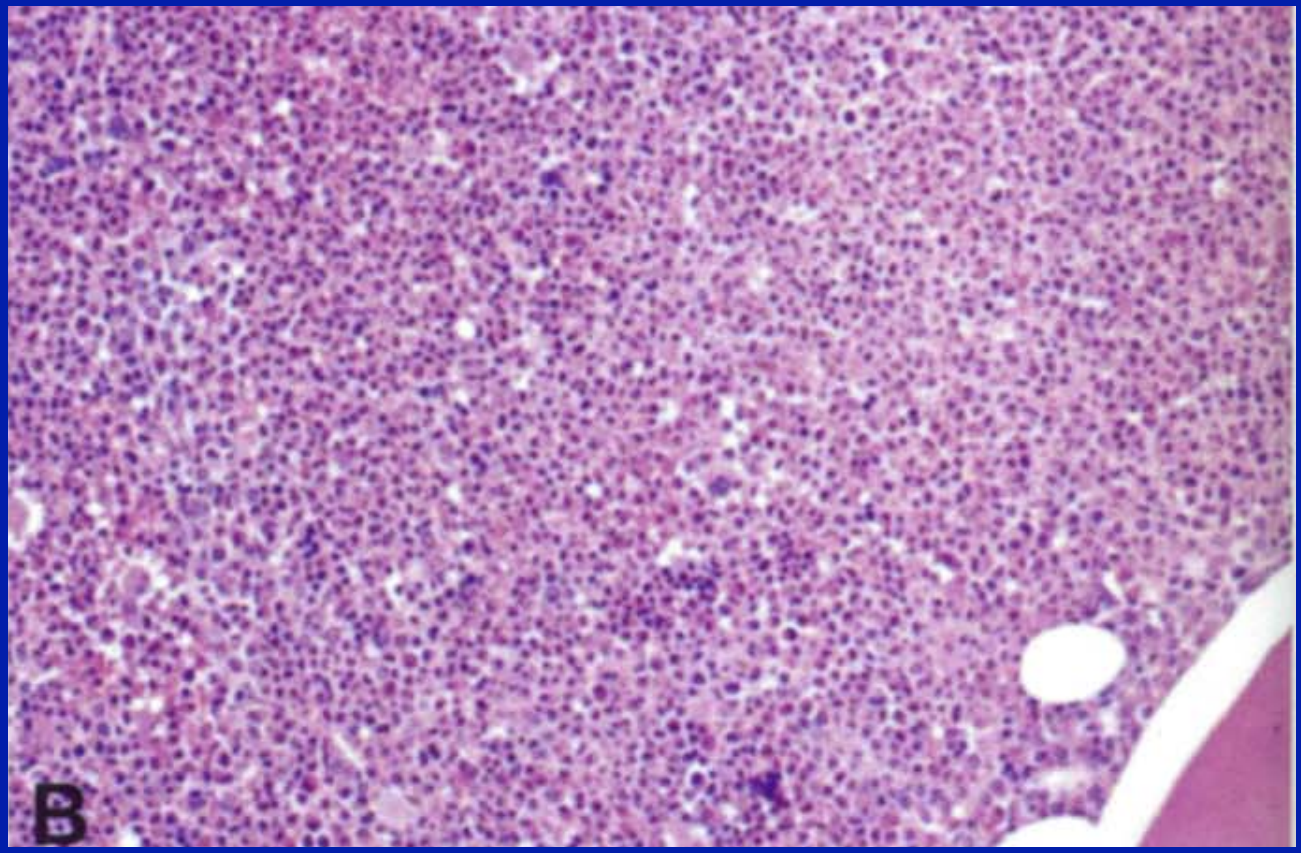
- Chronic phase (CP)
- Leukocytosis, Platelet count usually ranges from normal to greater than 1000x10e9/L
- Accelerated phase (AP)
- Blast phase (BP)

CML - chronic phase



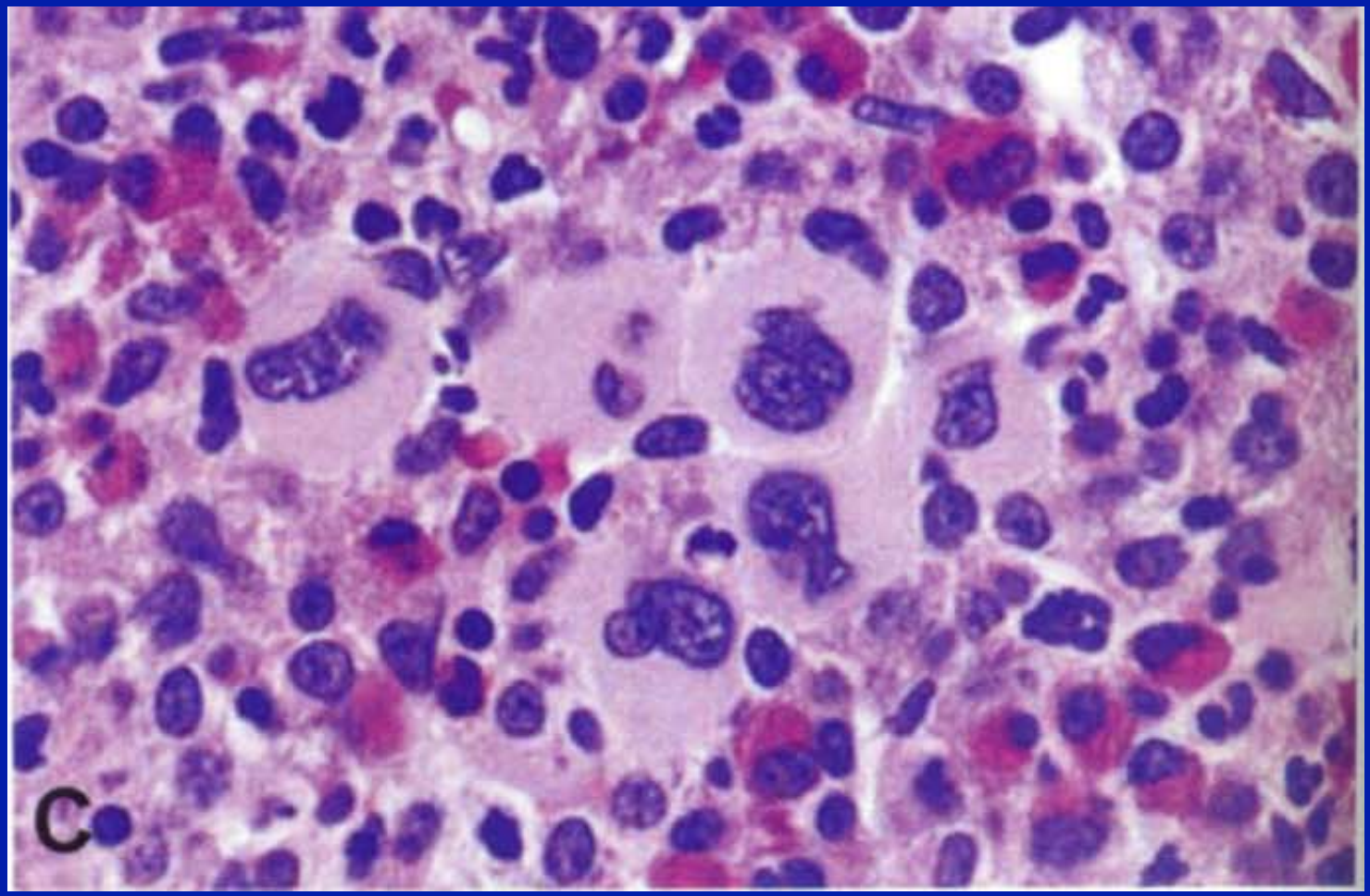
A) Peripheral blood smear showing leukocytosis and neutrophilic cells at varying, stages of maturation. Basophilia is prominent. No dysplasia is present.

CML - chronic phase



B) Bone marrow biopsy shows marked hyper- cellularity due to granulocytic proliferation.

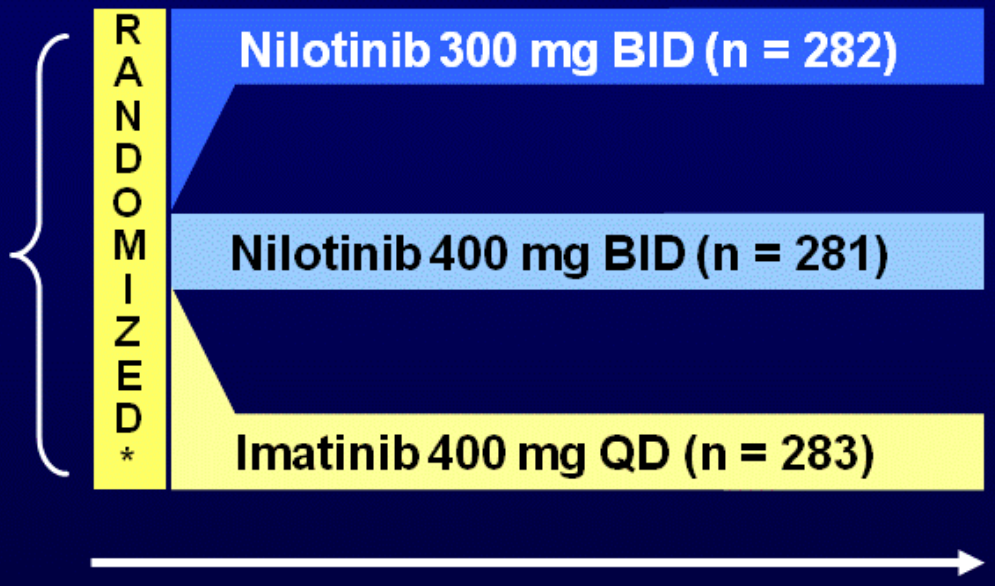
CML - chronic phase



C) The i megakaryocytes in CML are characteristically smaller than normal megakaryocytes.

Study Design and Endpoints

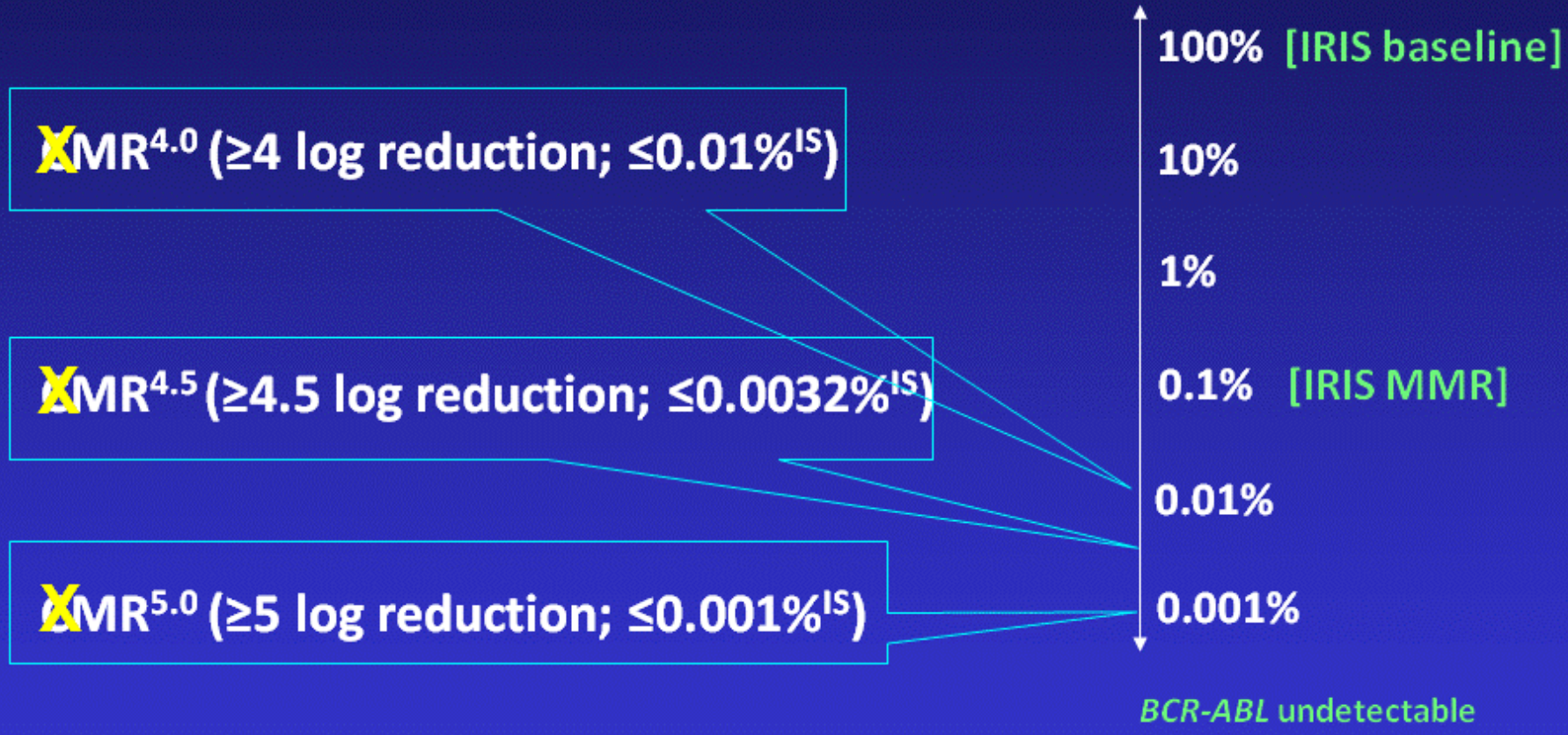
- N = 846
- 217 centers
- 35 countries



- Primary endpoint: MMR at 12 months
- Key secondary endpoint: Durable MMR at 24 months
- Other endpoints: CCyR, time to MMR and CCyR, EFS, PFS, time to AP/BC, OS

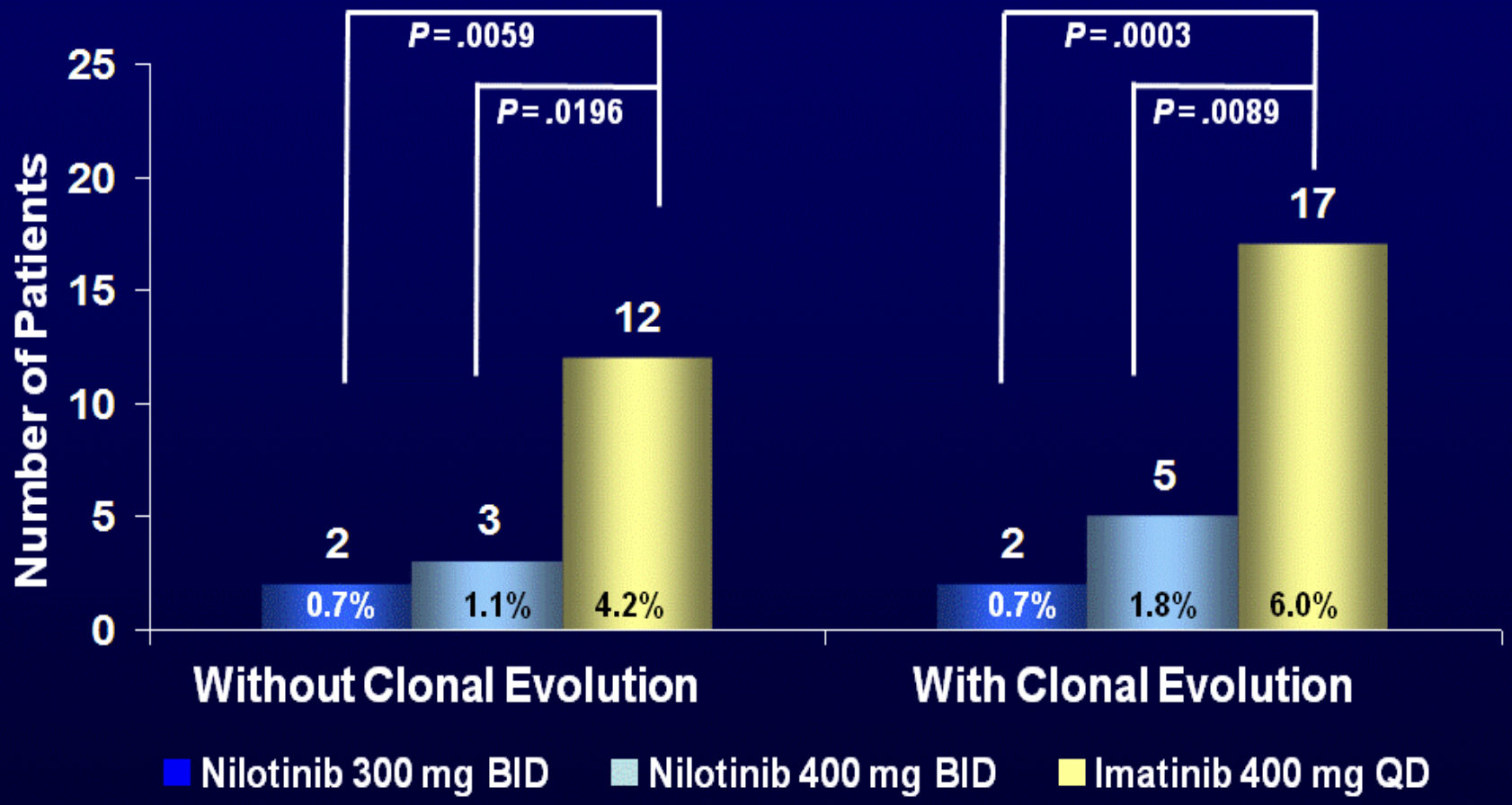
*Stratification by Sokal risk score

Definition of (Complete) Molecular Response: Disease (detectable or undetectable) below a defined level



log reduction = reduction from IRIS baseline, not individual pretreatment levels

Progression to AP/BC (on Treatment)*†



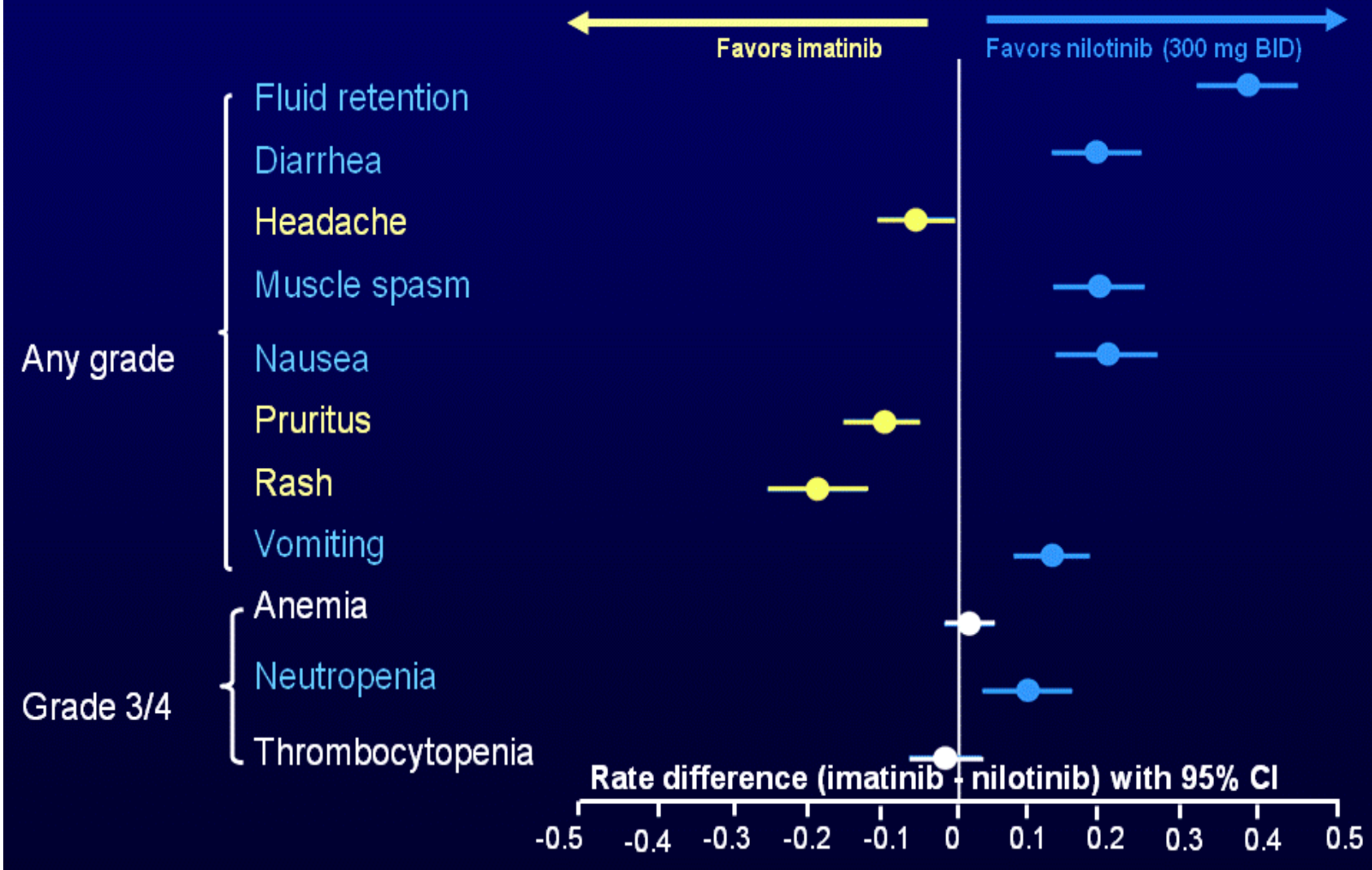
*ITT population

† Progression to AP/BC or death due to CML while on study drug

Kantarjian H, et al. *Lancet Oncol.* 2011 Sep;12(9):841-51. Epub 2011 Aug 17.

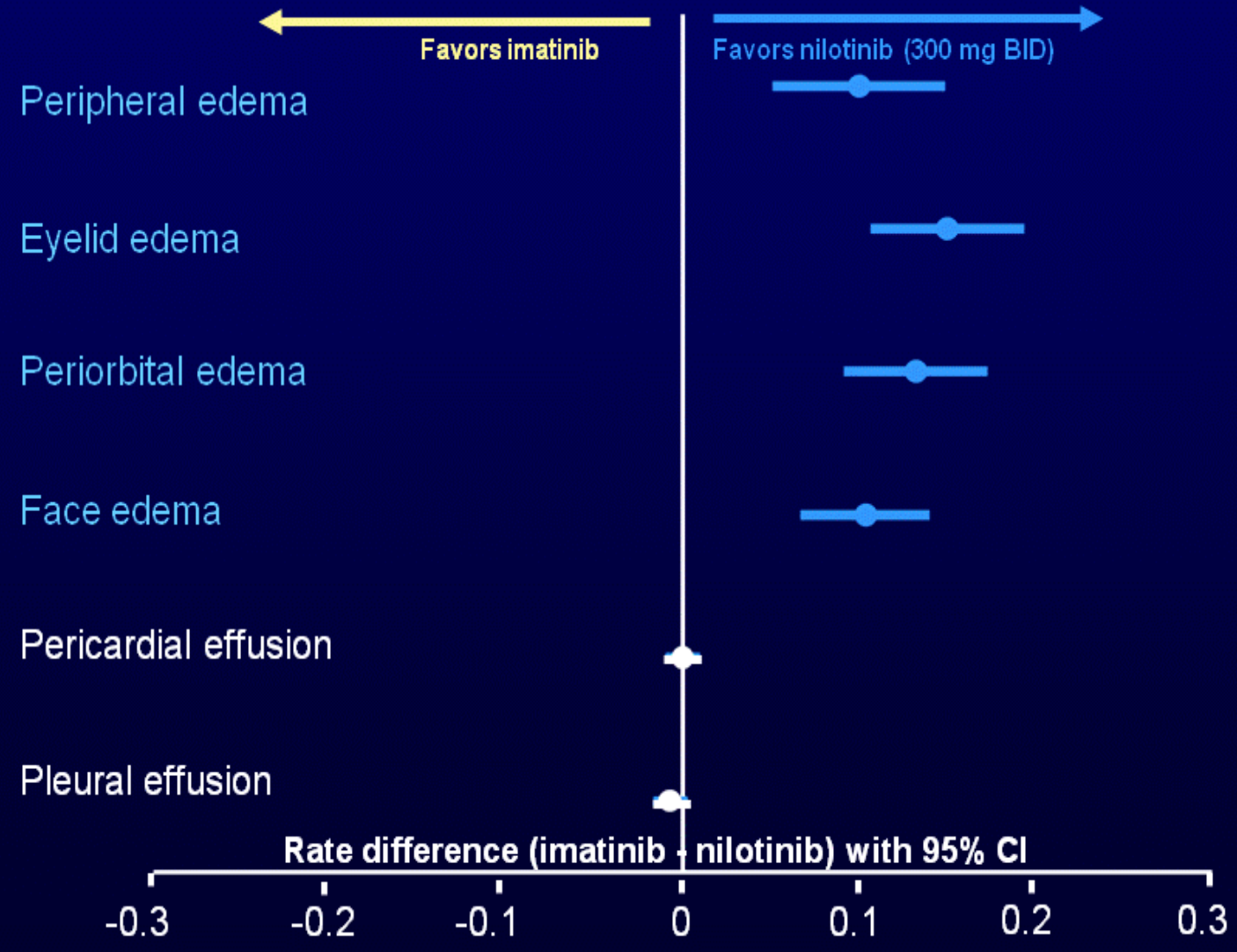
Data cut-off: 20Aug2010

Study Drug-Related Adverse Events and Grade 3/4 Myelosuppression



Larson RA, et al. J Clin Oncol. 2011;29(15s):421s [abstract 6511].

Study Drug-Related Fluid Retention Events (All Grades)



Larson RA, et al. J Clin Oncol. 2011;29(15s):421s [abstract 6511].

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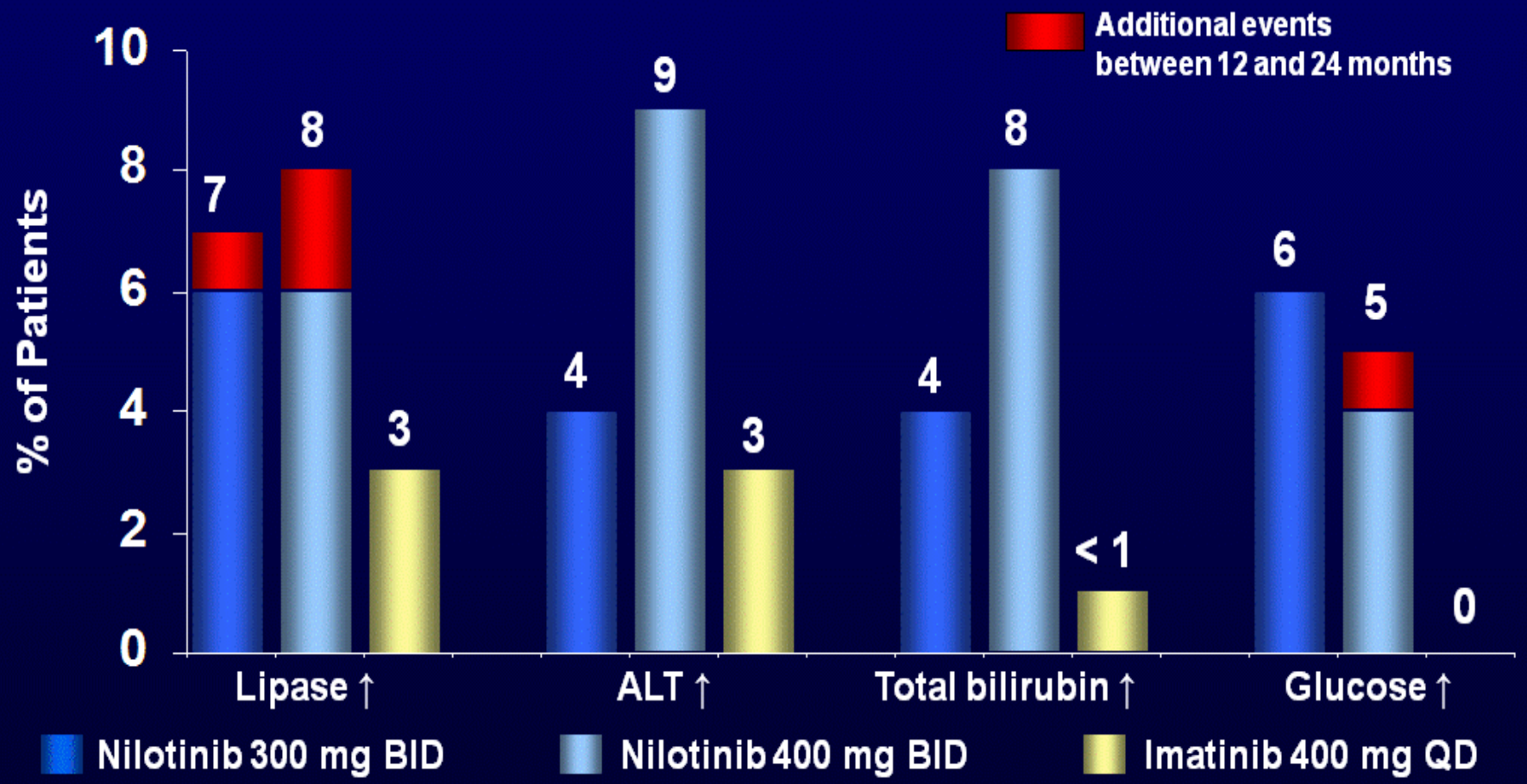
Grade 3/4 Pancreatic and Liver Toxicity and Hyperglycemia



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Data cut-off: 20Aug2010

Hyperglycaemia and Nilotinib

- Cause unknown
- Incidence
  - 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 DM therapy
  - CML response not affected

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

Cardiac Effects of TKIs

CHF and LV dysfuntion

- Imatinib: The overall incidence of CHF is 1-2%
- Dasatinib: 4% of patients developed CHF or LV dysfunction, (50% grade III or IV)
- Nilotinib in <65 y vs ≥65 y: Myocardial infarction (<1% vs 4%), CHF (2% vs 1%), and QTcF prolongation >500 msec (<1% vs 2%)

Sudden deaths

	N (%)
Imatinib CP	3/532 (0.6%)
Imatinib AP	2/235 (0.9%)
Dasatinib	3/511 (0.4%)
Nilotinib (All)	5/940 (0.5%)

QTc prolongation

	QTcF >500 ms, N (%)
Dasatinib	<1%
Nilotinib (All)	<1%

Atallah et al. Blood 2007;110(4):1233-1237.
Lipton et al. Blood 2008;112(11) [abs 3233].
Bristol-Myers Squibb. Sprycel (dasatinib) Prescribing Information (2006).
Novartis. Data on Safety Reports, BMS, idem.

Phosphocalcium Metabolism and Bone Homeostasis

- Hypophosphatemia
  - Described in 20-50% (Imatinib >nilotinib >dasatinib)
- Pathogenesis mediated by
  - c-fms, Src, c-Kit inhibition
- Bone Homeostasis
  - Imatinib inhibits bone remodeling
  - Imatinib increases bone cortical density
  - Imatinib retards bone growth in children

Imatinib	Nilotinib	Dasatinib
Decreases osteoclast function	Decreases osteoclast function	Osteoclast dysfunction
Inhibits osteoclastogenesis	Strongly inhibits osteoclastogenesis	

Sharma et al. Ind. J. Derma. Venereol. Leprol. 2005;71(1):45-46.
Osorio et al. Am. J. Hematol. 2006;82(5):394-395.
Berman et al. N. Engl. J. Med. 2006;354 (19):2006-2013.
Kimoto et al. Int. J Hematol. 2009;89(2):251-252.
O' Sullivan et al. JBMR. 2007;22(11):1679-89.
Vandyke et al. Blood. 2010;115(4):766-74.
Bronlow , N , et al. Leukemia, 2008;23(590):594-98.
Bronlow, N et al Leukemia 2008;22(3):649-652.
Millot F, et al. ASH Annual Meeting Abstracts 2009;114:863.

Exposure To Imatinib During Pregnancy

- Imatinib is teratogenic, embryotoxic (not genotoxic) and causes increased rates of post implantation loss.
- Clinical trials excluded pregnant women.
- Most pregnancies are unplanned.
- Insufficient data available yet.
- “Specific” pharmacovigilance requested.

Foetal Abnormalities

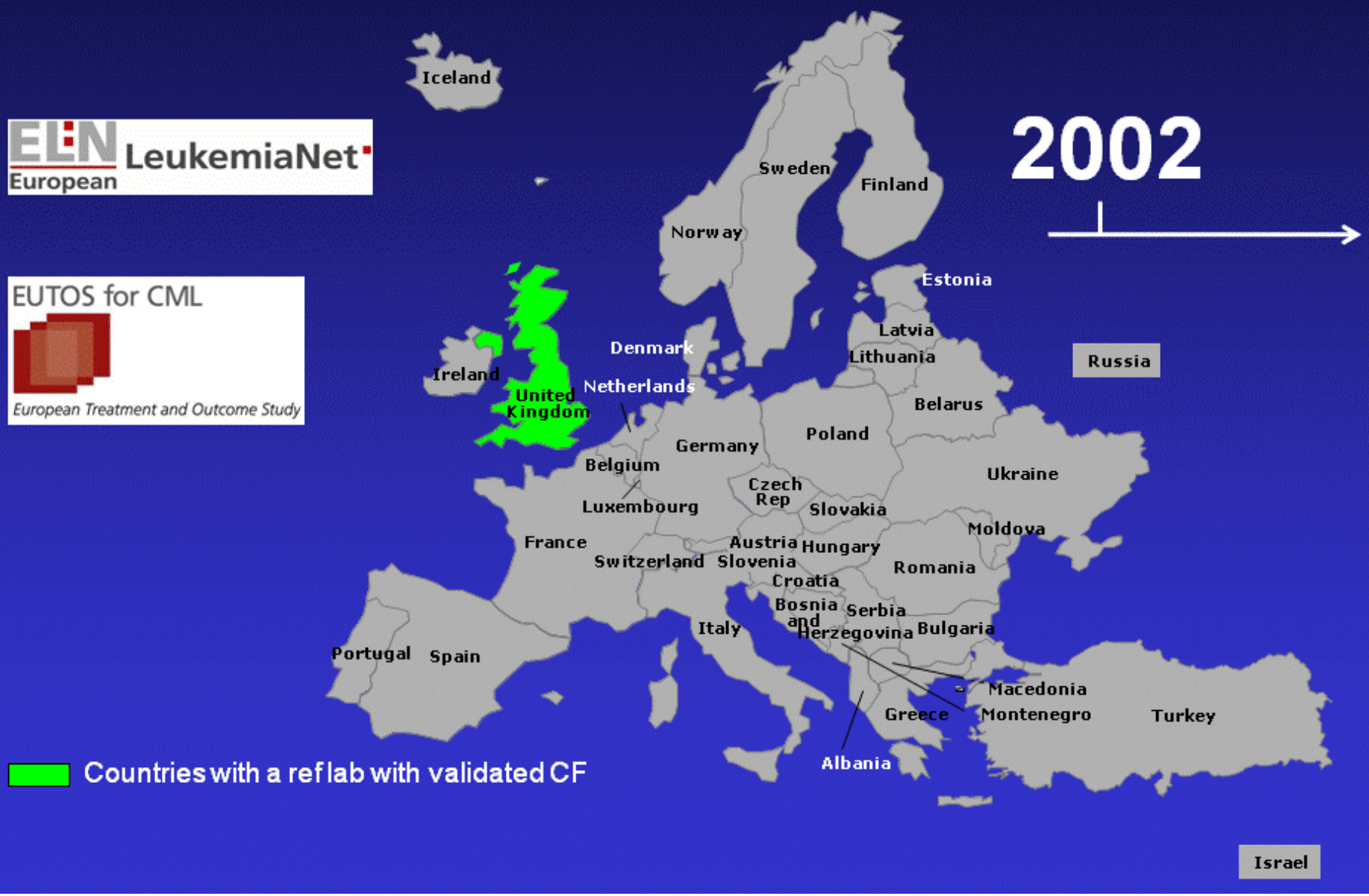
- **Case 1:** Premature closure of skull sutures (craniosynostosis).
- **Case 2:** Hypoplastic lungs, exomphalos, left duplex kidney, right absent kidney, hemivertebrae and right shoulder anomaly.
- **Case 3:** Exomphalos, right renal agenesis and hemivertebrae.
- **Case 4:** Small exomphalos, scoliosis.

Basic Prescribing Information

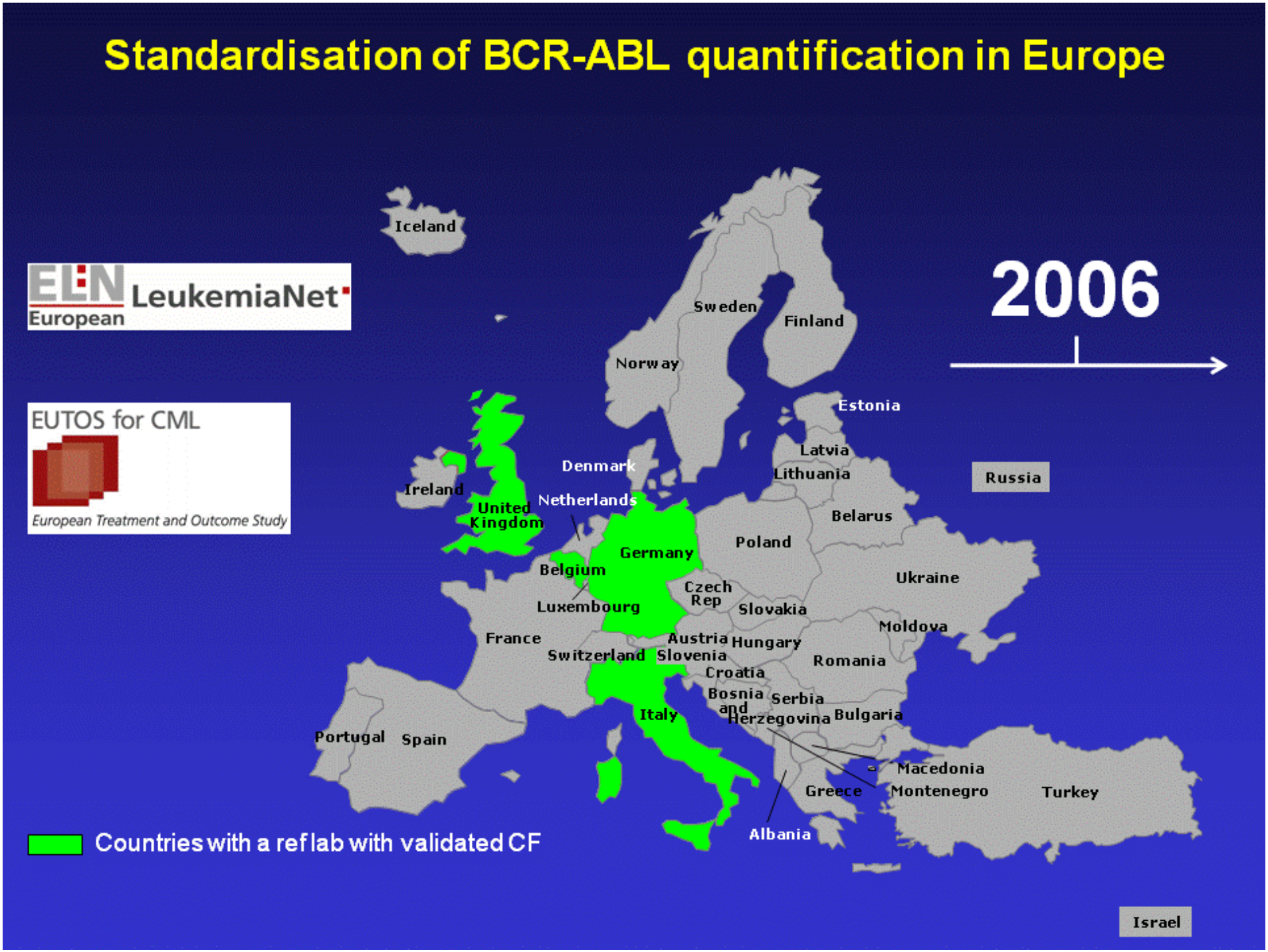
- Effective contraception during treatment is therefore strongly recommended for women of child bearing age.
- No special precautions for male patients who wish to father a child during treatment.

FDA: TKIs are CLASS D drugs

Standardisation of BCR-ABL quantification in Europe

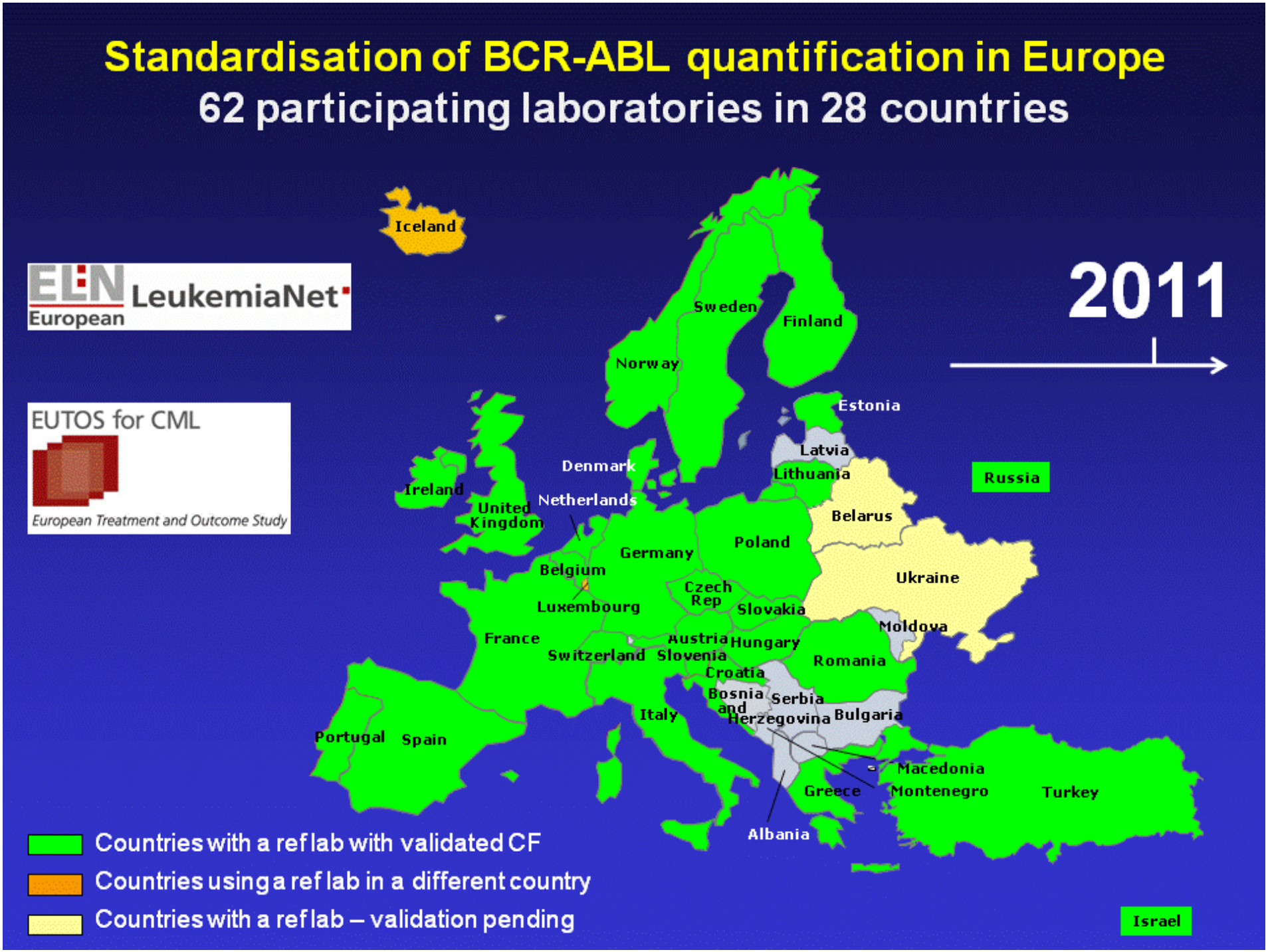


Standardisation of BCR-ABL quantification in Europe



Standardisation of BCR-ABL quantification in Europe

62 participating laboratories in 28 countries



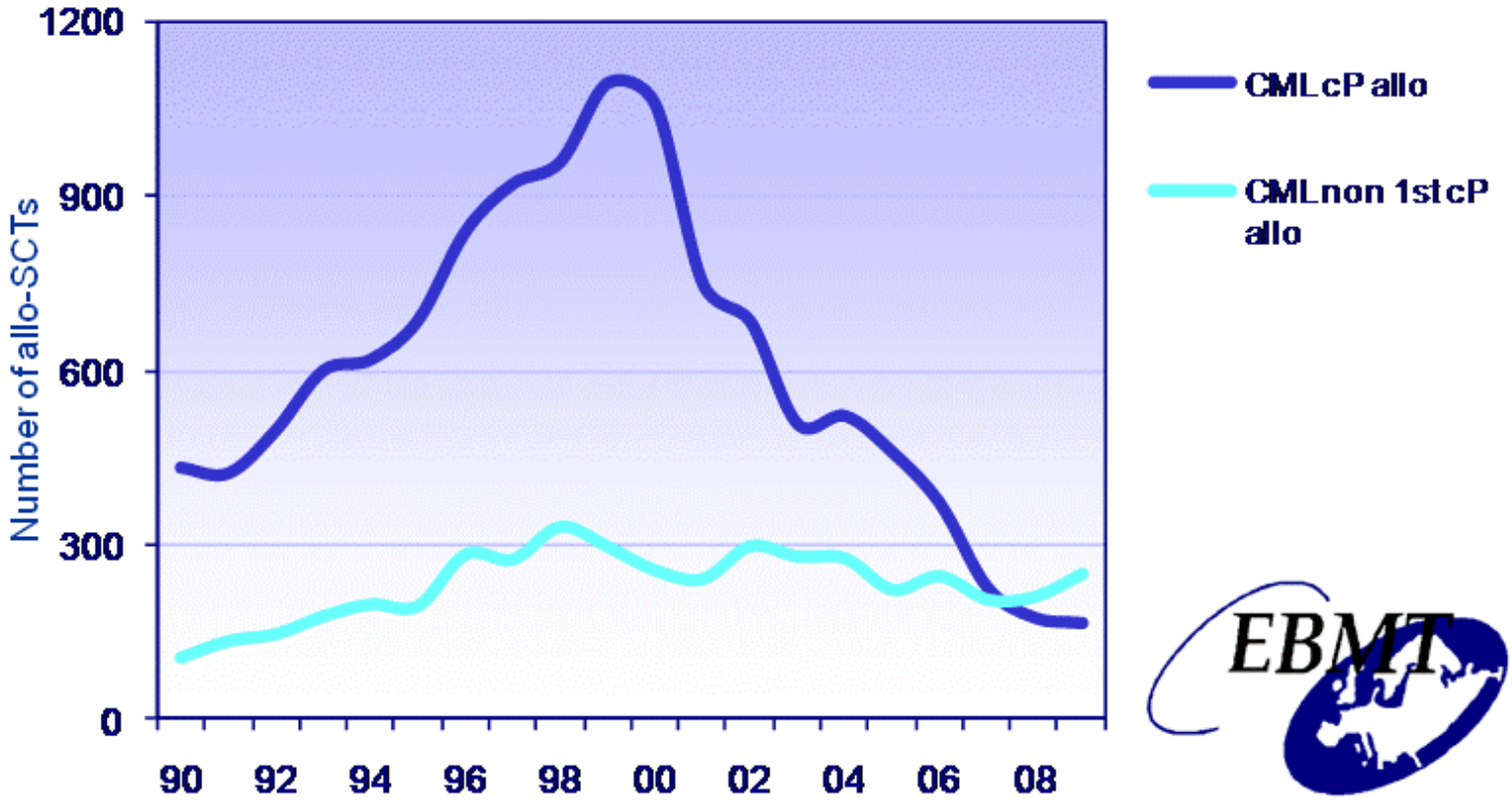
Standardisation of Complete Molecular Response (CMR)

- Achievement of $CMR^{4.0}$ at 18 months is the primary endpoint of the ongoing ENEST1st study (European single arm study of front-line nilotinib 300 mg BID)
- Standardisation of CMR is ongoing
  - Conversion factors are not sufficient to standardise CMR
- ENEST1st: Limited number of monitoring centres
  - Measurement of laboratory performance
  - Agreement of common laboratory definitions and protocols
  - Optimisation of assay sensitivity
- Expand to other EUTOS reference labs in 2011-12

EUTOS for CML

European Treatment and Outcome Study

Stem Cell Transplantations in Europe 1990-2008



16th CONGRESS OF THE EUROPEAN HEMATOLOGY ASSOCIATION
LONDON, 9-12 JUNE 2011
BLOOD 2011;118(3):686-692

A NEW PROGNOSTIC SCORE (EUTOS SCORE) PREDICTING COMPLETE CYTOGENETIC RESPONSE AND PROGRESSION-FREE SURVIVAL IN 2060 PATIENTS WITH CHRONIC MYELOID LEUKEMIA ON IMATINIB TREATMENT

J. HASFORD, M. BACCARANI, V. HOFFMANN, J. GUILHOT, S. SAUSSELE, G. ROSTI, F. GUILHOT, K. PORKKA, G. OSSENKOPPELE, D. LINDOERFER, B. SIMONSSON, M. PFIRRMANN, R. HEHLMANN

BOLOGNA, MÜNCHEN, MANNHEIM / HEIDELBERG, POITIERS, HELSINKI, AMSTERDAM, UPPSALA

ELN European LeukemiaNet

EUTOS for CML
European Treatment and Outcome Study

VARIABLES INFLUENCING CCgR AT 18 MONTHS

Significant in univariate analysis:

- **Spleen size**
- **Basophils**
- Blast cells
- Eosinophils
- Leukocytes

ELN European LeukemiaNet

Hasford and Baccarani et al., Blood 2011;118(3):686-692.

EUTOS for CML
European Treatment and Outcome Study

MODEL FOR PREDICTING CCgR AT 18 MONTHS

EUTOS SCORE

7 * Basophils + 4 * Spleen Size

- > 87 ➡ high risk
- ≤ 87 ➡ low risk

Basophils : % in blood

Spleen size : cm below costal margin, manual palpation

ELN LeukemiaNet European

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EUTOS for CML
European Treatment and Outcome Study

WHY SPLEEN AND BASOPHILS ?

SPLEEN SIZE, THOUGH IT IS ASSESSED BY MANUAL PALPATION, HAS BEEN ASSOCIATED WITH PROGNOSIS IN ALL STUDIES, OVER THE LAST 50 YEARS

SPLEEN CAN PROVIDE AN ALTERNATIVE NICHE TO Ph+ STEM AND PROGENITOR CELLS

BASOPHILS ARE MORPHOLOGICALLY ABNORMAL IN CML - A HIGH PERCENTAGE OF BASOPHILS (MORE THAN 20%) IS A CONFIRMED MARKER OF ACCELERATED PHASE

ELN LeukemiaNet European

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EUTOS for CML
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THE ELN / EUTOS CML REGISTRY
THE EUTOS SCORE

"HIGH RISK" PTS ARE 10 % OF ALL PATIENTS

34% OF THEM DO NOT ACHIEVE A CCgR WITIHIN 18 MONTHS

"LOW RISK" PTS ARE 90 % OF ALL PATIENTS

14% OF THEM DO NOT ACHIEVE A CCgR WITHIN 18 MONTHS

ELN European LeukemiaNet

Hasford and Baccarani et al., Blood 2011;118(3):686-692.

EUTOS for CML
European Treatment and Outcome Study

EUTOS RISK SCORE CONCLUSIONS

- CCgR at 18 months is an important prognostic factor for progression-free survival

The new model:

- is clinically simple, with only two variables (spleen size and basophils), and easy to calculate.
- balances the size of the high-risk group, positive predictive value, sensitivity and specificity, well.
- the model has statistical value, has been validated in an independent dataset, and can be easily applied in clinical practice.

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EUTOS for CML
European Treatment and Outcome Study

When CP Ph+ CML patients show sings of Glevec resistance or- intolerance

THINK TASIGNA

- **TASIGNA helps patients optimize treatment outcomes**
- Powerful, durable response with favorable tolerability
- Highly targeted for Bcr-Abl, the key cause and driver of CP Ph+ CML

- CHR=complete hematologic response; PCyR=partial cytogenetic response;
- CCyR=complete cytogenetic response; MMR=major molecular response.