

Highlights from EHA

Novità dall'EHA >> [Leucemia mieloide cronica]
CML EHA: what's new?

Relatore: **G. MARTINELLI**

27-28 ottobre 2008

Borgo S. Luigi – Monteriggioni (Siena)

CML EHA: What's new?

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- **TKI in Front line**
- Nilotinib in Newly Diagnosed CML-CP
 - M.D. Anderson Cancer Center (MDACC)
 - Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA)
- Dasatinib in Newly Diagnosed CML-CP
 - M.D. Anderson Cancer Center (MDACC) (0881)
 - Other experiences
- **HD imatinib in Newly Diagnosed CML-CP**
 - M.D. Anderson Cancer Center (MDACC)
 - Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) (0405)
 - TOPs (0402)
 - Austria (Andreas's) experience (0406)

Nilotinib in Newly Diagnosed CML-CP (MDACC) (#0121)

Study Design

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- Phase II, open-label trial by M.D. Anderson Cancer Center (MDACC)
- Patient Population
 - Newly diagnosed Ph+ CML-CP
 - No prior therapy or <1 month of IFN-a or imatinib
- Nilotinib 400 mg po bid
- Primary endpoint: Major molecular response (MMR) at 12 months
- Secondary endpoints
 - CCyR rate
 - Time to response
 - Duration of response
 - Event-free survival
 - Overall survival

www.clinicaltrials.gov. NCT00129740.

Cortes J, et al. ASCO 2008. Abstract 7016.

Cortes JC, et al. European Hematology Association 2008. Abstract 0121.

Nilotinib in Newly Diagnosed CML-CP (GIMEMA) (#0404)

Study Design

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- Phase II, open-label, multicenter trial by Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA)
- Patient Population
 - ▣ Adults with newly diagnosed CML-CP (within 6 months from diagnosis)
 - ▣ No prior treatment with antileukemic drugs (except hydroxyurea and anagrelide)
- **Nilotinib 400 mg po bid**
- Primary endpoint: **Rate of CCyR at 1 year**
- Secondary endpoints:
 - ▣ Rate of CCyR and PCyR at 6 months
 - ▣ Rate of MMR at 1 year
 - ▣ Kinetics of hematologic, cytogenetic and molecular response
 - ▣ Development of mutations during nilotinib treatment
 - ▣ Safety and tolerability

Available at: www.clinicaltrials.gov. NCT00481052.

Rosti G, et al. ASCO 2008. Abstract 7054.

Rosti GR, et al. European Hematology Association 2008. Abstract 0404.

Nilotinib in Newly Diagnosed CML-CP

MDACC vs Gimema

Demographics and Nilotinib Exposure

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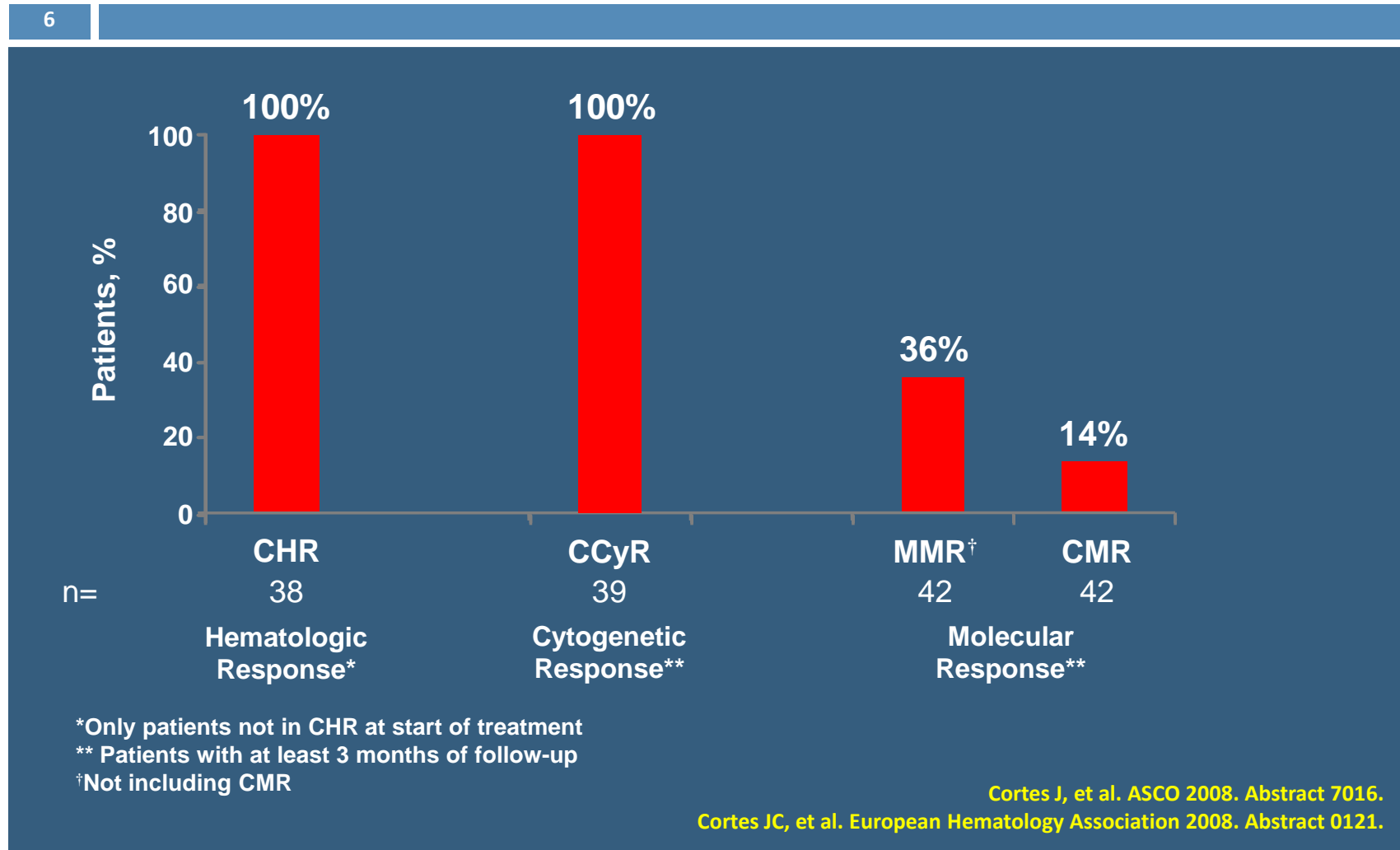
| | MDACC (n=47) | GIMEMA (n=73) |
|---|-----------------|------------------|
| Median age, years (range) | 47 (21–81) | 51 (18–83) |
| Sokal risk, n (%) | | |
| Low | 27 (57) | 39 (53) |
| Intermediate | 14 (30) | 25 (34) |
| High | 6 (13) | 9 (13) |
| Median dose, mg/day (range) | 800 (200–800) | 794 (301–800) |
| Median duration of nilotinib exposure, days (range) | / | 200 (66–332) |
| Patients with dose interruptions, n (%) | 16 (34%) | 31 (42%) |
| Median days of dose interruption, (range) | 29 (3–84) | 7 (1–51) |
| Dose reductions, n (%) | 13 (28%) | / |
| Off study | 3 | 0 (0) |

Rosti G., et al. EHA 2008. Abstract0404 .

Cortes JC, et al. European Hematology Association 2008. Abstract 0121.

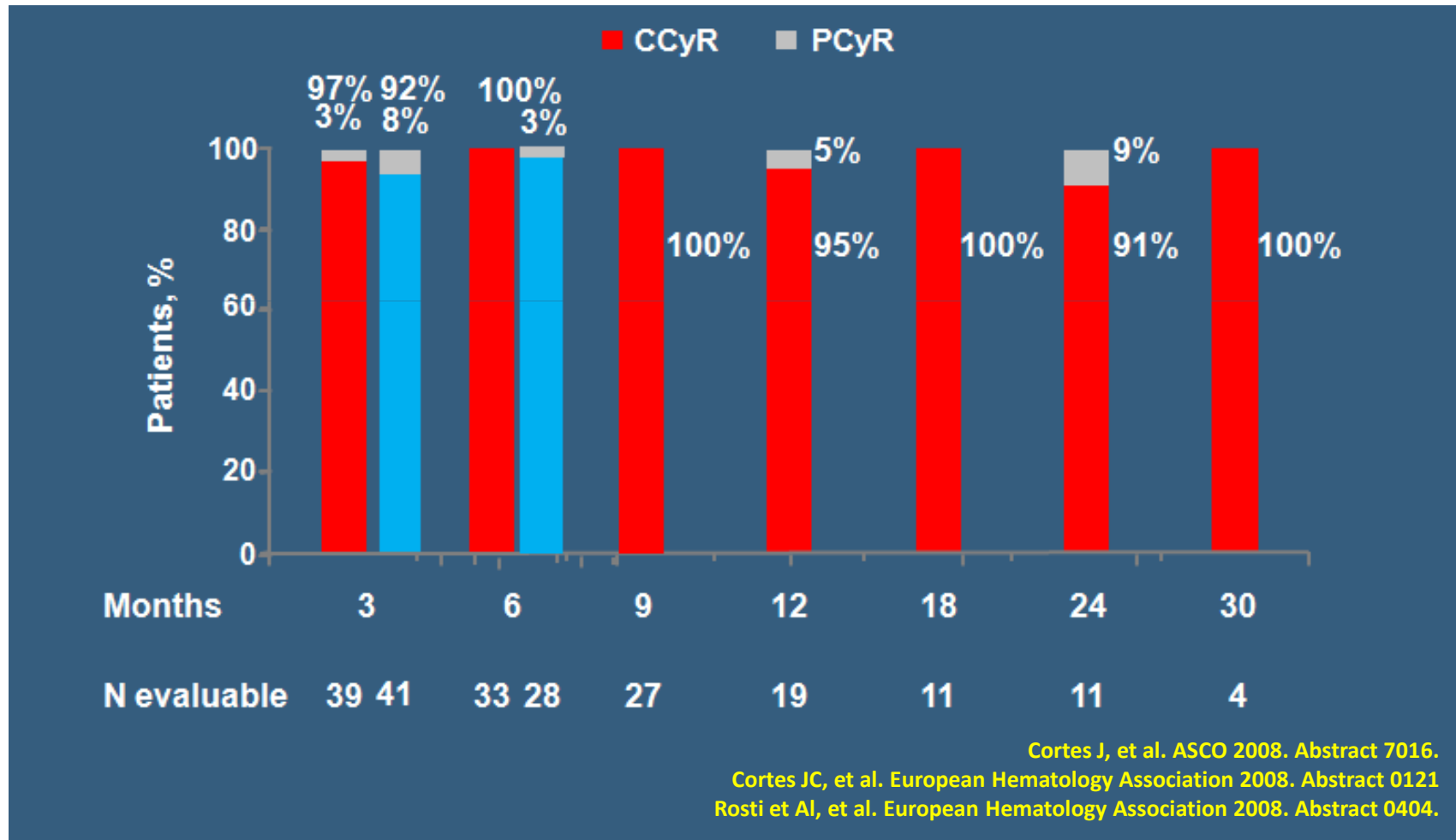
Nilotinib in Newly Diagnosed CML-CP (MDACC) Best Response

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Nilotinib in Newly Diagnosed CML-CP (MDACC vs Gimema) *Cytogenetic Response*

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Nilotinib in Newly Diagnosed CML-CP (MDACC) Response by Treatment

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| | Imatinib 400mg (MDACC) N=50 | Imatinib 800mg (MDACC) N=205 | Nilotinib (MDACC) N=47 | Nilotinib (GIMEMA) N=41 |
|----------------------|-----------------------------------|------------------------------------|------------------------------|-------------------------------|
| Percent CCyR* | | | | |
| 3 months | 37 | 62 | 97 | 84 |
| 6 months | 54 | 82 | 100 | 97 |
| 12 months | 65 | 86 | 95 | / |
| Percent MMR** | | | | |
| 3 months | 6 | 8 | 14 | 62 |
| 6 months | 0 | 34 | 50 | 75 |
| 12 months | 24 | 47 | 48 | 7 |

*Evaluable nilotinib patients: 39 at 3 mo, 33 at 6 mo, 19 at 12 mo

**Evaluable nilotinib patients: 42 at 3 mo, 36 at 6 mo, 21 at 12 mo

Cortes J, et al. ASCO 2008. Abstract 7016.

Cortes JC, et al. European Hematology Association 2008. Abstract 0121.

Nilotinib in Newly Diagnosed CML-C (GIMEMA and MDACC)

Conclusions

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- Nilotinib had significant activity in the first-line treatment of CML-CP patients with CCyR rates of 97% at 6 months
- Median dose intensity was near the planned dose at 794 mg/day
- No patient progressed to the accelerated or blast phases to date
- Most of the adverse events were grade 1 and did not require dose interruptions
- Transient and manageable bilirubin increase was the single most frequent reason for dose adaptation
- There was minimal severe hematopoietic toxicity
- Results achieved so far strongly support the hypothesis that in early chronic phase Ph+ CML patients, the response to nilotinib may be faster than the response to imatinib

Rosti G, et al. ASCO 2008. Abstract 7054.

Rosti GR, et al. European Hematology Association 2008. Abstract 0404.

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CML EHA: What's New?

Dasatinib as Frontline Therapy in Early Chronic Phase CML

Jorge Cortes, MD

#0881 EFFICACY OF DASATINIB IN PATIENTS (PTS) WITH
PREVIOUSLY UNTREATED CHRONIC MYELOGENOUS LEUKEMIA
(CML) IN EARLY CHRONIC PHASE (CML-CP) J Cortes et Al.

Patient Characteristics (N=27)

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| Characteristics | No. (%) or Median (range) |
|-----------------|---------------------------|
| Age, y | 41 (18-76) |
| F/M | 14/13 |
| <u>Sokal</u> | |
| Low | 18 (67) |
| Intermediate | 8 (30) |
| High | 1 (3) |

Cytogenetic Response by Time

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| Response | No./No. Evaluable (%) | |
|----------|-----------------------|------------|
| | 3 months | 6 months |
| CCyR | 19/26 (73) | 20/21 (95) |
| PCyR | 2/26 (8) | 0/21 (0)* |

* 1 mCyR

TKI in Newly Diagnosed CML-CP (MDACC)

Response by Treatment

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| | Imatinib 400mg (MDACC) N=50 | Imatinib 800mg (MDACC) N=205 | Nilotinib (MDACC) N=47 | Nilotinib (GIMEMA) N=41 | Dasatinib (MDACC) N=26 |
|----------------------|--------------------------------------|---------------------------------------|------------------------------|-------------------------------|------------------------------|
| Percent CCyR* | | | | | |
| 3 months | 37 | 62 | 97 | 84 | 73 |
| 6 months | 54 | 82 | 100 | 97 | 95 |
| 12 months | 65 | 86 | 95 | / | / |
| Percent MMR** | | | | | |
| 3 months | 6 | 8 | 14 | 62 | / |
| 6 months | 0 | 34 | 50 | 75 | / |
| 12 months | 24 | 47 | 48 | 7 | / |

*Evaluable nilotinib patients: 39 at 3 mo, 33 at 6 mo, 19 at 12 mo

**Evaluable nilotinib patients: 42 at 3 mo, 36 at 6 mo, 21 at 12 mo

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Cortes JC, et al. European Hematology Association 2008. Abstract 0121.

What's new?

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- **HD imatinib** in Newly Diagnosed CML-CP
 - M.D. Anderson Cancer Center (MDACC)
 - Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) (#0405)
 - TOPs #(0402)
 - Austrian experience (#0406)

High Dose Imatinib: TOPs, Gimema 023; AustriaCMLSG.

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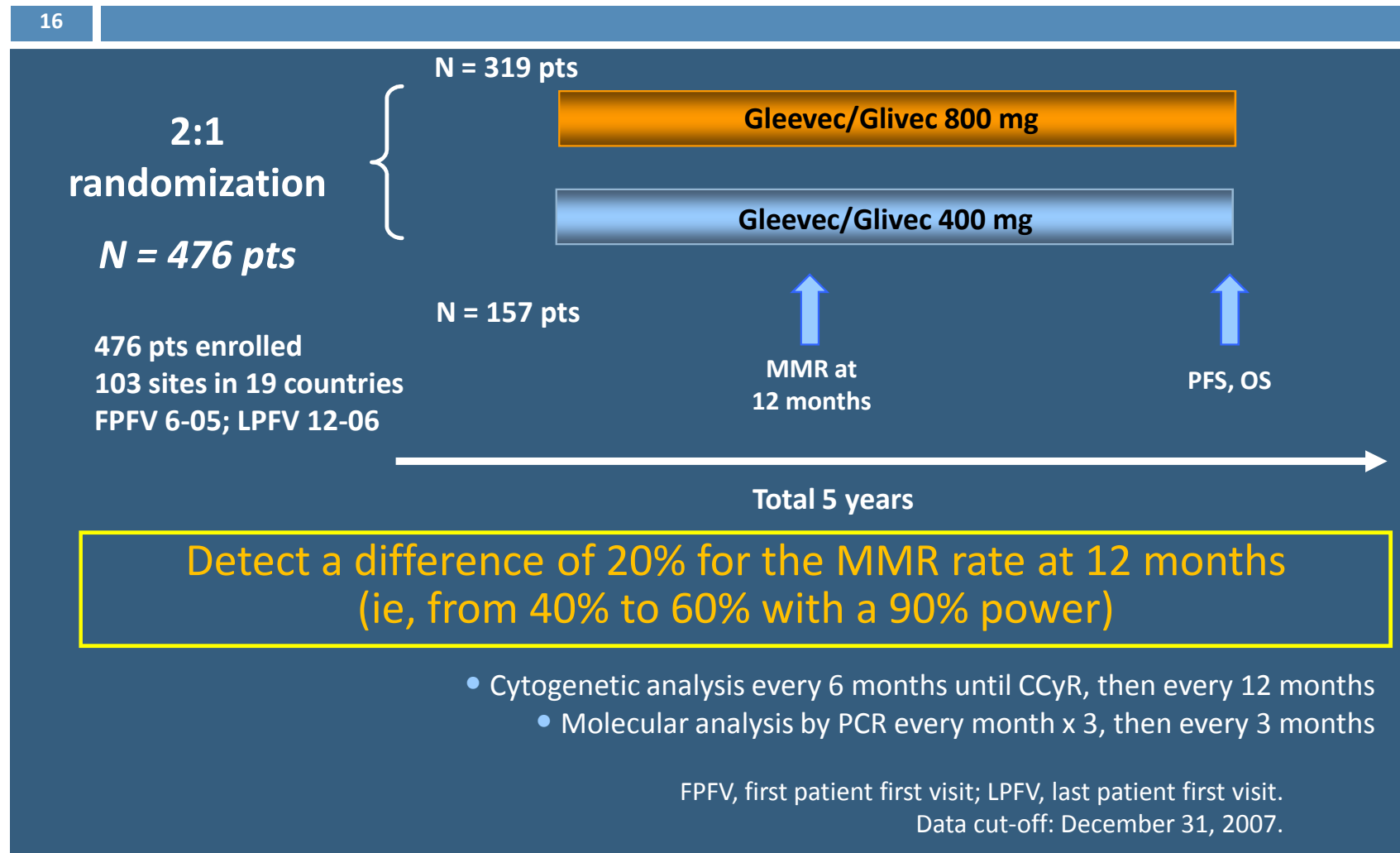
#0402 FIRST REPORT OF THE TOPS STUDY: A RANDOMIZED PHASE III TRIAL OF 400MG VS 800MG IMATINIB IN PATIENTS WITH NEWLY DIAGNOSED, PREVIOUSLY UNTREATED CML IN CHRONIC PHASE USING MOLECULAR ENDPOINTS 0402 JG Cortes, M. Baccarani, F. Guilhot, B.J. Druker, R. Yu, M. Rudoltz, T Krahnke, T. Hughes (Houston, United States of America) 08:15-08:30

#0405 A PROSPECTIVE RANDOMIZED STUDY OF IMATINIB 400 MG VS 800 MG AS A FRONTLINE THERAPY IN SOKAL HIGH RISK (HR) PH-POS CHRONIC MYELOID LEUKEMIA (CML) PATIENTS 0405 M Baccarani, I MD Haznedaroglu, K MD Porkka, F MD Castagnetti, D MD Alberti, G MD Alimena, M BD Amabile, H MD Bostrom, H MD Hjorth-Hansen, V MD Kairisto, G MD Martinelli, J MD Nielsen, F MD Palandri, F MD Pane, G MD Rege-Cambrin, D MD Russo, G MD Saglio, G MD Specchia, N BD Testoni, O MD Weiss-Bjerrum, G MD Rosti, B MD Simonsson (Bologna, Italy)

#0406 HIGH DOSES OF IMATINIB MESYLATE (800MG/DAY) SIGNIFICANTLY IMPROVE RATES OF MAJOR AND COMPLETE CYTOGENETIC REMISSIONS (MCR, CCR) - RESULTS FROM THE FIRST PLANNED INTERIM ANALYSIS OF A MULTICENTER, RANDOMISED, 2-ARM - PHASE III STUDY COMPARING IMATINIB STANDARD DOSE (400 MG/DAY) WITH IMATINIB HIGH DO 0406 AP Andreas, DW Wolf, DF Fong, LT Lion, ID Dyagil, ZM Masliak, DB Boskovic, LG Giskevicius, SL Lejniece, SG Goranov, LG Gercheva, AS Stojanovic, DP Peytchev, NT Tzvetkov, RG Griniute, RO Oucheveva, GF Fincato, HU Ulmer, GG Gastl (Linz, Austria)

Imatinib 400 mg vs 800 mg in CML-CP: Study Design

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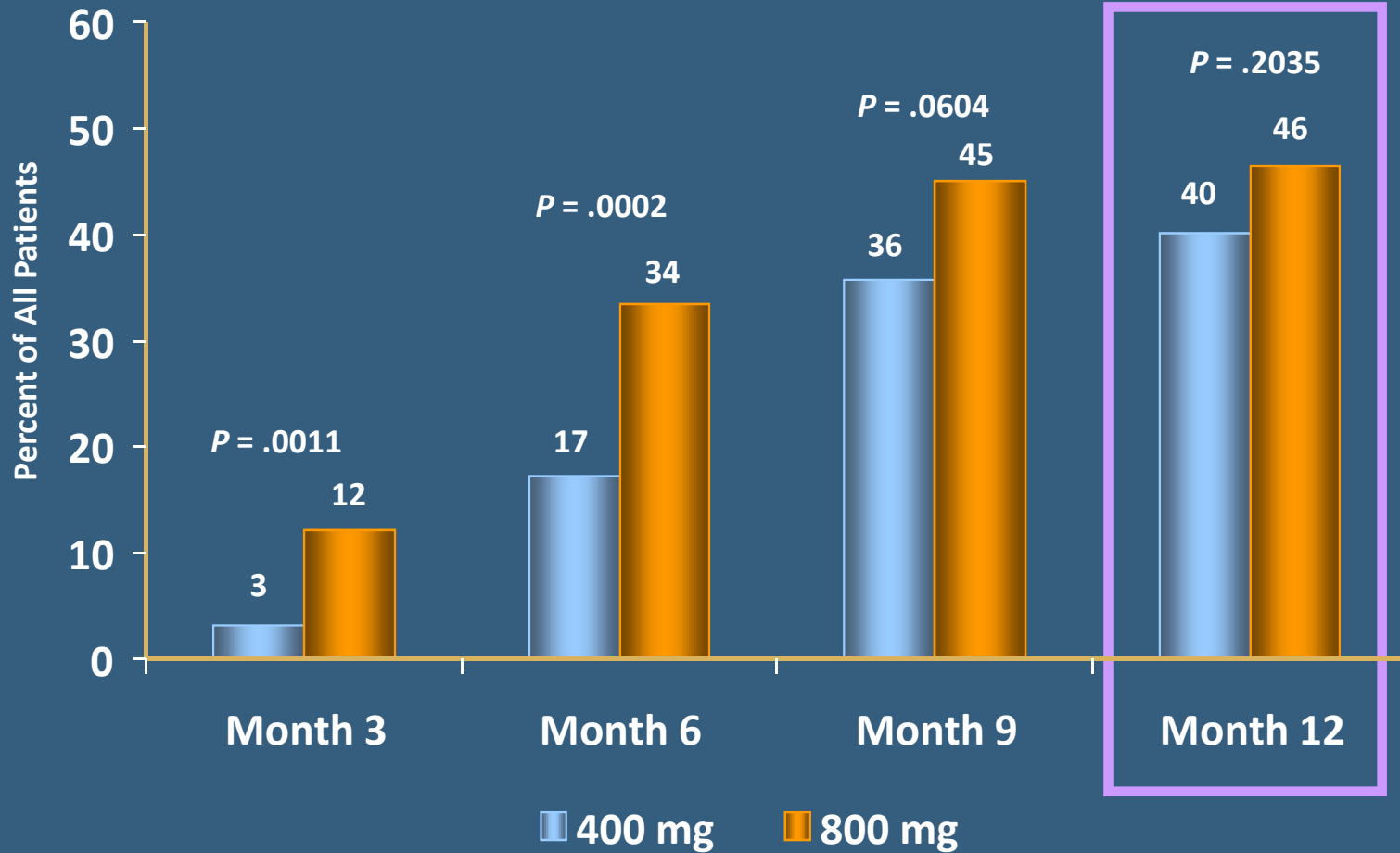
Tops

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| Characteristic | N = 476 |
|-------------------------|--------------------|
| Age, median (range) | 48 (18 – 75) years |
| Time since diagnosis | 28 days |
| Sokal Risk Score | |
| Low | 41% |
| Intermediate | 35% |
| High | 24% |

Imatinib 400 mg vs 800 mg in CML-CP: MMR Rates Over Time (ITT)

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Glivec 400 vs 800 and new TKI in Newly Diagnosed CML-CP (MDACC vs TOPs)

Response by Treatment

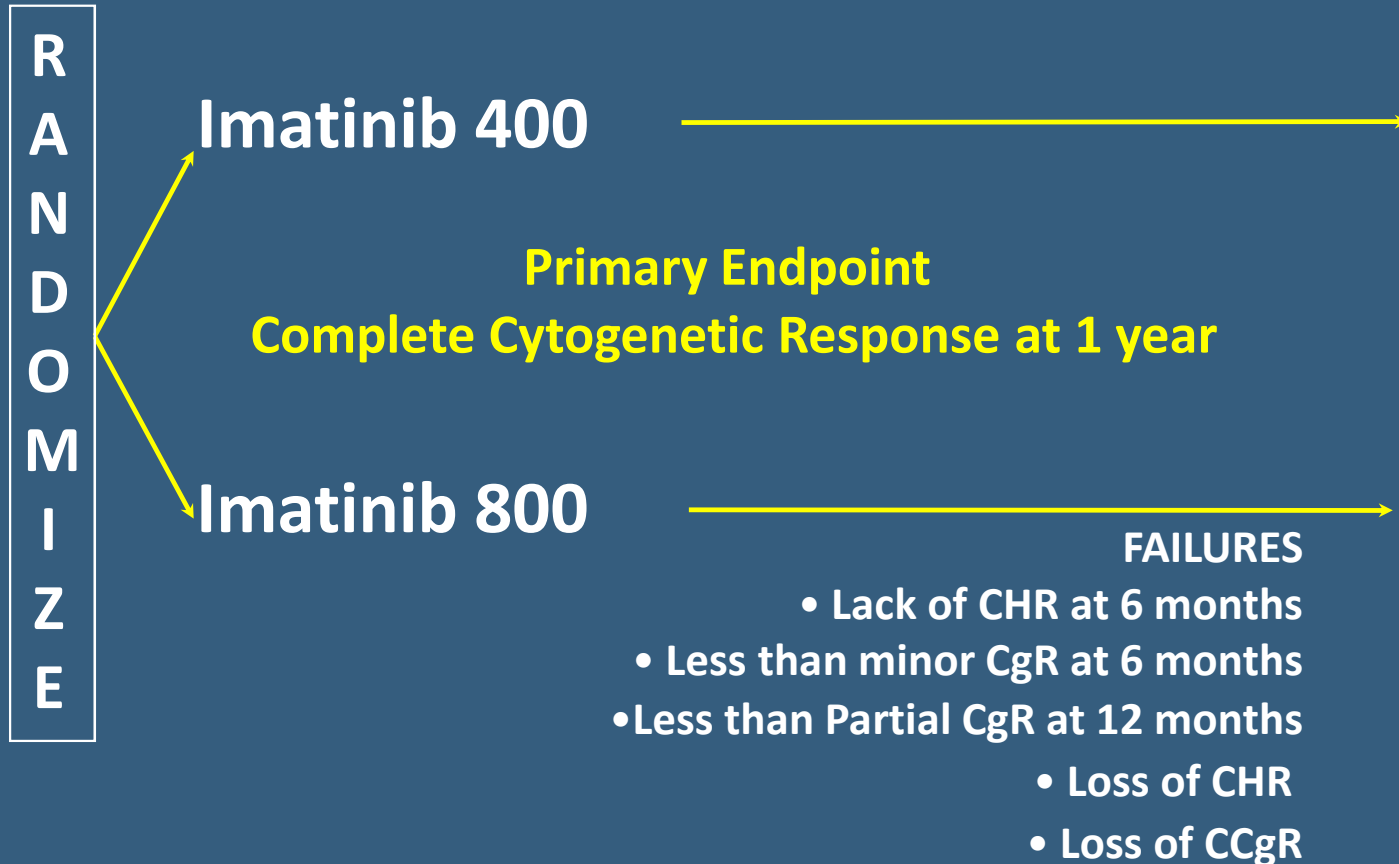
19

| | Imatinib 400mg (MDACC) N=50 | Imatinib 800mg (MDACC) N=205 | TOPs 400mg N=157 | Tops 800mg N=316 | Nilotinib (MDACC) N=47 | Nilotinib (GIMEMA) N=41 | Dasatinib (MDACC) N=26 |
|----------------------|--------------------------------------|---------------------------------------|---------------------|---------------------|------------------------------|-------------------------------|------------------------------|
| Percent CCyR* | | | | | | | |
| 3 months | 37 | 62 | 36 | 62 | 97 | 84 | 73 |
| 6 months | 54 | 82 | 45 | 57 | 100 | 97 | 95 |
| 12 months | 65 | 86 | 66 | 70 | 95 | / | / |
| Percent MMR** | | | | | | | |
| 3 months | 6 | 8 | 3 | 12 | 14 | 62 | / |
| 6 months | 0 | 34 | 17 | 34 | 50 | 75 | / |
| 12 months | 24 | 47 | 40 | 46 | 48 | 7 | / |

EUROPEAN LEUKEMIANET STUDY (ITALY, NORDIC, TURKEY, ISRAEL)

1st CHRONIC PHASE, FRONT LINE
SOKAL HIGH RISK (RR > 1.2)

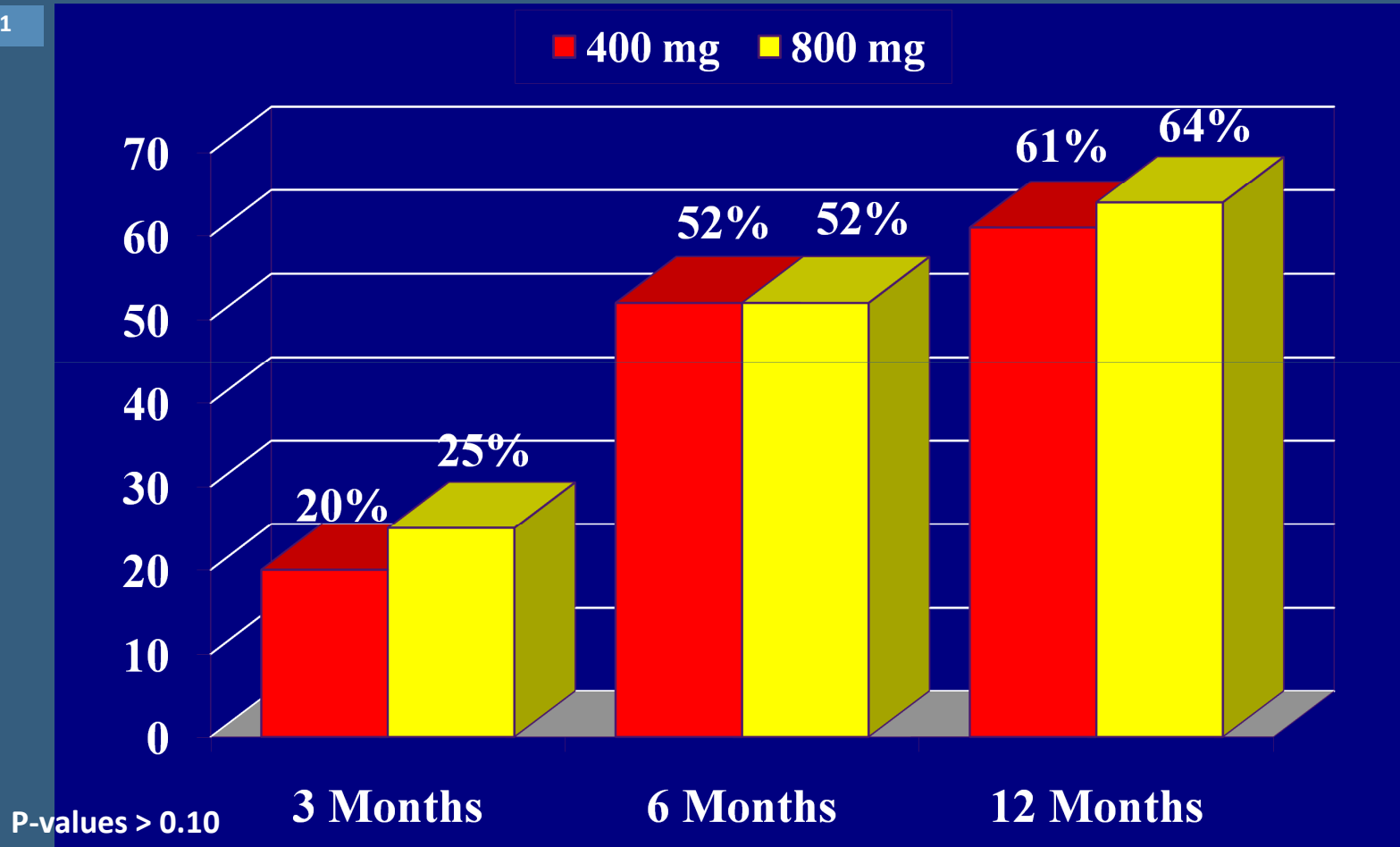
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REGISTERED AT CLINICAL TRIALS GOV . NCT 00514488

**EUROPEAN LEUKEMIANET STUDY (ITALY, NORDIC, TURKEY, ISRAEL)
COMPLETE CYTOGENETIC RESPONSE
PER CENT OF ALL PATIENTS (INTENTION-TO-TREAT)**

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BACCARANI et al, Abstract 0405, EHA 2008, HAEMATOLOGICA 2008; 93 (s1): 161

Glivec 400 vs 800 and new TKI in Newly Diagnosed CML-CP (MDACC)

Response by Treatment

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| | Imatinib 400mg (MDACC) N=50 | Imatinib 800mg (MDACC) N=205 | TOPs 400mg N=157 | Tops 800mg N=316 | Leukemia Net 400mg (022) High Sokal | Leukemia Net 800mg (022) High Sokal | Nilotinib (MDACC) N=47 | Nilotinib (GIMEMA) N=41 | Dasatinib (MDACC) N=26 |
|---------------|--------------------------------------|---------------------------------------|------------------------|------------------------|--|--|------------------------------|-------------------------------|------------------------------|
| Percent CCyR* | | | | | | | | | |
| 3 months | 37 | 62 | 37 | 62 | 20 | 25 | 97 | 84 | 73 |
| 6 months | 54 | 82 | 45 | 57 | 52 | 52 | 100 | 97 | 95 |
| 12 months | 65 | 86 | 66 | 70 | 61 | 64 | 95 | / | / |
| Percent MMR** | | | | | | | | | |
| 3 months | 6 | 8 | 3 | 12 | / | / | 14 | 62 | / |
| 6 months | 0 | 34 | 17 | 34 | / | / | 50 | 75 | / |
| 12 months | 24 | 47 | 40 | 46 | / | / | 48 | 7 | / |

CML EHA: What's new?

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- **Busutinib and Omacetaxine: Phase II CML-CP and CML-AP**

0403 BOSUTINIB (SKI-606) SHOWS HIGH TOLERABILITY AND CLINICAL ACTIVITY IN PATIENTS WITH PHILADELPHIA CHROMOSOME POSITIVE LEUKEMIAS 0403 C

Gambacorti-Passerini, J Cortes, H Kantarjian, D Kim, A Turkina, T Fischer, F Cervantes, S Agarwal, B Hewes, TH Brummendorf (Monza, Italy)

#0546 MULTICENTER OPEN LABEL STUDY OF SUBCUTANEOUS (SC) OMACETAXINE (OMA) IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS (PTS) THAT ARE RESISTANT OR INTOLERANT TO TWO OR MORE TYROSINE KINASE INHIBITORS (TKIS) 0546 J Cortes, M Wetzler, L Akard, JH Lipton, AC Benichou, AR Craig, E Humphriss, H Kantarjian (Houston, United States of America)