FIFTH
INTERNATIONAL SYMPOSIUM ON
SECONDARY LEUKEMIA
AND LEUKEMOGENESIS

Comparative genomic analysis of *PML* and *RARA* breakpoints in paired diagnosis/relapse samples of patients with acute promyelocytic leukemia treated with ATRA and chemotherapy

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Rome, September 23, 2016

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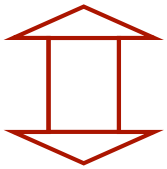
✓ “Therapy-related” acute promyelocytic leukemia has been reported in **cancer patients** treated with:

- **Topoisomerase II inhibitors**
- **Radiation therapy**

Autoimmune diseases

Multiple sclerosis Inflammatory bowel disease Rheumatoid arthritis



✓ t-APL has been reported in patients with primary neoplasms before t-APL who received **chemotherapy** for a **non-malignant disorder**.

Breast cancer Tumors of the genitourinary system Non Hodgkin lymphoma

Molecular insights in therapy-related APL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

DNA Topoisomerase II in Therapy-Related Acute Promyelocytic Leukemia

Anita R. Mistry, Ph.D., Carolyn A. Felix, M.D., Ryan J. Whitmarsh, B.A., Annabel Mason, B.Sc., Andreas Reiter, M.D., Bruno Cassinat, Pharm.D., Anne Parry, Ph.D., Christoph Walz, Joseph L. Wiemels, Ph.D., Mark R. Segal, Ph.D., Lionel Adès, M.D., Ian A. Blair, Ph.D., Neil Osheroff, Ph.D., Andrew J. Peniket, B.A., Marina Lafage-Pochitaloff, Ph.D., Nicholas C.P. Cross, Ph.D., Christine Chomienne, Ph.D., Ellen Solomon, Ph.D., Pierre Fenaux, Ph.D., and David Grimwade, Ph.D.

blood®

2008 112: 3383-3390
doi:10.1182/blood-2007-10-115600 originally published online July 23, 2008

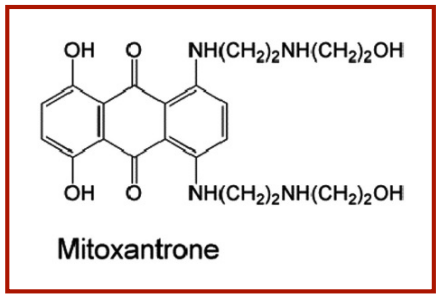
Molecular analysis of t(15;17) genomic breakpoints in secondary acute promyelocytic leukemia arising after treatment of multiple sclerosis

Syed Khizer Hasan, Ashley N. Mays, Tiziana Ottone, Antonio Ledda, Giorgio La Nasa, Chiara Cattaneo, Erika Borlenghi, Lorella Melillo, Enrico Montefusco, José Cervera, Christopher Stephen, Gnanam Satchi, Anne Lennard, Marta Libura, Jo Ann W. Byl, Neil Osheroff, Sergio Amadori, Carolyn A. Felix, Maria Teresa Voso, Wolfgang R. Sperr, Jordi Esteve, Miguel A. Sanz, David Grimwade and Francesco Lo-Coco

Breast cancer and multiple sclerosis

↓

6 t-APL arising after mitoxantrone



Mitoxantrone

Multiple sclerosis

↓

12 t-APL arising after mitoxantrone

Clustered distribution of genomic breakpoints in *PML*

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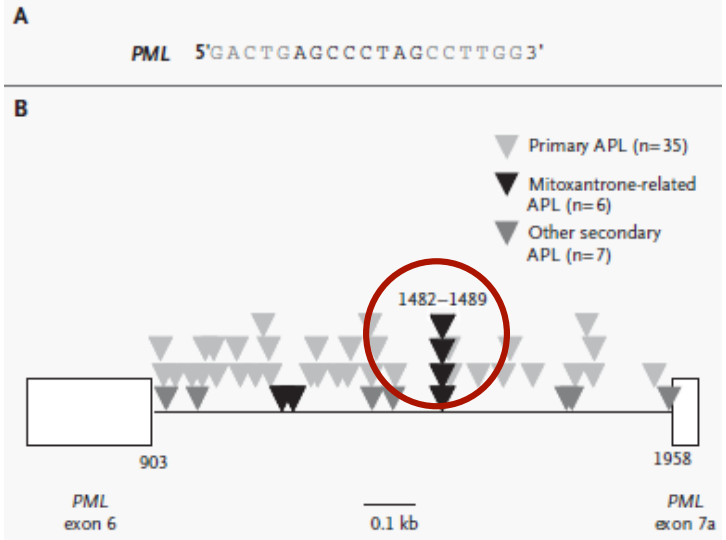

Figure 1. Identification of a Breakpoint Hot Spot in *PML* Intron 6 in Mitoxantrone-Related APL.

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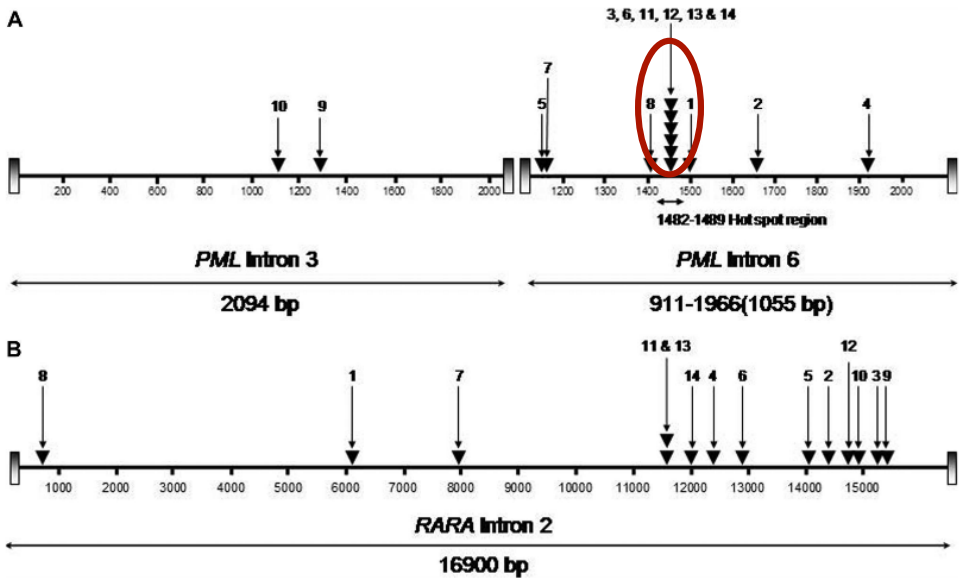
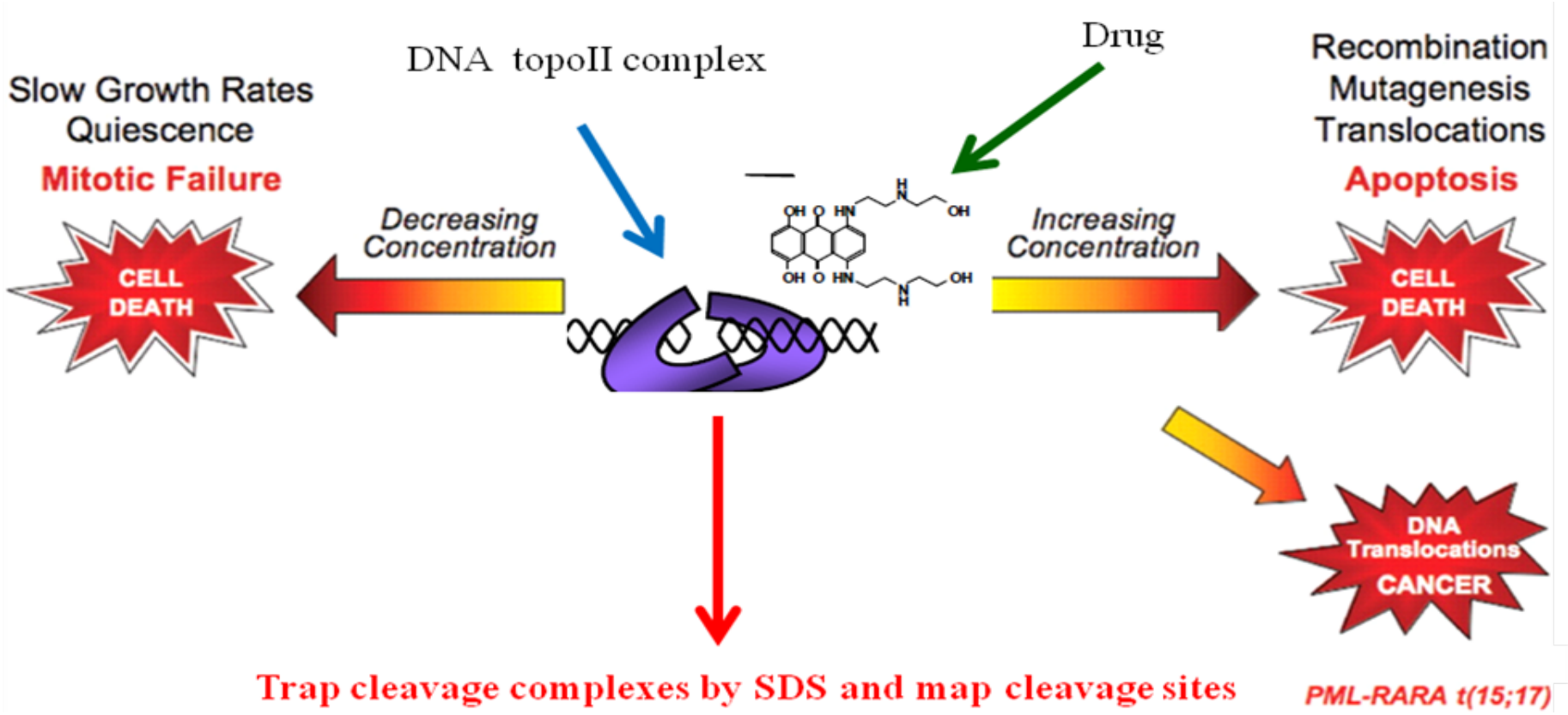


Topoisomerase II inhibitors



Two main classes:

1. Catalytic inhibitors: Anthracylines (epirubicin and daunorubicin)

2. TOPO-IIA poisons: Etoposide and Mitoxantrone

t-MN can develop after first-line treatment for APL

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Therapy-Related Myeloid Neoplasms in Patients With Acute Promyelocytic Leukemia Treated With All-*Trans*-Retinoic Acid and Anthracycline-Based Chemotherapy

Pau Montesinos, José D. González, José González, Chelo Rayón, Elena de Lisa, Maria L. Amigo, Gert J. Ossenkoppele, María J. Peñarrubia, Manuel Pérez-Encinas, Juan Bergua, Guillermo Debén, María J. Sayas, Javier de la Serna, Josep M. Ribera, Javier Bueno, Gustavo Milone, Concha Rivas, Salut Brunet, Bob Löwenberg, and Miguel Sanz

918 *de novo* APL patients treated with ATRA + anthracycline-based CHT

↓

17 patients developed a t-MN (MDS, AML, ALL), after a median of 43 months from CR. The 6-year cumulative incidence of t-MN was 2.2%

Despite t-MN is relatively infrequent after first-line treatment of APL with ATRA and standard CHT, therapeutic strategies to avoid / minimize this severe complication are warranted.

Topo-II inhibitors and APL development

Research Paper

Multiple Sclerosis

Revision of the risk of secondary leukaemia after mitoxantrone in multiple sclerosis populations is required

Ana M Pascual[1], Neus Téllez[2], Isabel Boscá[1], Javier Mallada[3], Antonio Belenguer[4], Inmaculada Abellán[5], Angel P Sempere[6], Pascual Fernández[7], Mª José Magraner[1], Francisco Coret[8], Miguel A Sanz[9], Xavier Montalbán[2] and Bonaventura Casanova[1]

The incidence of t-APL after mitoxantrone in multiple sclerosis is 2%.

CLINICAL TRIALS AND OBSERVATIONS

Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group

Francesco Lo-Coco,[1,2] Giuseppe Avvisati,[3] Marco Vignetti,[4] Massimo Breccia,[4] Eugenio Gallo,[5] Alessandro Rambaldi,[6] Francesca Paoloni,[7] Giuseppe Fioritoni,[8] Felicetto Ferrara,[9] Giorgina Specchia,[10] Giuseppe Cimino,[4] Daniela Diverio,[4] Erika Borlenghi,[11] Giovanni Martinelli,[12] Francesco Di Raimondo,[13] Eros Di Bona,[14] Paola Fazi,[7] Antonio Peta,[15] Alberto Bosi,[16] Angelo M. Carella,[17] Francesco Fabbiano,[18] Enrico M. Pogliani,[19] Maria C. Petti,[20] Sergio Amadori,[1] and Franco Mandelli,[7] for the Italian GIMEMA Cooperative Group

The rate of relapse of APL is ~10% after combined ATRA + anthracycline-based chemotherapy.

Hypothesis

Disease Recurrence in APL ⇒ **Therapy related APL or true relapse?**

Investigate possible switches of breakpoints in *PML* and/or *RARA* between diagnosis and relapse with potential involvement of therapy-related "hotspot" regions at "relapse"

Methods

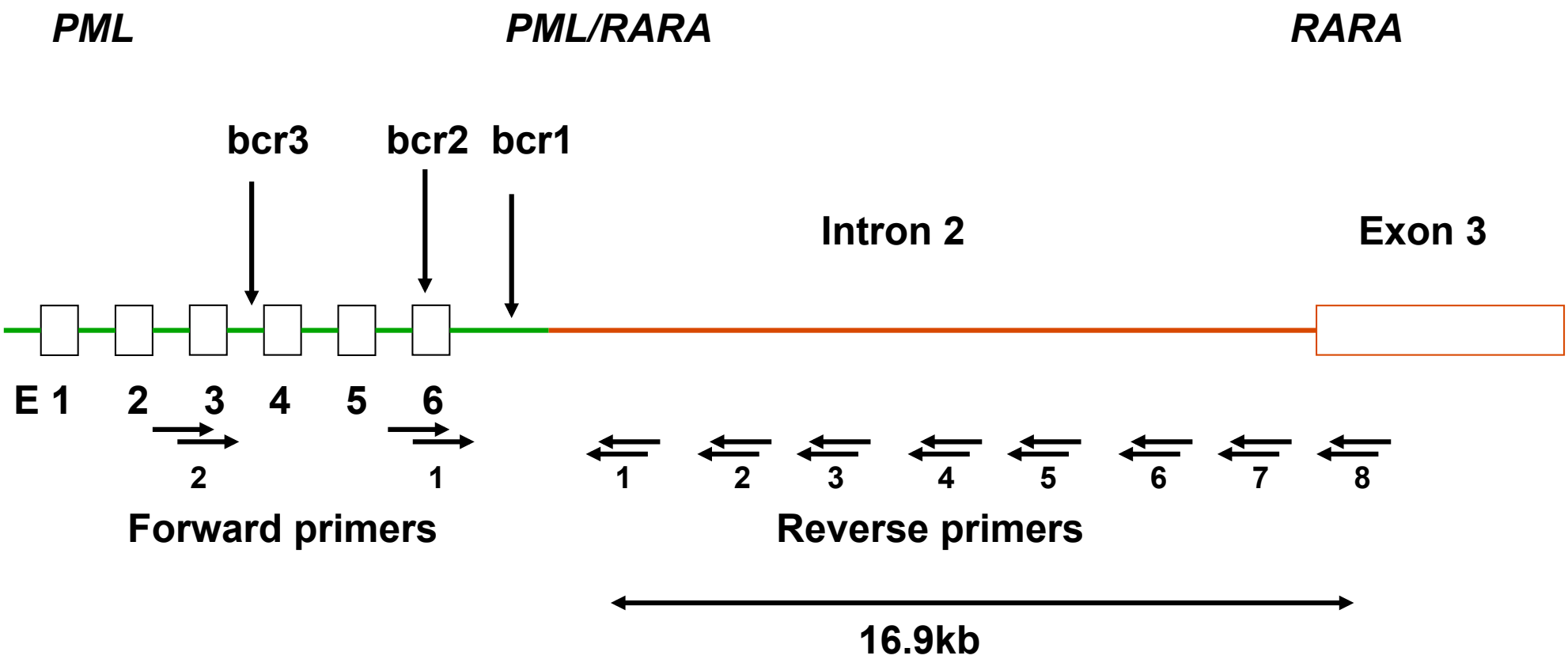
- 30 APL paired diagnosis/relapse cases with available DNA
- Identification of *PML/RARA* isoforms
- Long-range PCR to amplify the genomic *PML/RARA* rearrangement
- Direct sequencing to identify the exact location of the breakpoint

Clinical characteristics of APL patients (n=30)

Median age (range)	36 years (5-77 years)
Sex (M/F)	16/14
Treatment	LPA99 (n=4) AIDA2000 (n=16) IC-APL (n=3) ICC-APL01 (n=2) MRC (n=5)
Mitoxantrone (total median dose)	90 mg (20-90 mg)
Anthracyclines (total median dose)	144 mg (51-756 mg)
Median latency (range)*	19 months (5-105 months)

* Latency between APL diagnosis and relapse

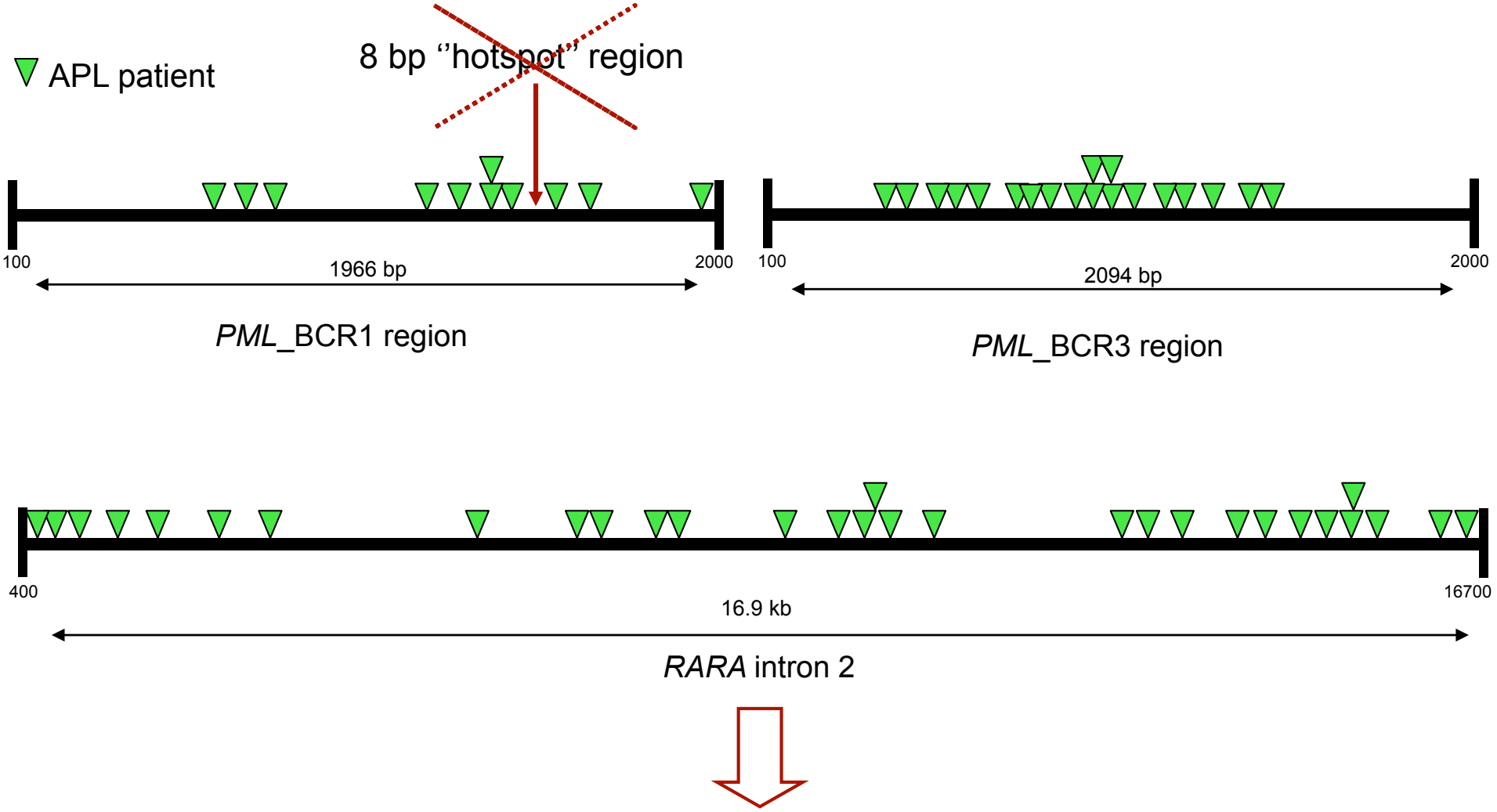
Primer positioning for long-range PCR



Chromatogram obtained revealing the breakpoint junction sequence

Mistry et al, *NEJM* 2005; Hasan et al, *Blood* 2008

Results: distribution of *PML/RARA* breakpoints



The location of the breakpoint was in all cases identical

at diagnosis and at relapse

Conclusions

- **The molecular profile** of the breakpoints at the t(15;17) translocation was **identical** at diagnosis and relapse in 30 analysed pts

- ***PML*** breakpoints were never localized within the **hotspot region** at position 1482-1489, previously identified in t-APL developing after mitoxantrone treatment

- Considering the rarity of APL relapse, a larger series of patients analysed at diagnosis and relapse are needed to better investigate whether a “relapse” may mask t-APL.

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