Secondary Leukemia in Patients Treated for APL and APL as a second tumor

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University Tor Vergata of Rome

Fifth International Symposium on
Secondary Leukemia and Leukemogenesis
Rome, 22-24 September 2016

FIFTH
INTERNATIONAL SYMPOSIUM ON SECONDARY LEUKEMIA AND LEUKEMOGENESIS

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Case History

- FL, aged 50, dx of APL (high risk) on June 2009
- Receives Atra-Ida (AIDA) + cons. + mainten.

blood

1996 88: 1390-1398

AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study

G Avvisati, F Lo Coco, D Diverio, M Falda, F Ferrara, M Lazzarino, D Russo, MC Petti and F Mandelli

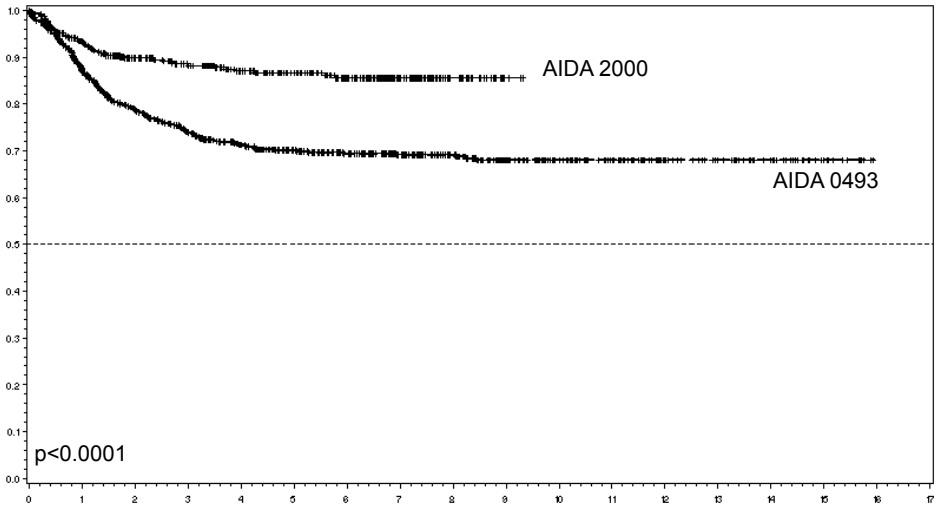
Case History

- FL, aged 50, dx of APL (high risk) on June 2009
- Receives Atra-Ida (AIDA) + cons. + mainten.
- Consults FL (doctor) for second opinion

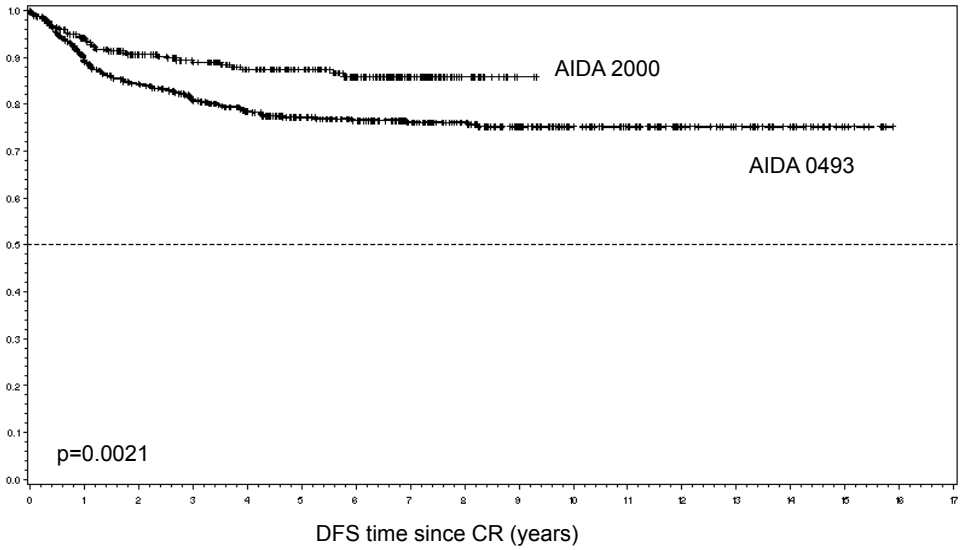
  No complaints apart from anxiety, normal BCC
- Molecular CR of 28m+ duration

AIDA 2000 Outcome results

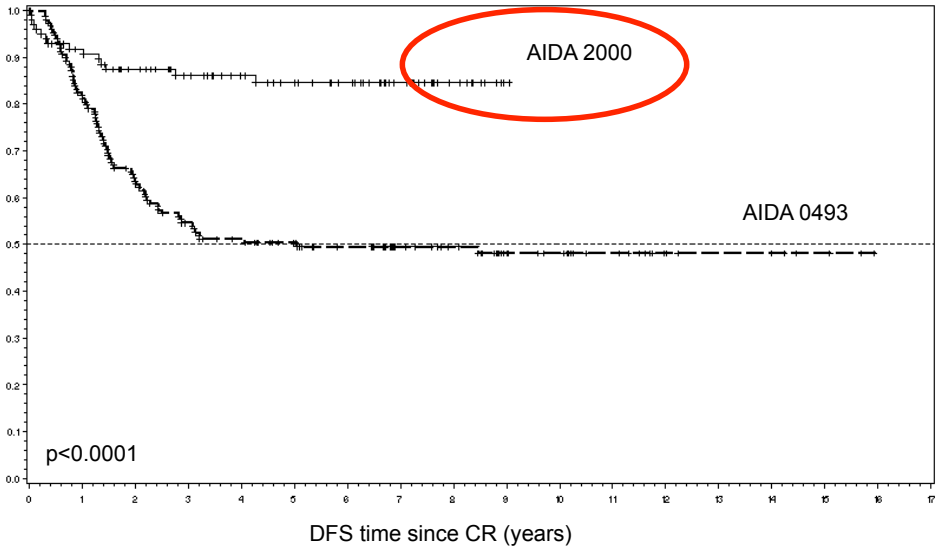
A: all patients



B: Low/Intermediate



C: High



Lo-Coco *et al*, Blood 2010

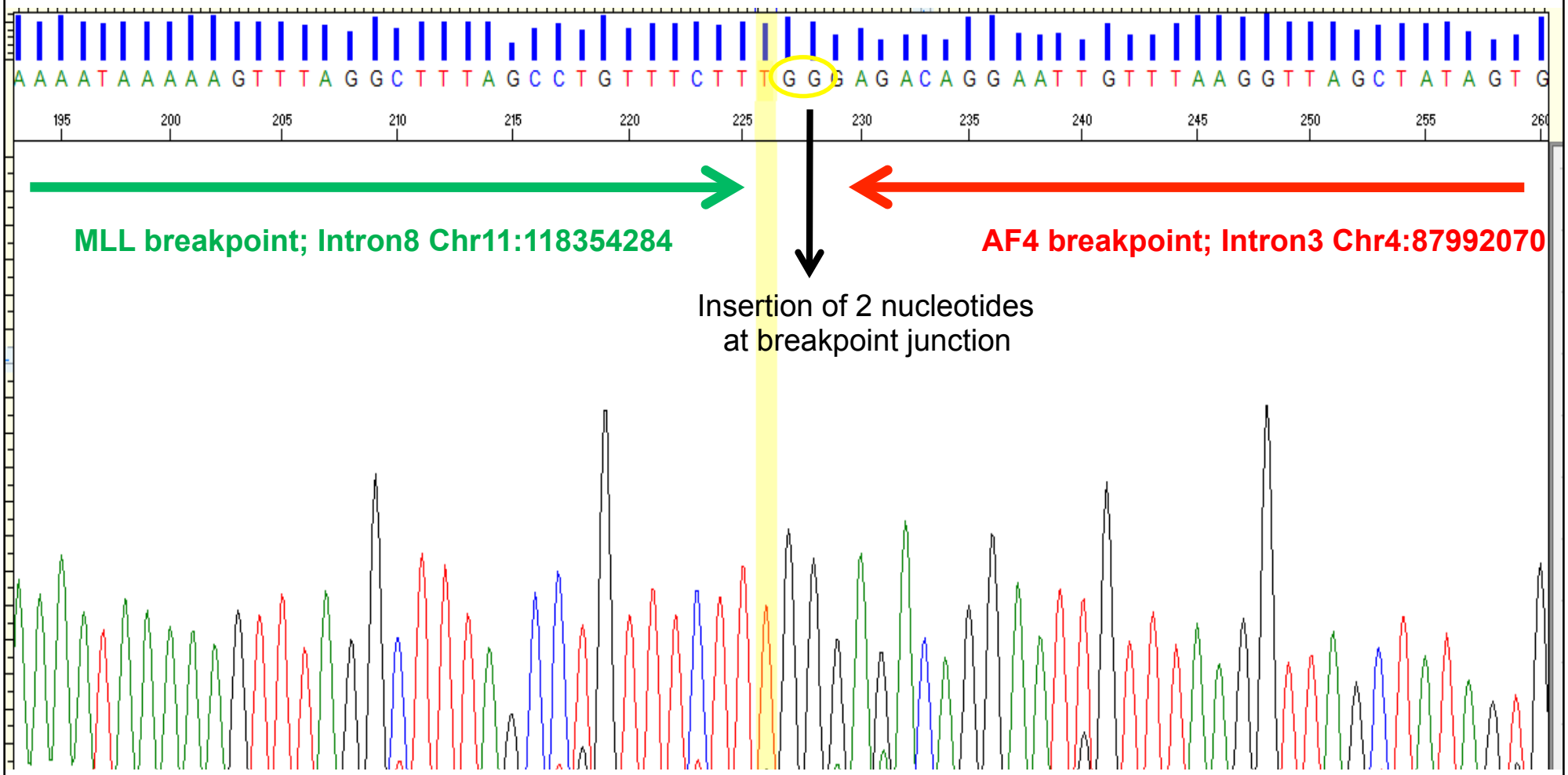
Case History

- Due to prolonged neutropenia, BM aspirate is performed. Laboratory studies reveal t(4,11) ALL

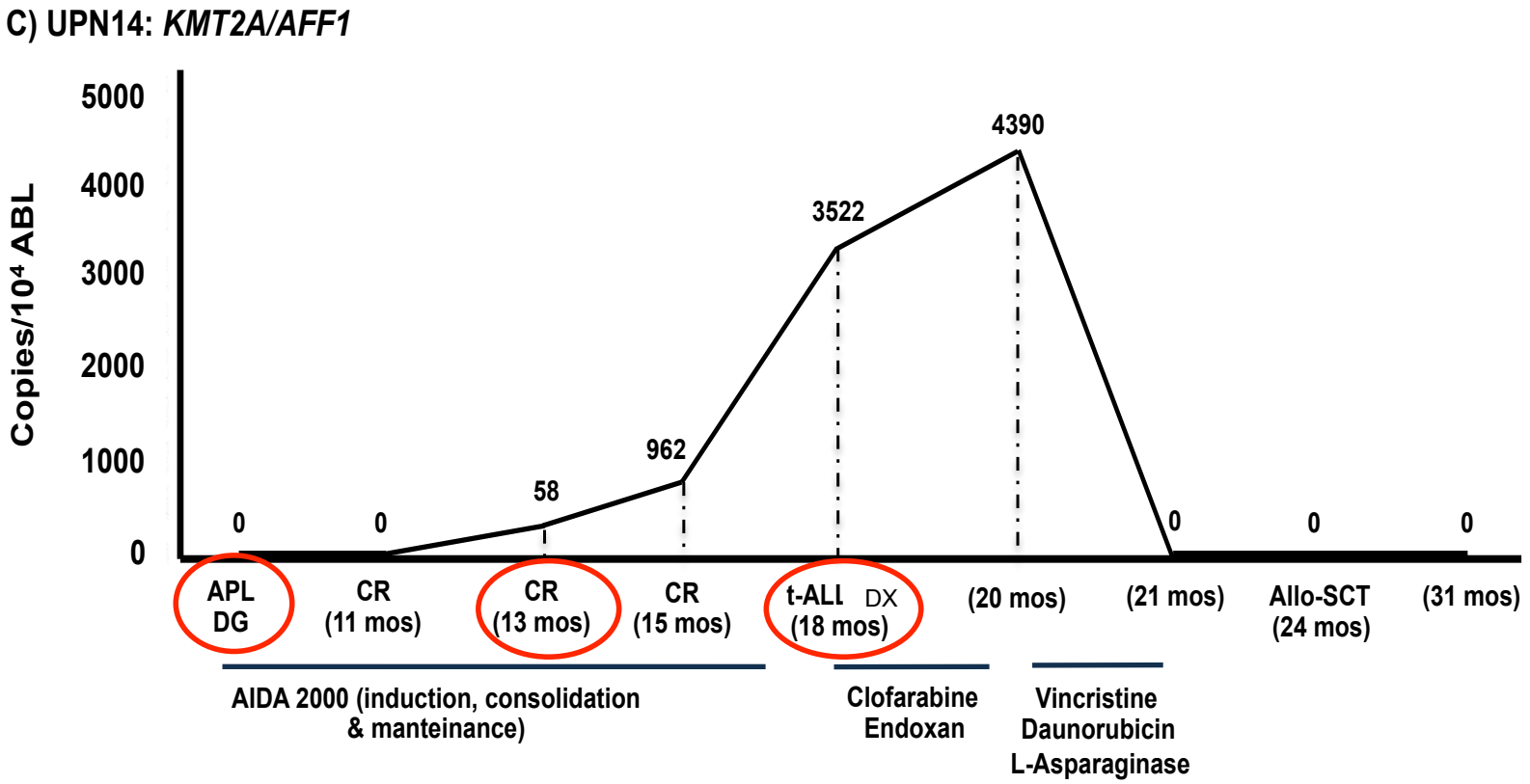
- Patient shows primary resistance to initial chemo

Is this therapy-related acute leukemia?

Genomic *MLL-AF4* breakpoint junction sequences of case FL



Retrospective qPCR of t(4;11) in samples previously collected for PML/RARa monitoring



Fabiani et al., submitted

Lessons from FL (the patient) to FL (the doctor)

- Acute leukemia (probably) therapy-related after CHT may develop at an early time (1year)
- Monitoring and careful evaluation of cytopenia (K / molecular assessment). Diff. dx with toxicity due to maintenance
- You never make a prognostic guess to your patients

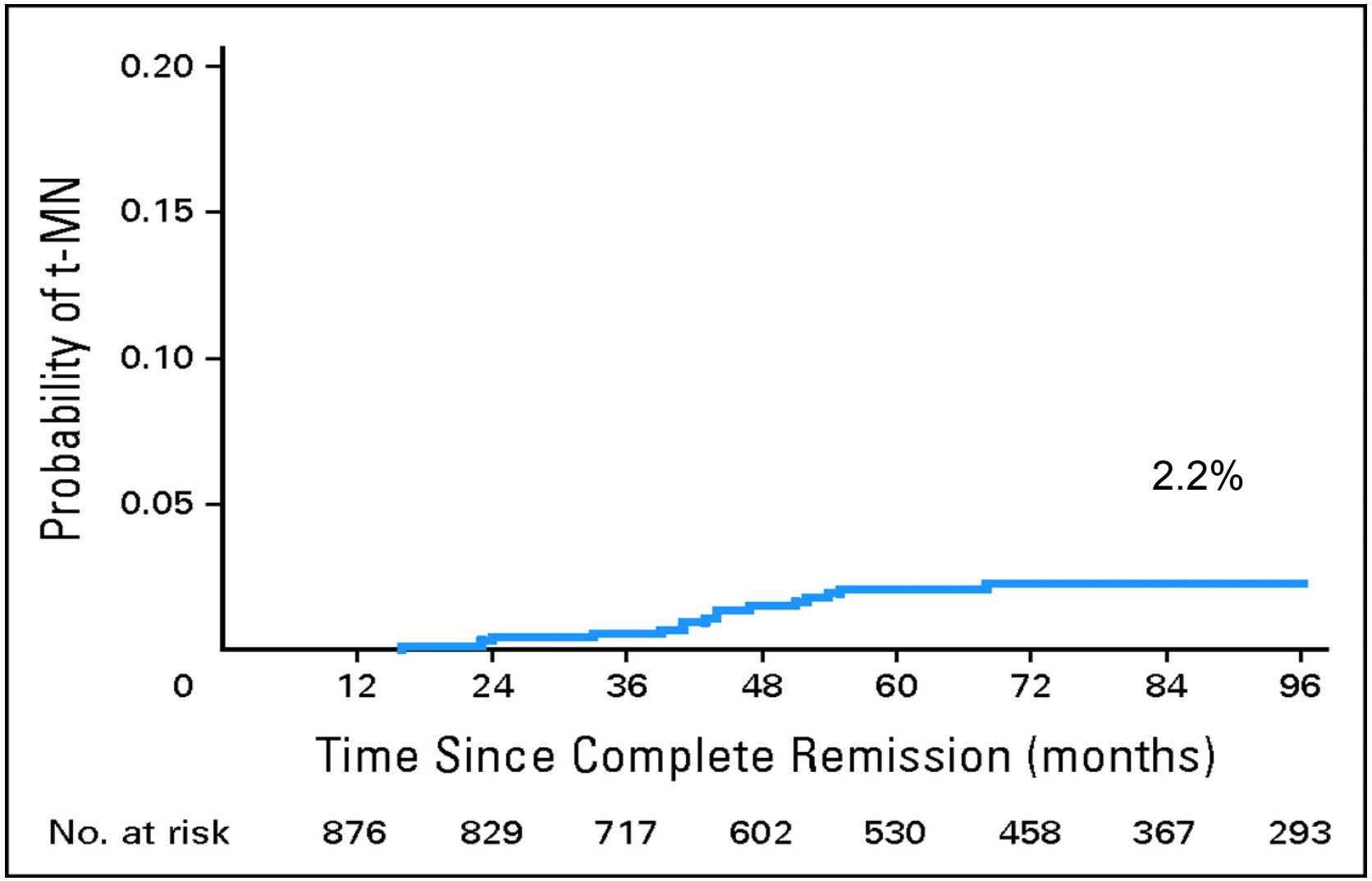
t-MN after therapy for APL

- t-MN relatively infrequent, late & poor prognosis complication in APL pts treated with Atra+Chemo
- Monosomal K & other cytogenetic abnormalities with a highly adverse prognosis commonly observed
- Relationship b/w chemotherapy type & dose-intensity & development of t-MN has not be clearly established

t-MN after therapy for APL

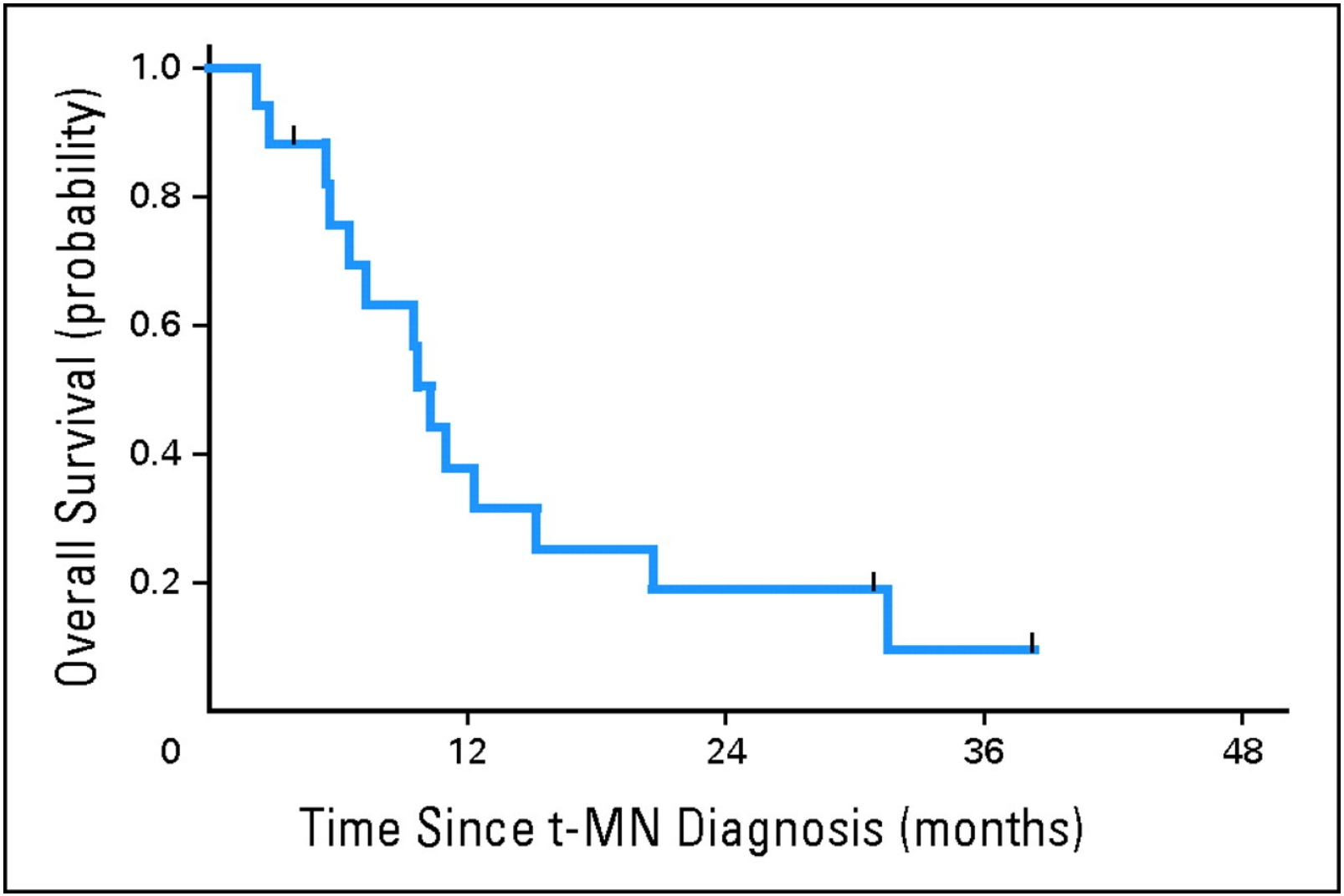
	La Sapienza University, Rome	French-Belgian-Swiss	PETHEMA, Spain
No. of t-MN/APL patients	3/46	6/617	17/918
Crude incidence, %	6.5	1	1.8
Cumulative incidence, %	-	-	2.2 (6 yrs)
Median follow up of APL, months (range)	- (> 24)	51 (39 – 118)	77 (17 – 158)
Time interval from APL to t-MN, months (range)	46 (43 – 48)	47 (13 – 74)	43 (17 – 68)

Cumulative incidence of t-MN in APL patients enrolled in PETHEMA trials



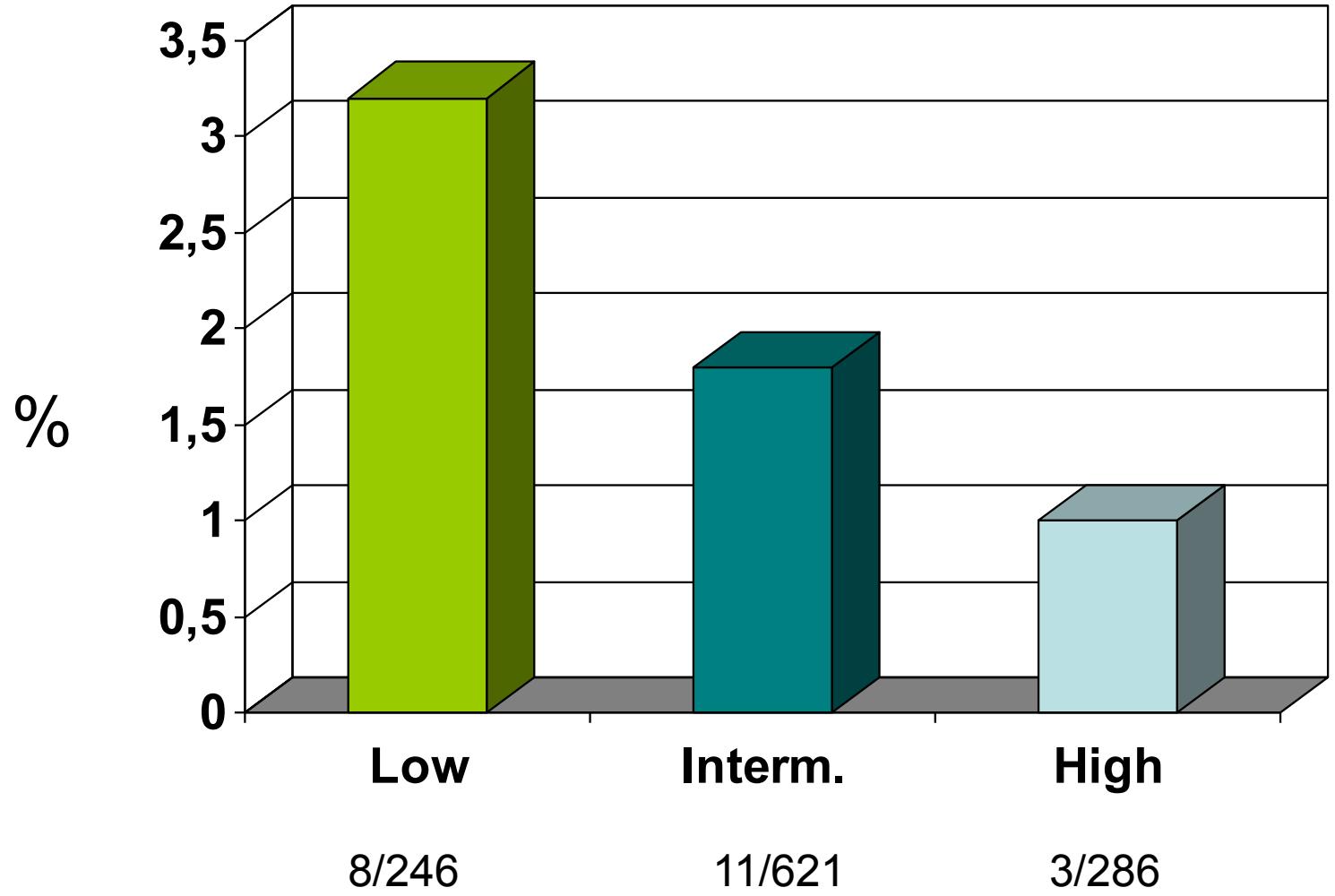
Montesinos P et al. J Clin Oncol 2010

Kaplan-Meier estimate curve of overall survival after development of t-MN in pts with APL



Montesinos P et al. JCO 2010

Crude incidence of t-MN by APL risk group



t-MN in pts with APL (PETHEMA)
Karyotype

	t-MDS	t-AL	Overall
Cytogenetics	8/9	6/7	14/16
-5/del(5q) &/or -7/del(7q)	8	1	9
11q23 rearrangements	1	2	3
Complex karyotype	5	1	6
Normal karyotype	0	1	1


6th INTERNATIONAL SYMPOSIUM ON
ACUTE PROMYELOCYTIC LEUKEMIA
Rome, September 29th - October 2nd, 2013
www.apl2013.com

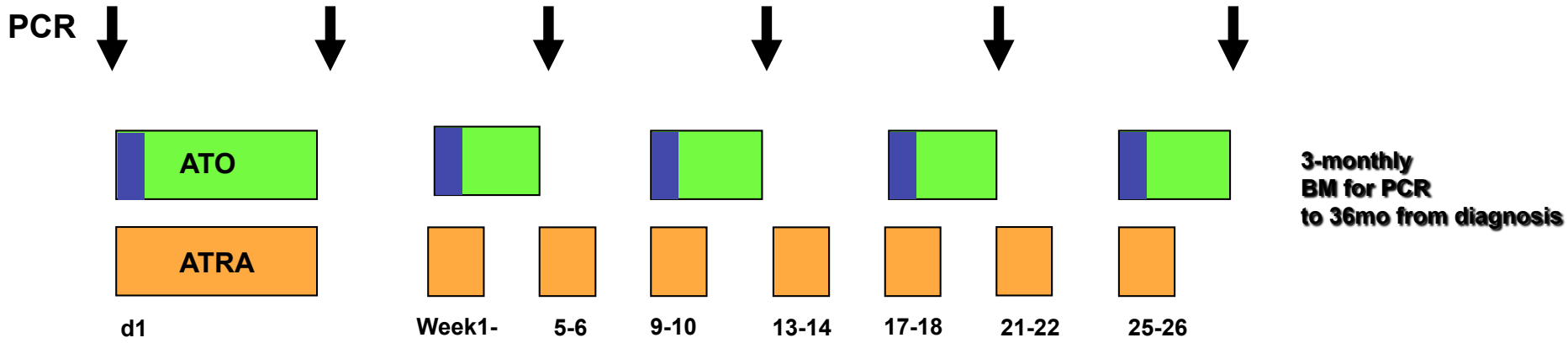
APL: Less is Just as Good

Alan K Burnett
School of Medicine
Cardiff University
Cardiff, UK

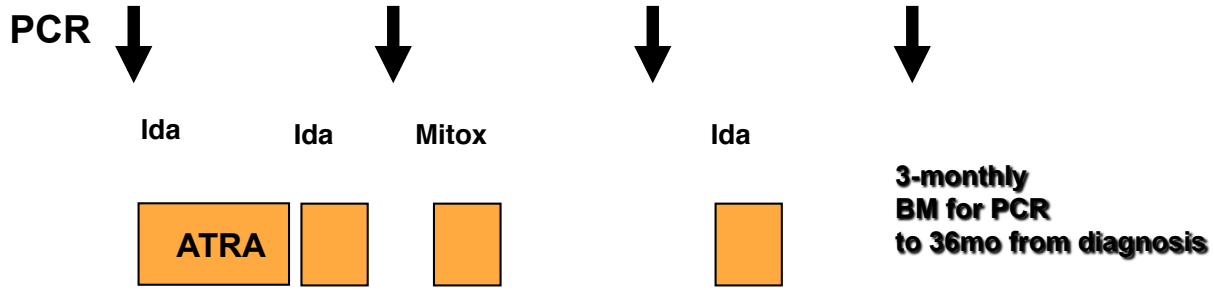
Rome October 2013

AML17 APL Protocol: 2009-2013

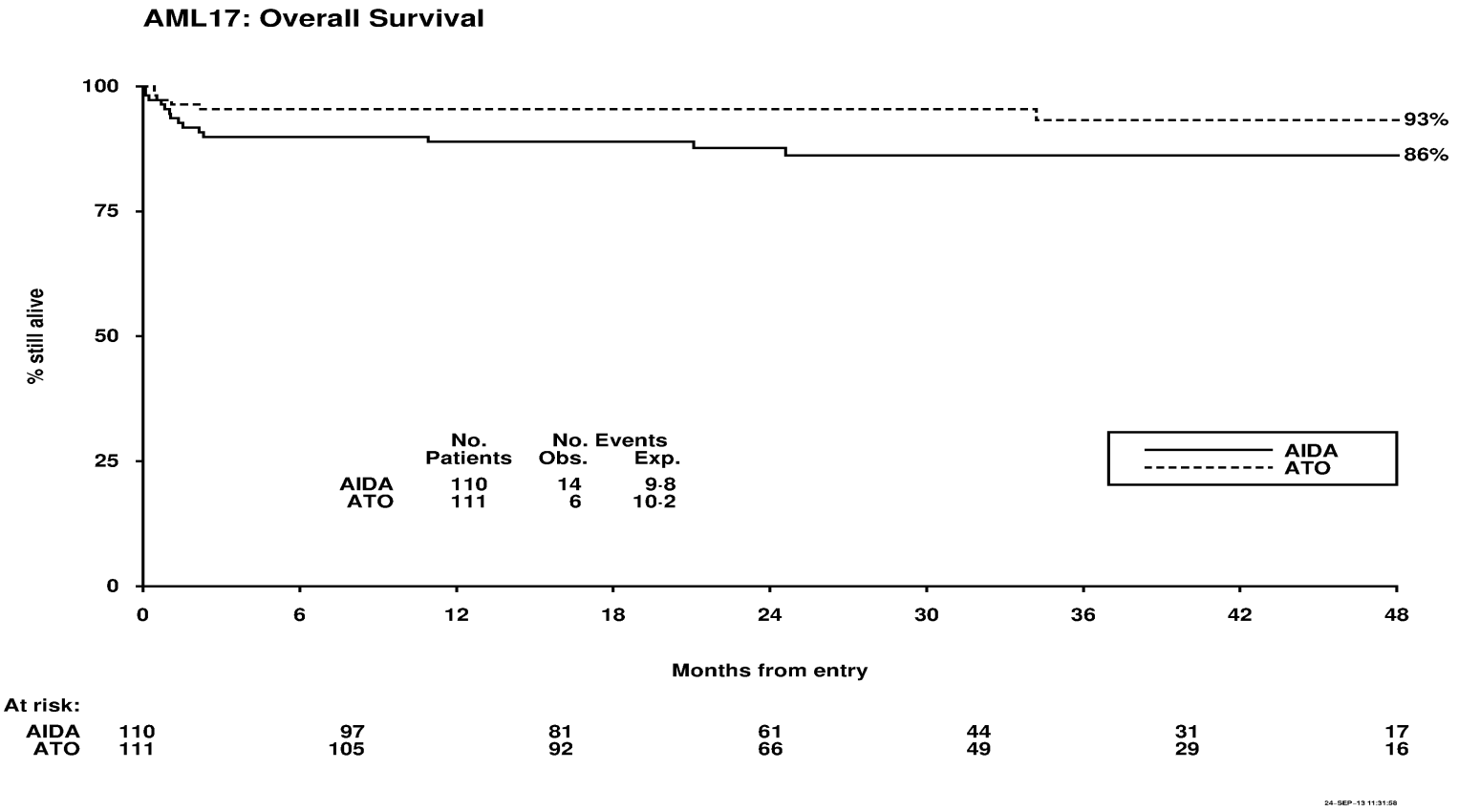
CHEMO-FREE



AIDA



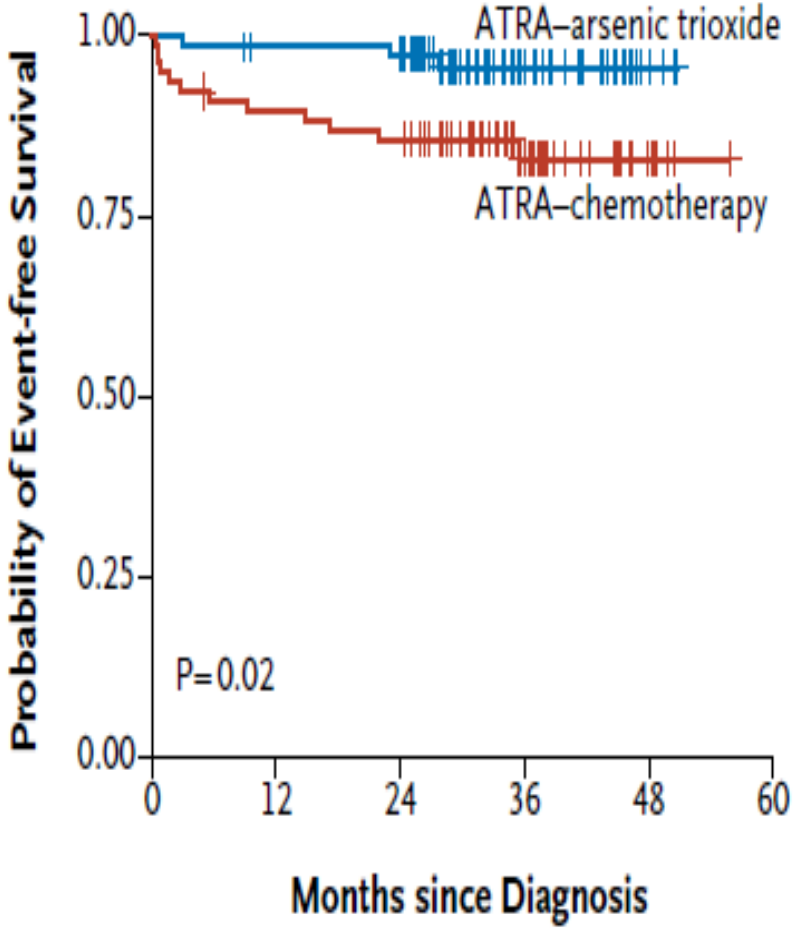
AML 17: Overall Survival

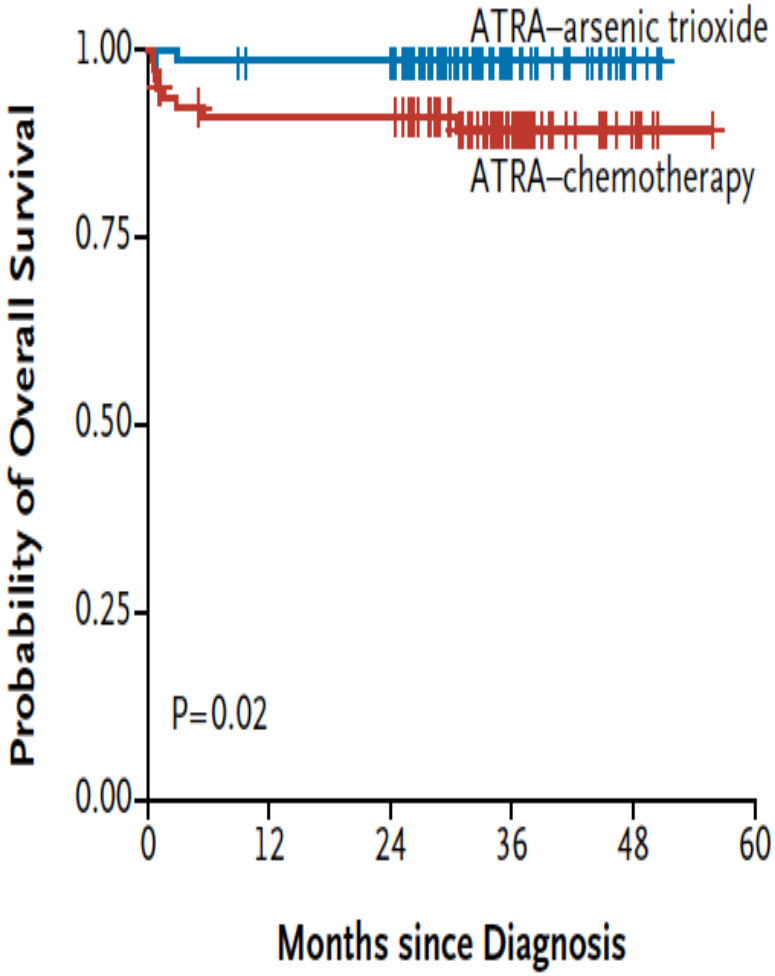


Burnett et al, Lancet Oncology 2015

APL0406 Italian-Germa trial

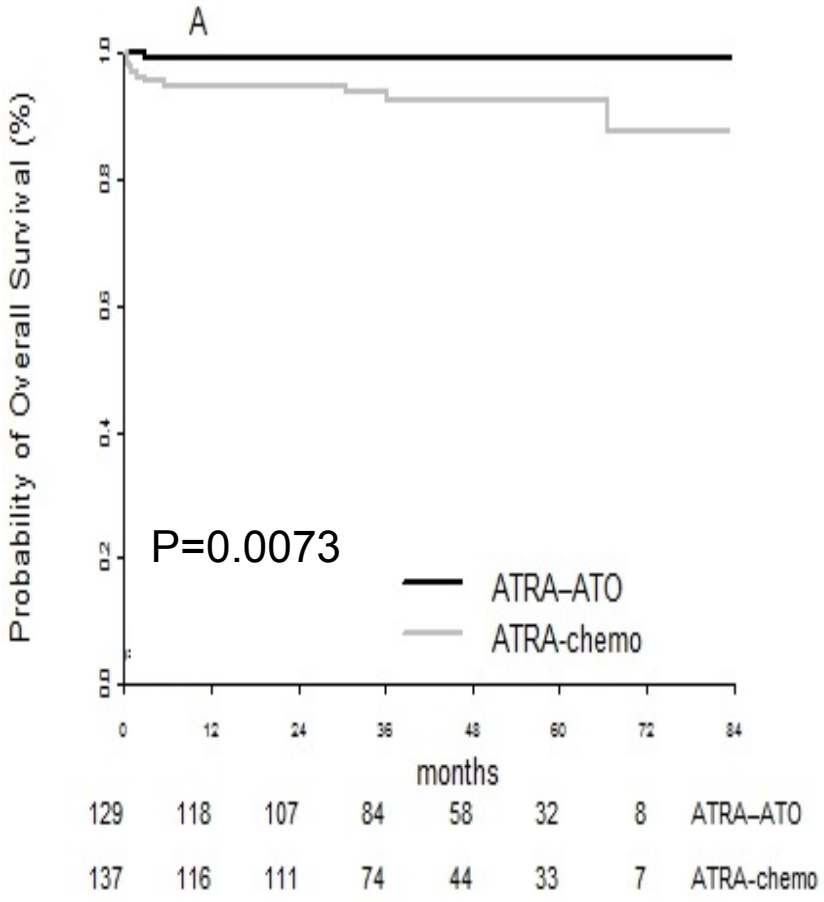
Newly diagnosed APL

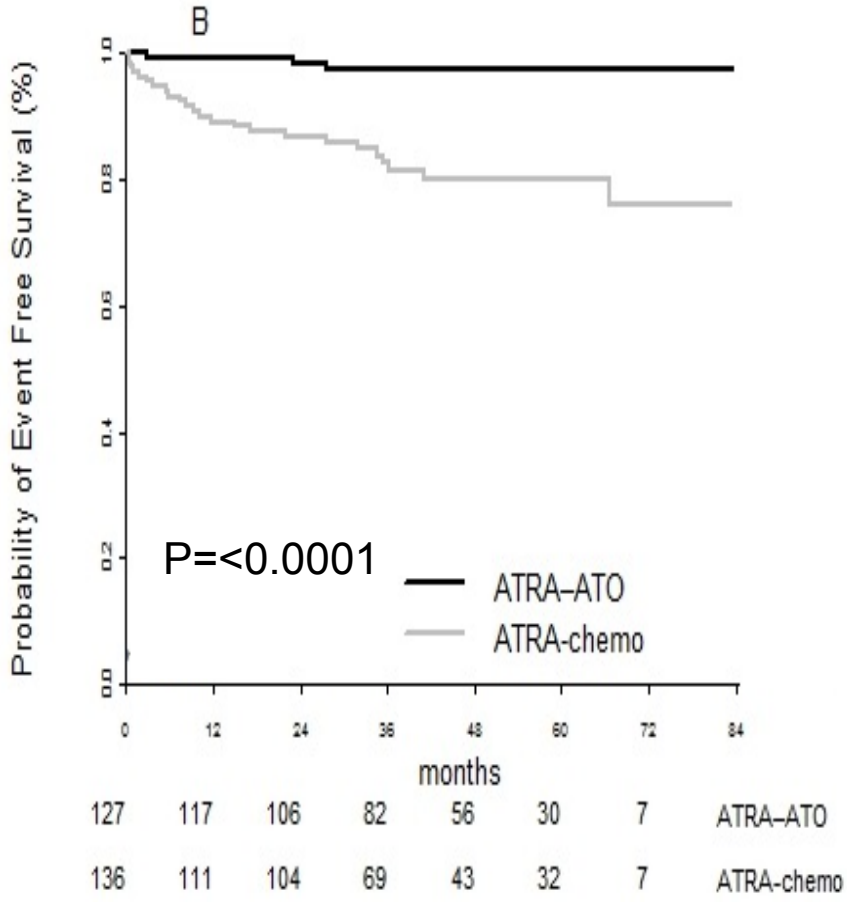




NEJM 369; 111-121, 2013

APL 0406: Extended series of 276 patients
Median follow-up 42 months





Platzbecker et al. J Clin Oncol 2106

APL 0406 Post-remission events

ATO arm (n=3)

1 death in CR (H1N1 pneumonia)

2 relapses

Chemo arm (n=21)

5 deaths in CR (**1 sec. AML)**

1 additional sec. AML

13 relapses

2 molecular resistance

Conclusions from 2 R studies

- Chemo-free (ATO+ATRA) regimen new standard for low risk APL.
- Feasible in high risk if + minimal chemo (e.g. GO)
- Effective in older patients
- Who, if anyone, to be monitored ?

blood

2006 107: 3469-3473
Prepublished online December 22, 2005;
doi:10.1182/blood-2005-10-4006

Use of all-*trans* retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia

Elihu Estey, Guillermo Garcia-Manero, Alessandra Ferrajoli, Stefan Faderl, Srdan Verstovsek, Dan Jones and Hagop Kantarjian

Elihu Estey

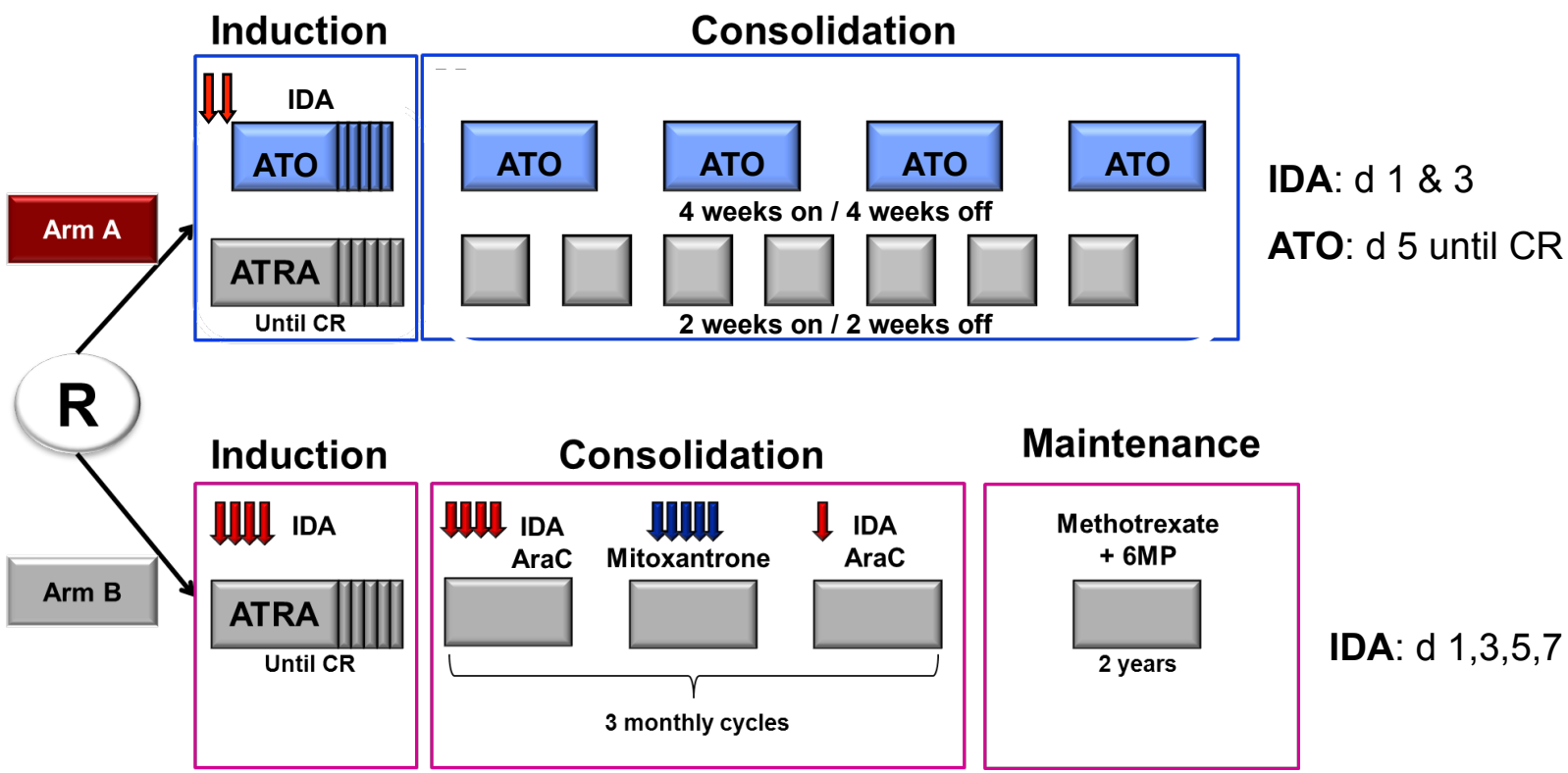
ATO+ATRA vs ATRA+CHT for high-risk APL

APOLLO-Trial

A European R Study for High risk APL

To be started Oct.2016

Treatment schedule



IDA: d 1 & 3

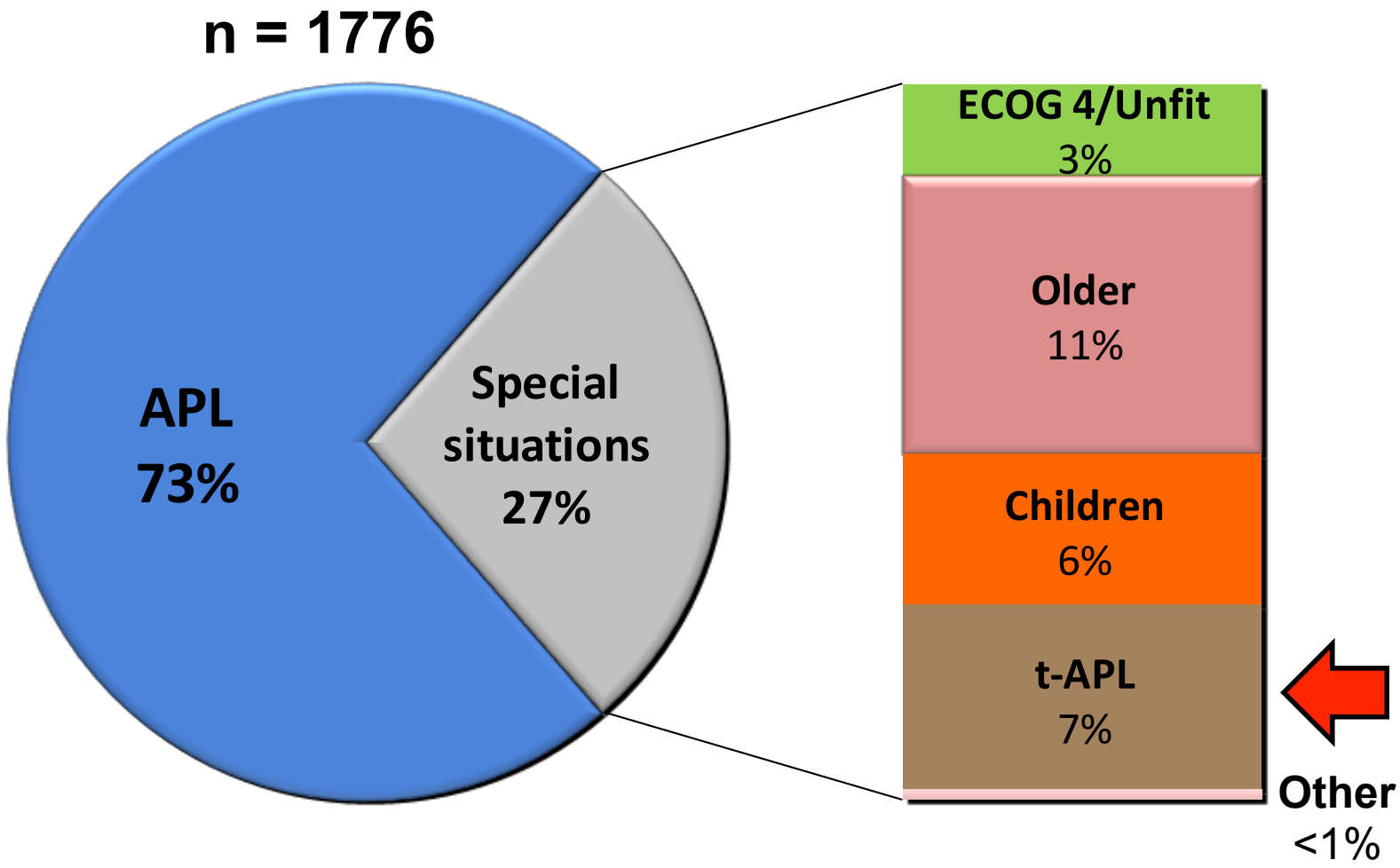
ATO: d 5 until CR

IDA: d 1,3,5,7

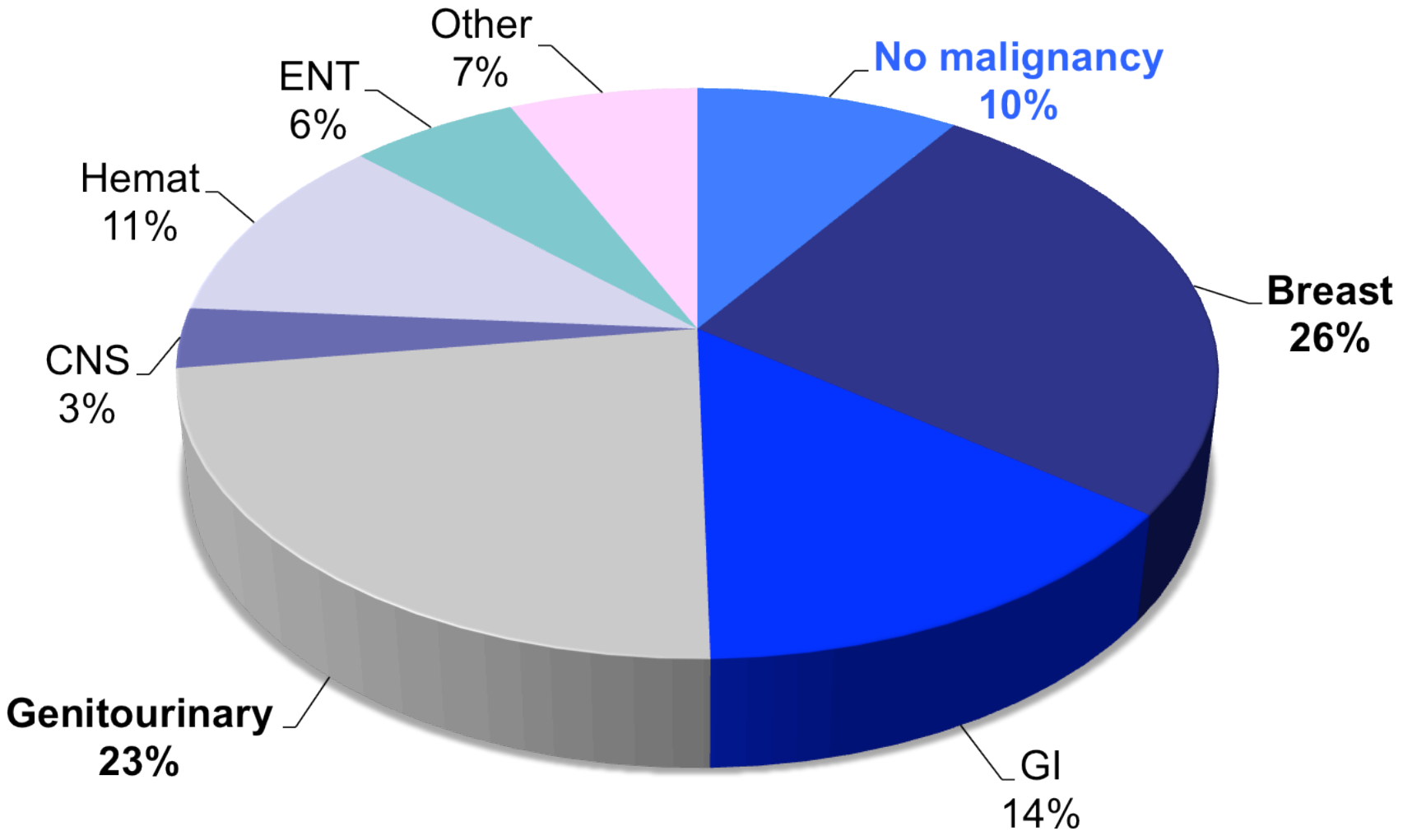
The first 4 days of therapy are identical in the two arms

Acute Promyelocytic Leukemia as a second tumor

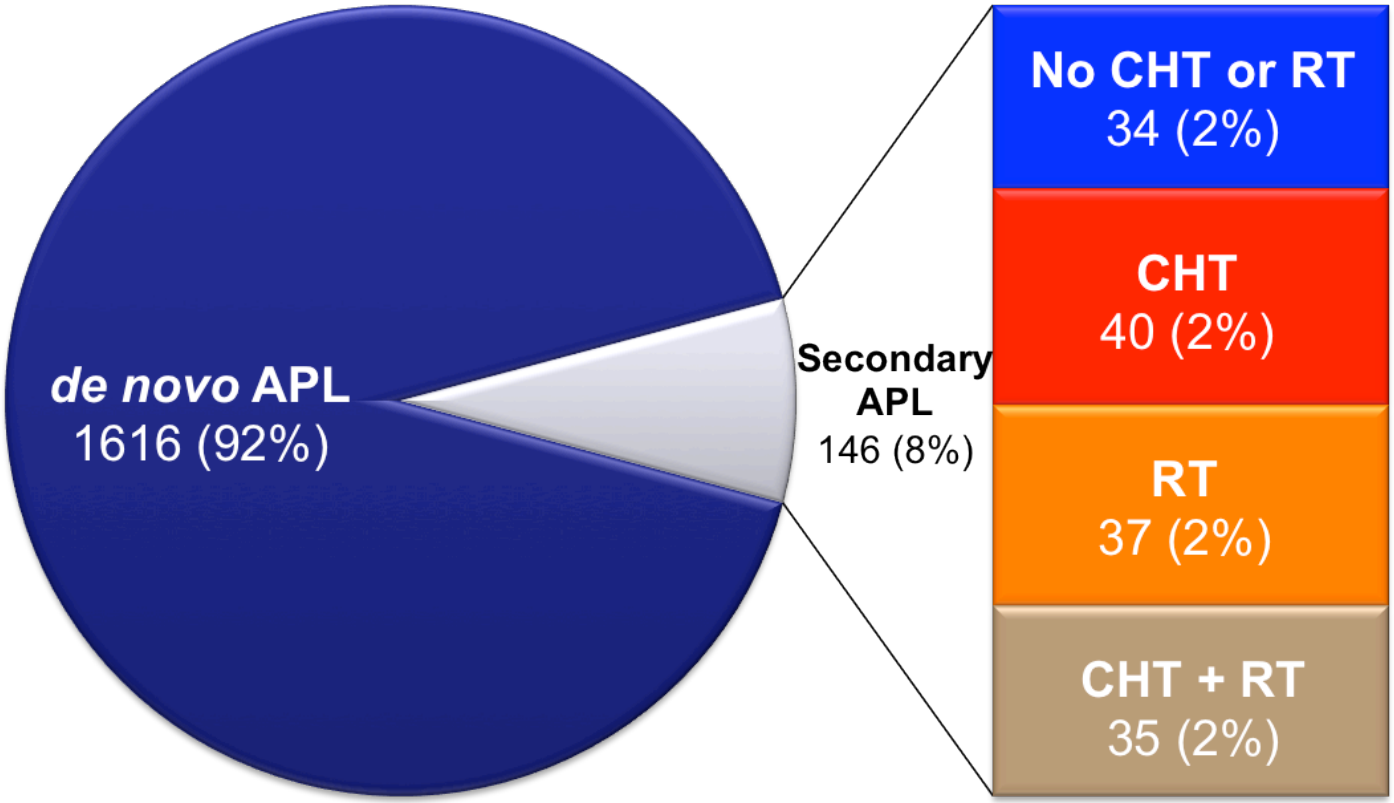
Incidence of special situations in APL



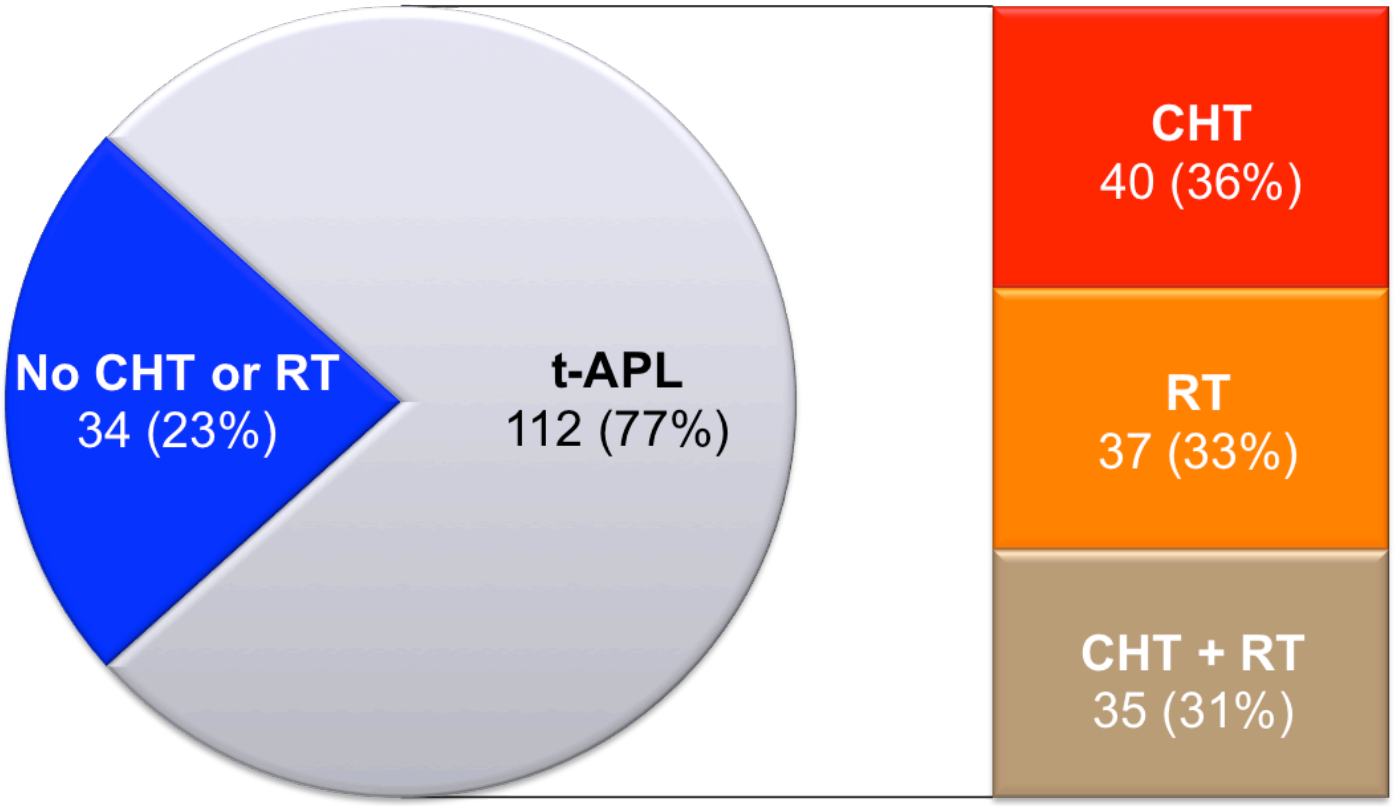
Secondary APL
The PETHEMA experience



Therapy-related APL
The PETHEMA experience



The PETHEMA experience
Secondary vs. therapy-related APL



Characteristics of sAPL

- The biology, pathologic features, clinical course and prognosis of patients with t-AML with recurrent genetic translocations, and particularly with t(15;17), have not been extensively studied.
- Exceptions:
  - Mistry et al.
  - Hasan et al.

  } **Preferential DNA breakpoints**

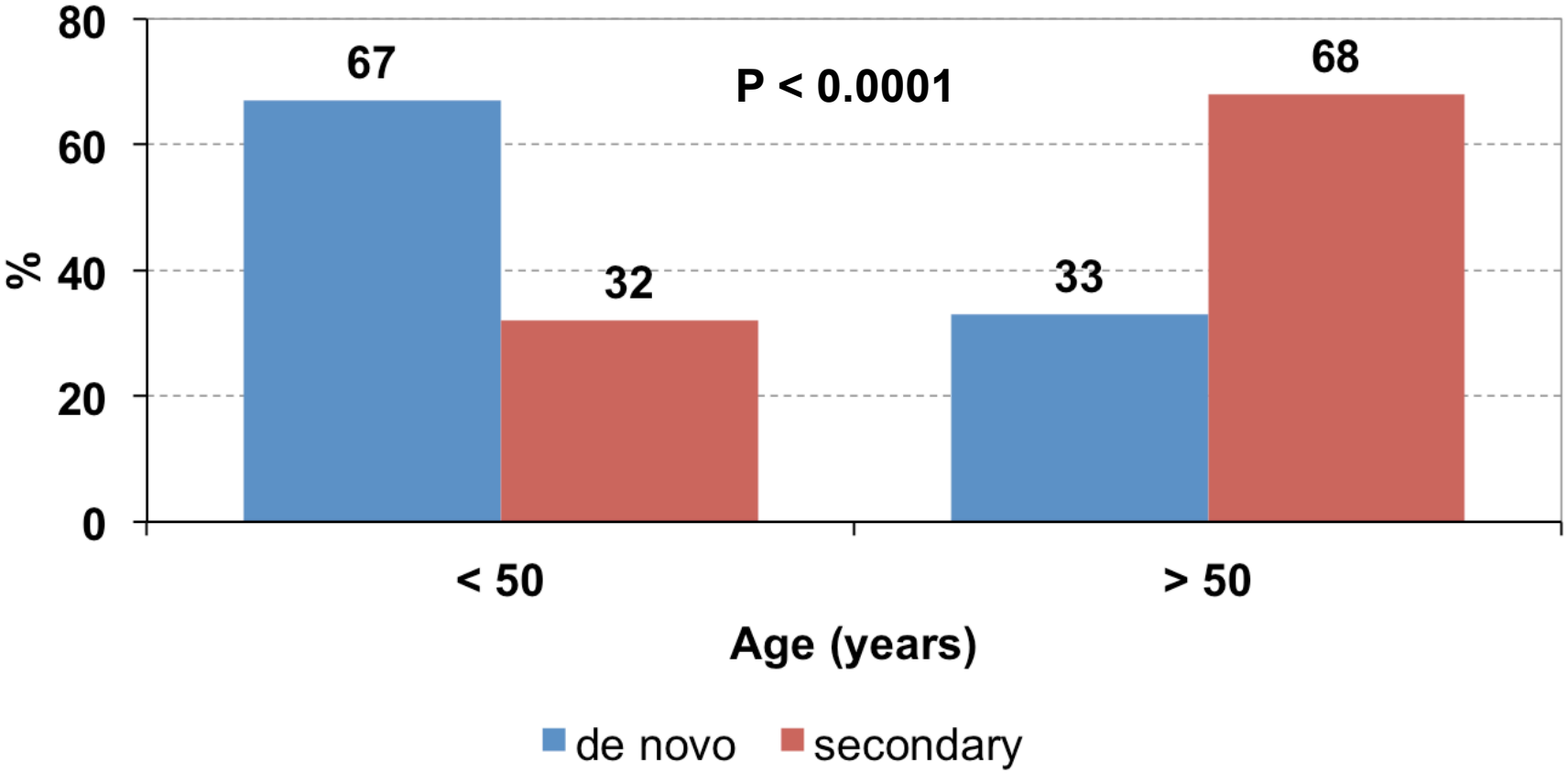
  - European APL Group[1]

  } **Clinical features**
- Need for cooperation due to the relatively low incidence of secondary APL (<1% of AML)

1. Beaumont M, *et al*. J Clin Oncol 2003;21:2123-37

De novo APL *vs.* secondary APL

Distribution of age groups

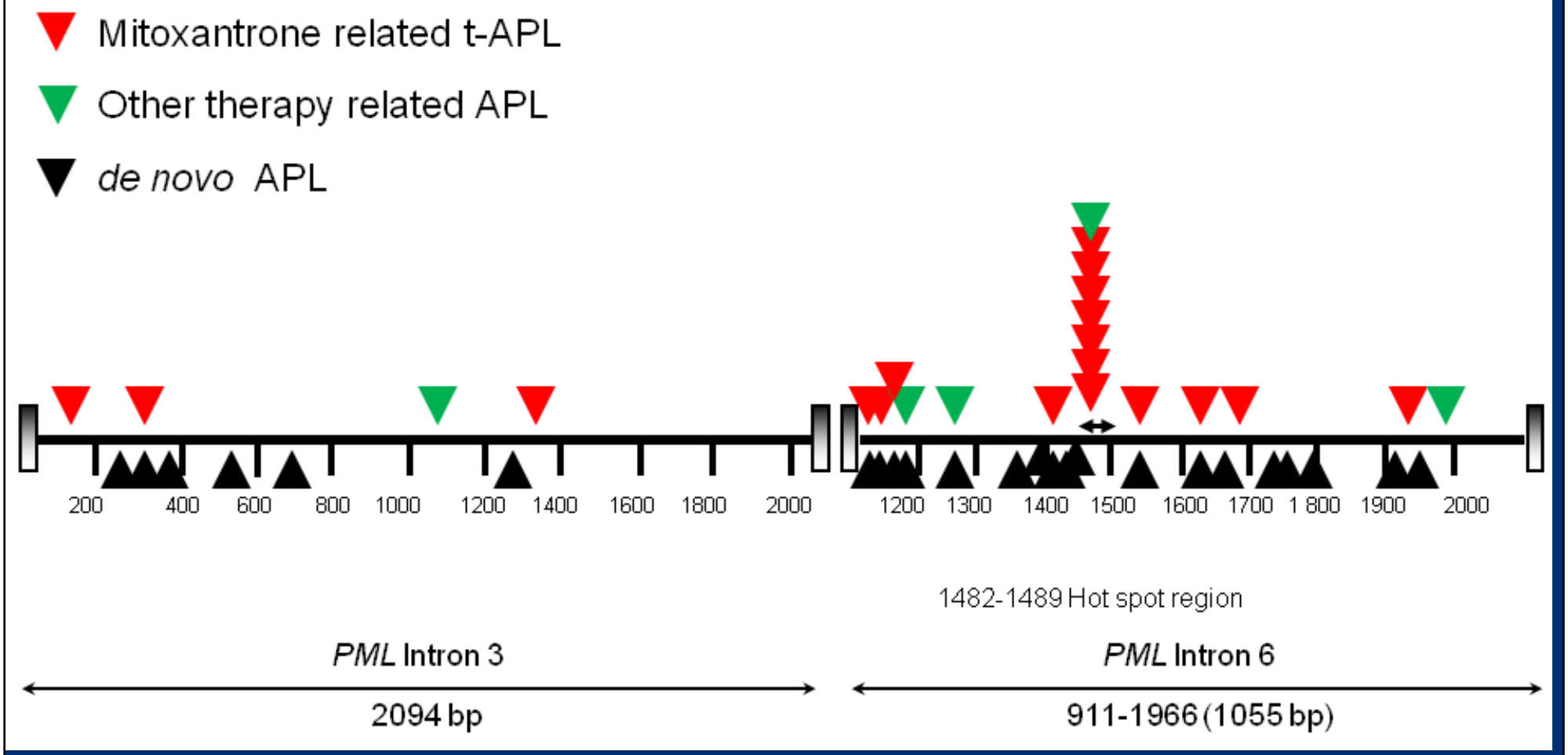


Should therapy-related APL be managed differently?

- Different features compared with *de novo* APL
  - More common in older patients
  - Lower proportion of high-risk patients
  - Previous exposure to chemotherapy (topo inhibitors, alkylating agents), radiation, or both

Biology: biased breakpoint distribution in *PML* and *RARA*

Characterization of *PML* breakpoints



8 bp Hotspot region A G C C C T A G

t-APL cases N= 8/23

de novo APL N= 0/25

P = 0.003

Genomic analysis of therapy-related acute promyelocytic leukemias arising after malignant and non-malignant disorders

✓12 t-APL: non-malignant (n=7) and malignant (n=5) disorders

✓7/12 patients received topo-II inhibitors for the treatment of primary disease

Data confirm the presence of "hotspots" on both *RARA* and *PML* genes

TABLE I. Clinical and Biological Profile of t-APL Patients

				Therapy of primary disease							
Patient number	Primary disease	Age (yrs) at time of primary disease	Sex	Type of treatment	Total cumulative dose (mg)	Latency between primary disease and APL, months	Latency between mitoxantrone and APL, months	*PML/RARA* isoform	*PML* breakpoint	*RARA* breakpoint
Pt 1	Multiple sclerosis	48	M	Mitoxantrone	120	264	24	1	1586–91	13459–64
Pt 2	Multiple sclerosis	43	F	Mitoxantrone	140	29	26	1	1158	**8373**
Pt 3	Multiple sclerosis	33	F	Mitoxantrone	133	78	42	1	**1483–88**	15960–65
Pt 4	Multiple sclerosis	54	F	Mitoxantrone	64	144	28	3	457	**7977**
Pt 5	Multiple sclerosis	46	M	Mitoxantrone	–	156	–	1	**1488**	**14449**
Pt 6	Multiple sclerosis	34	F	Mitoxantrone	130	124	32	1	**1488**	4428
Pt 7	Lewis-Sumner syndrome	46	M	Azathioprine	NA	120	NA	1	1871	**14919**
Pt 8	Histiocytoma	61	M	Surgery + RT	NA	29	NA	3	169	4438
Pt 9	Breast carcinoma	54	F	Surgery + RT	NA	48	NA	3	1200	12632
Pt 10	Breast carcinoma	78	F	Surgery + RT + Epirubicin + Cyclophosphamide	NA	45	NA	3	**1097–99**	**8368–70**
Pt 11	Prostate carcinoma	75	M	RT + HRT	NA	27	NA	1	996	13760
Pt 12	Chronic lymphocytic leukemia	68	M	Rituximab + Fludarabine + Cyclophosphamide	NA	24	NA	1	1132	13782

Ottone *et al*., American Journal of Hematology 2014

Leukemia Research 36 (2012) 474–478

Contents lists available at SciVerse ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Brief communication

Comparative molecular analysis of therapy-related and *de novo* acute promyelocytic leukemia

T. Ottone[a,b], L. Cicconi[a,b], S.K. Hasan[a,b], S. Lavorgna[a,b], M. Divona[a,b], M.T. Voso[c], E. Montefusco[d], L. Melillo[e], E. Barragán[f], U. Platzbecker[g], L. Giannì[a], M. Hubmann[h], M. Pagoni[i], S. Amadori[a], F. Lo-Coco[a,b,*]

- ✓17 t-APL: non-malignant (n=10) and malignant (n=7) disorders
- ✓11/17 patients received topo-II inhibitors for the treatment of primary disease
- ✓24 *de novo* APL

No role of additional mutations (*FLT3*, *IDHs*, *TET2* and *DNMT3A*) in therapy and *de novo* APL disease pathogenesis

Presenting features and treatment outcome of acute promyelocytic leukemia arising after multiple sclerosis

Emanuele Ammatuna,[1,2] Pau Montesinos,[3] Syed Khizer Hasan,[1,2] Safaa M. Ramadan,[1,2] Jordi Esteve,[4] Maximillian Hubmann,[5] Maria Pagoni,[6] David Grimwade,[7] Miguel Angel Sanz,[3] and Francesco Lo-Coco[1,2]

Haematologica 2011

✓33 t-APL arising after multiple sclerosis

✓30/33 patients received mitoxantrone

✓At median follow-up of 26 months, 23 patients were in CR, 4 relapsed and one developed t-AML.

✓The 5-year cumulative incidence of relapse and overall survival were 23% and 68%, respectively.

The occurrence of 3 deaths due to treatment-related toxicity (including one in CR) and of 1 case of secondary AML raises concerns on excessive exposure to chemo and in particular to MTZ.

APL as second tumor

- t-APL shows consistent genomic features with preferential hotspot DNA regions involved
- Milder clinical presentation / features and no additional K / molecular lesions
- Older age and previous treatment burden limits the use of too intensive Atra-CHT
- t-APL may benefit from CHT-free treatment approach

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