"Long term follow up of the International Consortium on Acute Promyelocytic Leukemia: achievements and limitations"

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Disclosures of Eduardo Rego

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					X		
TEVA					X		
Janssen					X		

Challenges for the diagnosis and treatment of APL in Latin America in early 2000's

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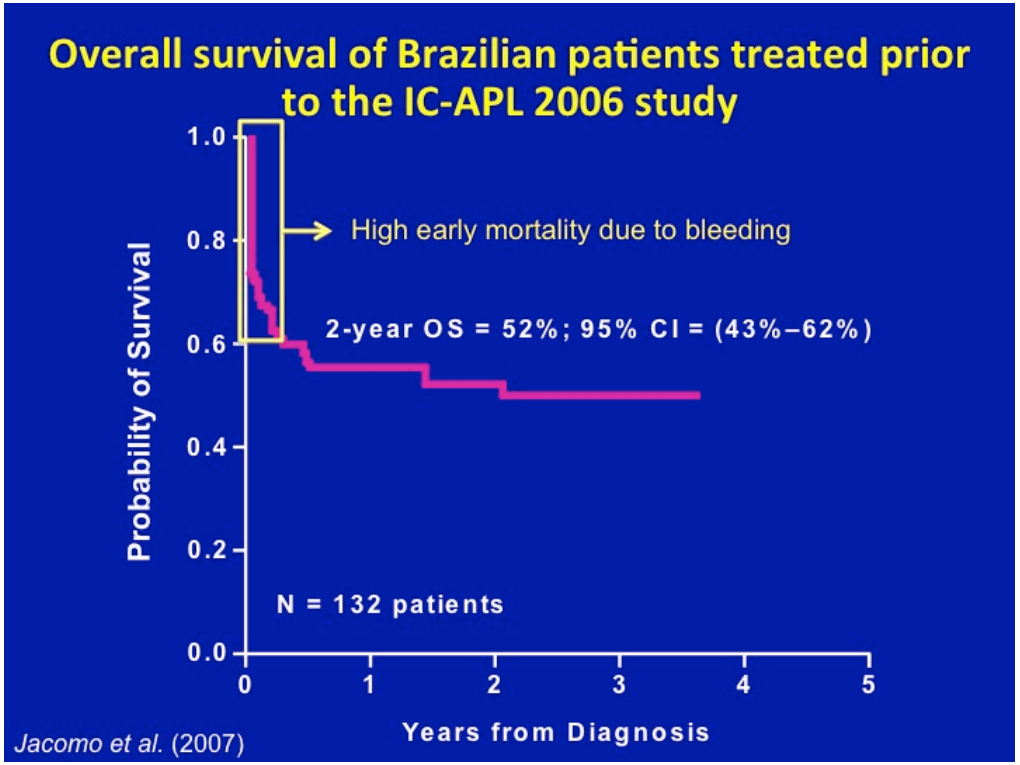
- Insufficient awareness about the disease among non-specialized doctors (high frequency of infectious disease causing thrombocytopenia, e.g. dengue fever)
- Low availability of confirmatory tests for the diagnosis (e.g. 30-40% of AML patients have access to cytogenetics)
- Insufficient training in the management of APL-associated coagulopathy and differentiation syndrome
- Lack of registries about the disease
- ATRA was not in stock in ERs

As consequence

- Delay in dx
- High early mortality rate (32% prior to IC-APL) due to bleeding
- Low overall survival rate (52% prior to IC-APL)
  - High early mortality
  - High mortality associated with DS
- Insufficient awareness about the problem



IC-APL mission

- IC-APL was created in 2004 by ASH International Members Committee with the mission of of fostering interactions between clinicians and researchers in developing countries, with the long-term goals of improving clinical care and creating a national infrastructure for clinical trials and research
- APL was selected as a model because although rapidly fatal if left untreated, it is highly curable if access to rapid diagnosis and specialized care is available. In addition, drugs are inexpensive (ATRA and daunorubicin)
- In 2006 the ICAPL study was initiated.

ICAPL Flowchart

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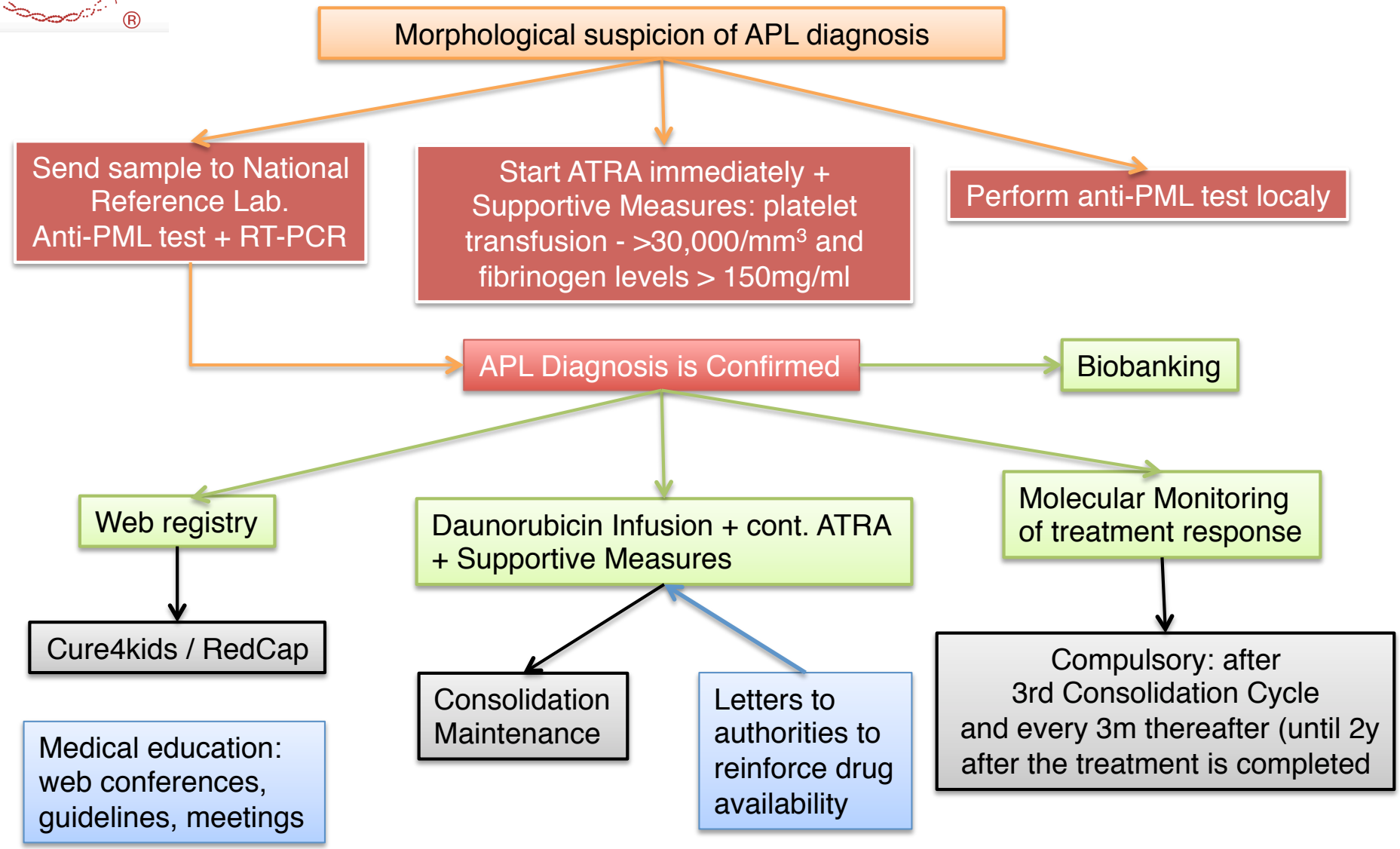

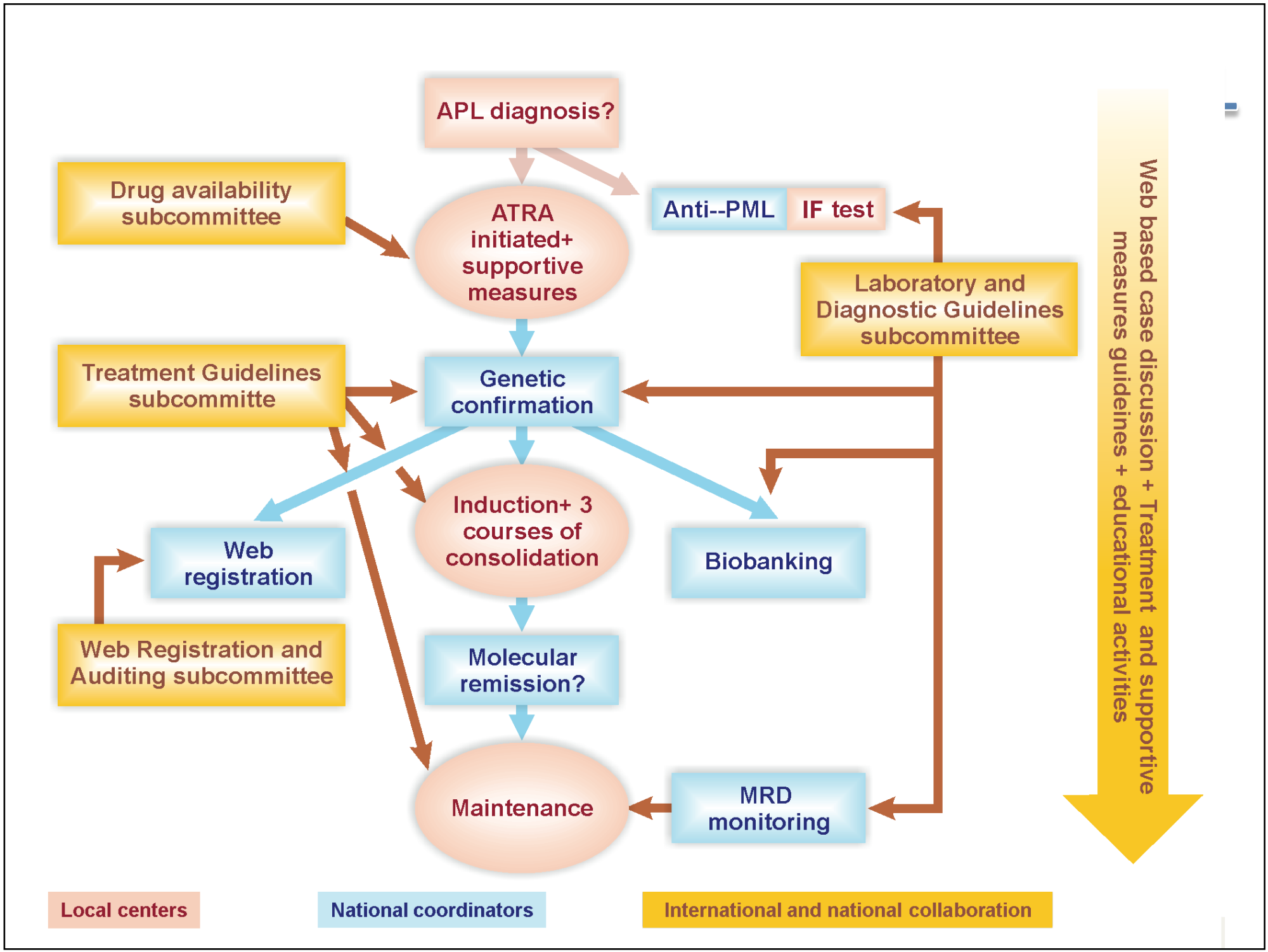
APL diagnosis?
Drug availability subcommittee
ATRA initiated+ supportive measures
Anti--PML
IF test
Laboratory and Diagnostic Guidelines subcommittee
Treatment Guidelines subcommitte
Genetic confirmation
Induction+ 3 courses of consolidation
Web registration
Biobanking
Web Registration and Auditing subcommittee
Molecular remission?
Maintenance
MRD monitoring
Web based case discussion + Treatment and supportive measures guideines + educational activities
Local centers
National coordinators
International and national collaboration

IC-APL2006 AND PETHEMA LPA2005 Twin Protocols

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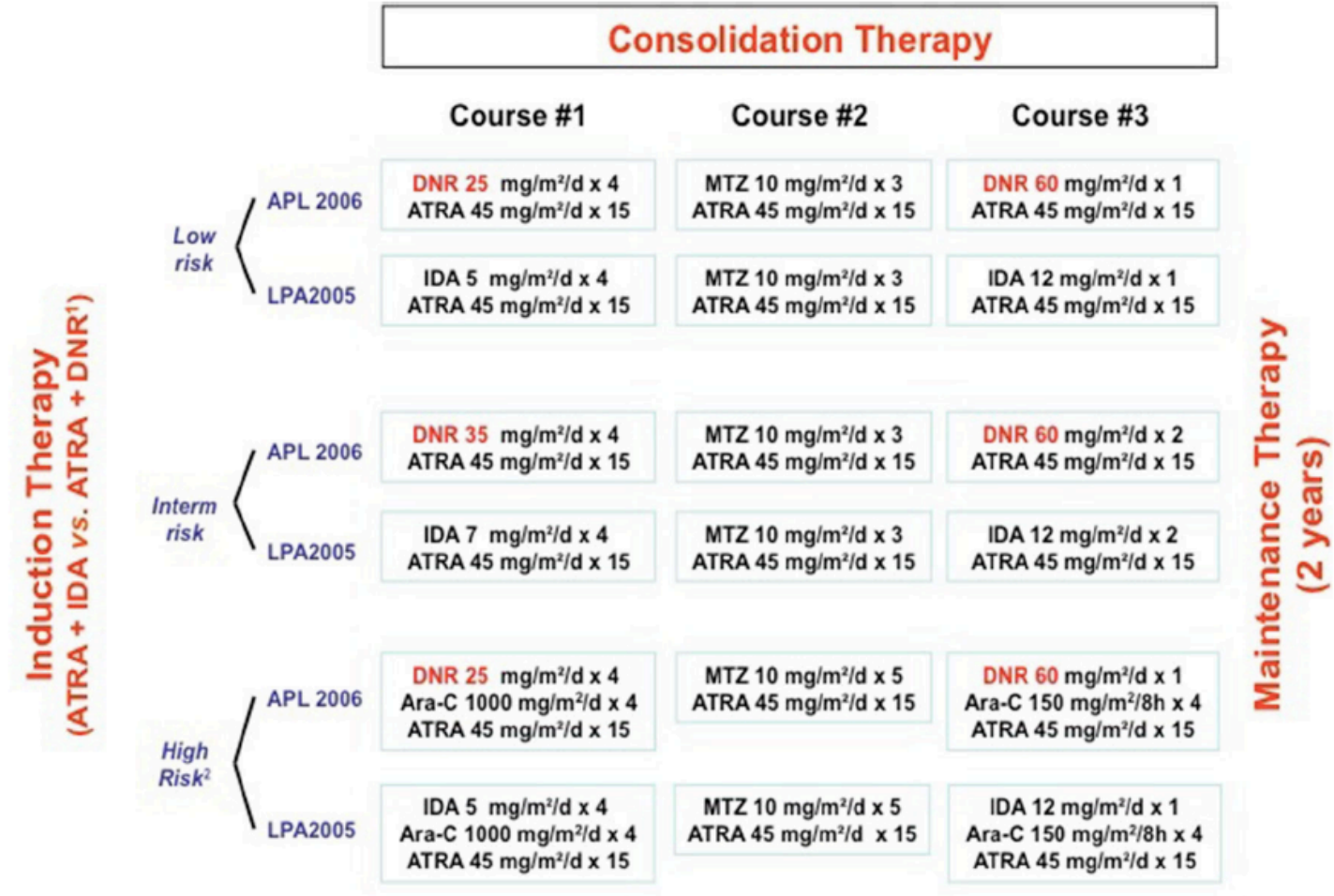

ATRA = all-*trans* retinoic acid; **IDA** = idarubicin; **DNR** = daunorubicin; **MTZ** = mitoxantrone; **Ara-C** = cytarabine

1. ATRA 45 mg/m²/d until CR (25 mg/m²/d for patients ≤20 years) + IDA 12 mg/m²/d or DNR 60 mg/m²/d on days 2, 4, 6, and 8
2. High-risk patients <60 years were treated like intermediate-risk patients (without cytarabine)

IC-APL: network of National Networks

2005/2006

2011/2012

ICAL International Network

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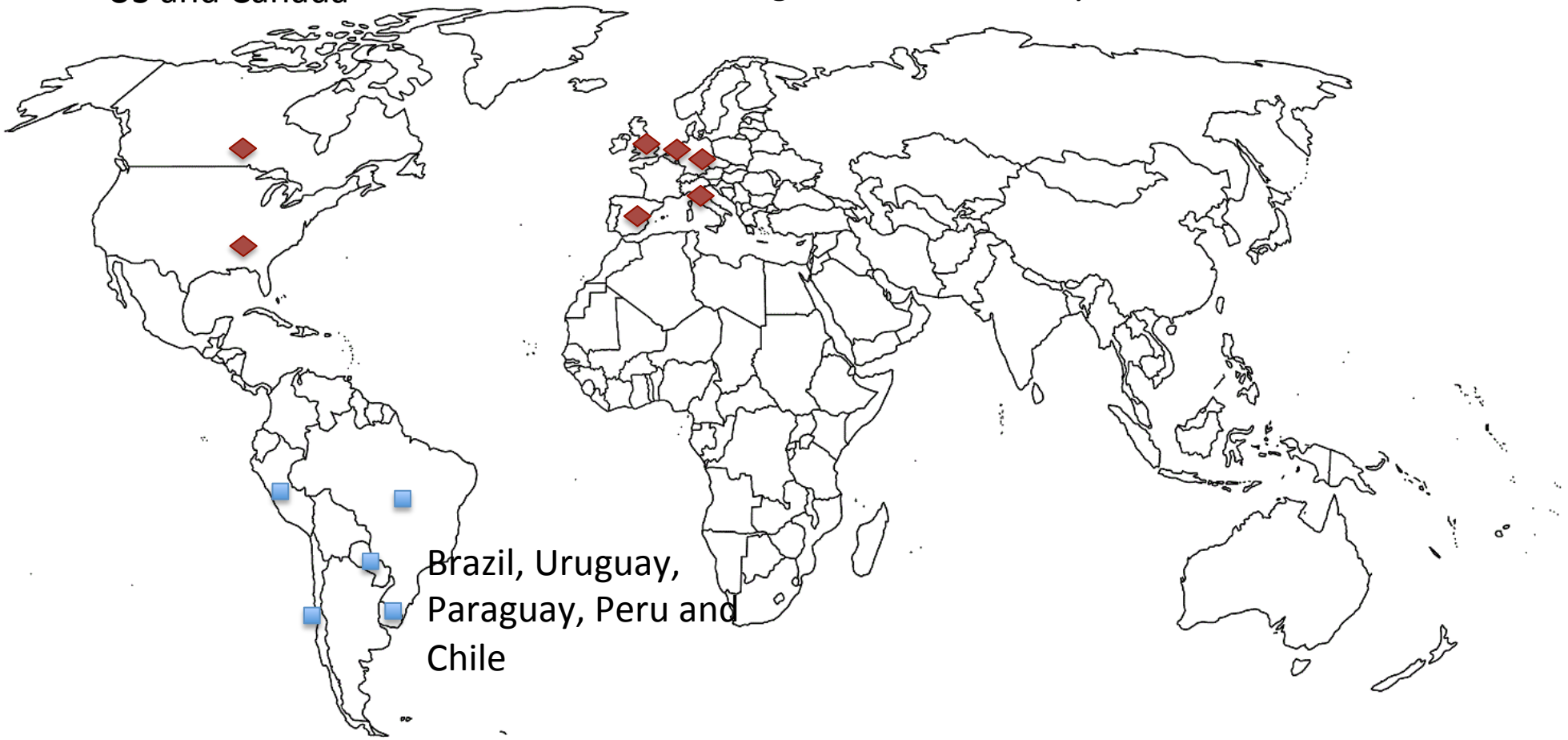
US and Canada

Italy, Spain, Netherlands, United Kingdom and Germany



Brazil, Uruguay, Paraguay, Peru and Chile

Number of patients recruited in ICAPL patients

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	Uruguay	Clile	Peru	Paraguay	Brazil
N	37	150	119	31	306
Age in years at diagnosis (median)	32	39	34.7	40	36.9
WBC (x10^9/L) (median)	2,650	5,300	15,840	1,900	15,900
% of high-rik patients	33%	34.6%	42%	32%	33.7%

N= 643

IC-APL in Brazil from 2006-2017

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- Number of screened patients: 374
- Number of eligible patients: 306 (25.4 pts/y)
  - Main reasons of ineligibility: PML/RARA was not detected (36%); previous chemo or radiotherapy (12%), drug unavailability (10%); age > 75 y (8%); pregnancy (7%)
  - One case of ZBTB16/RARA rearrangement
- Median time of follow up: 50 months

Demographics and lab. values	Median (range) *Frequency [n]*
Age (years)	36.9 (15.1 - 73.5)
Gender (Male)	*45.8% [n=140]*
Hemoglobin (g/dl)	8.5 (14.9 – 2.9)
WBC (x 10^9/L)	15.9 (0.2 – 126.8)
Platelet count (x 10^9/L)	27.6 (1 – 230)
Relapse risk (PETHEMA/GIMEMA classif.)	
Low	*11.1% [n=34]*
Intermediate	*53.9% [n=165]*
High	*33.7% [n=103]*
PT (RNI)	1.38 (0.9 – 3.61)
AAPTT (sec)	29.04 (14 – 67.5)
Fibrinogen (mg/dl)	160 (27 – 600)
Bleeding (all WHO grades)	*93.8% [n=236]*
Thrombosis	
Yes	*6.5% [n=20]*
No	*85.9% [n=263]*
Unknown	*7.5% [n=23]*
Morphologic subtype	
Classic	*87.6% [n=268]*
Variant	*7.8% [n=24]*

Bleeding at presentation

WHO SCORE	Frequency
1	47.1% (n=144)
2	15.4% (n=47)
3	4.9% (n=15)
4	9.8% (n=30)
0 (None)	6.2% (n=19)
Unknown	16.7% (n=51)

WHO Score of Bleeding

Grade 0	no bleeding
Grade 1	petechial bleeding;
Grade 2	mild blood loss (clinically significant);
Grade 3	gross blood loss, requires transfusion (severe);
Grade 4	debilitating blood loss, retinal or cerebral associated with fatality

Induction Outcome

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- CHR rate: 88.9%
- Number of deaths during induction among eligible patients: 33/306 (10.7%)

	Present Analysis (N=306)	Interim analysis (n=180)	Pre-ICAPL (n=134)
Deaths during induction	33 (10.7%)	27 (15%)	43 (32%)
DS frequency	69 (22.5%)	42 (23%)	N.R.
Causes of Death			
Hemorrhage	19 (57.7%)	13 (48.1%)	26 (60.5 %)
Infection	13 (39.4%)	7 (25.9%)	5 (11.6%)
DS	1 (3%)	5 (18.5%)	4 (9.3%)
Other	3 (9%)	2 (7.4%)	8 (18.5%)

Deaths during induction

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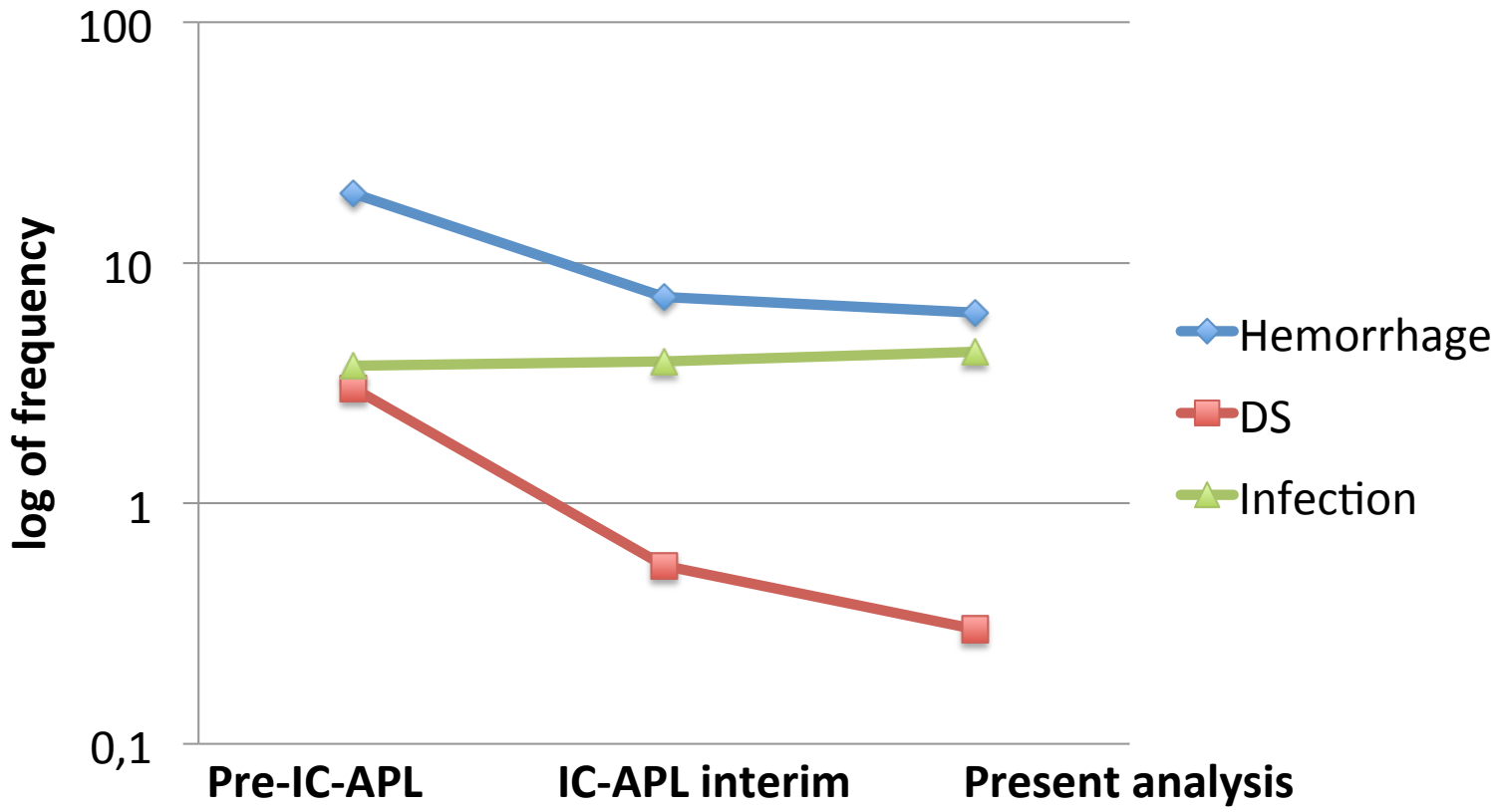
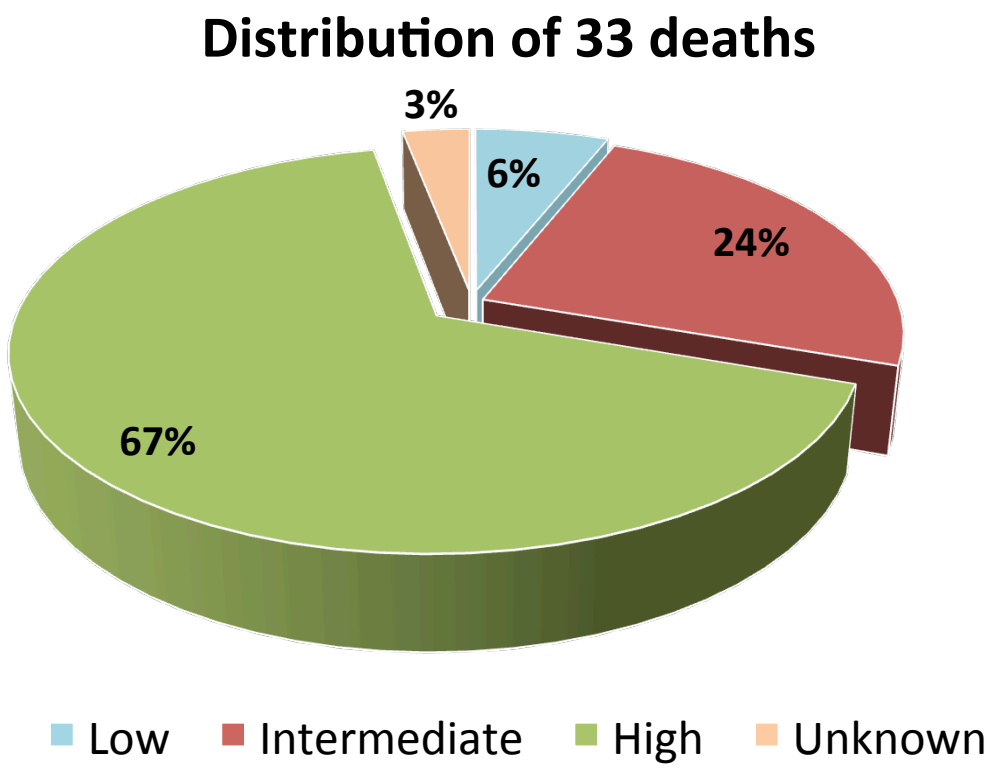
DEATH RATE 2006 to 2011: 14.5% (20/138)
DEATH RATE 2012 TO 2017: 7.8% (13/167)



Induction Death Rate according to Risk

Risk Category	Induction Death Rate
High-risk	22/103 (21.4%)
Intermediate-risk	8/165 (4.9%)
Low-risk	2/34 (5.9%)

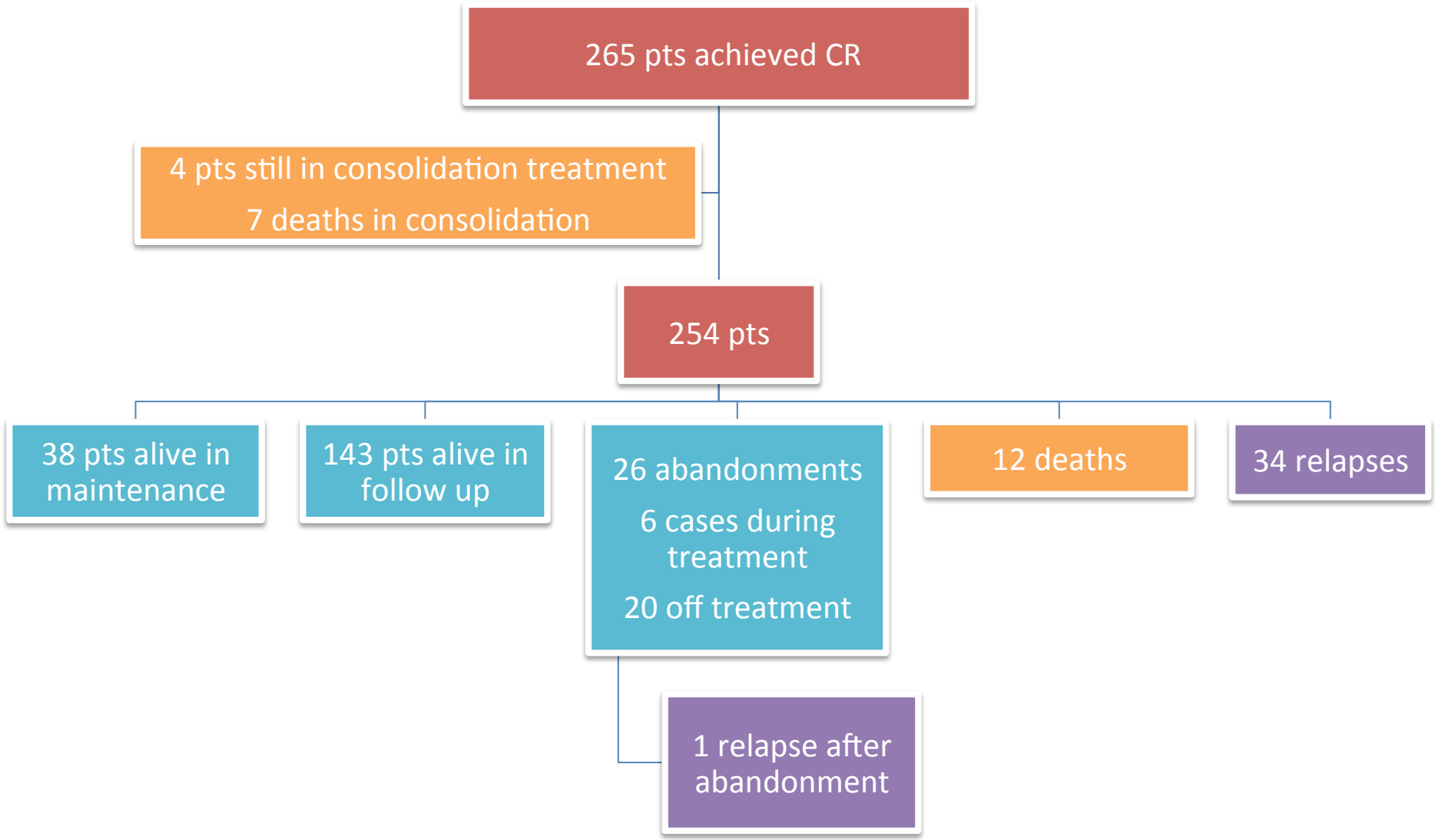


Comparison between PETHEMA/ HOVON 2005 and IC-APL2006

ICAL

- The PETHEMA/HOVON 2005 and the IC-APL trials were compared using a matched-pair analysis. 350 pts from the PETHEMA/HOVON cohort (July 2005 – Dec. 2011) were matched with 175 patients in the IC-APL cohort(Jun 2006 – Sept 2010).
- CR rate in the ICAPL cohort was of 85 %; and in the matched PETHEMA cohort of 94 % (P=0.003).
- In the present analysis, CR rate was of 88.9% suggesting a continuous improvement over time.
- The two trials had comparable cumulative incidence of relapse (CIR) and disease-free survival (DFS) rates,
- Lower overall (OS) and event-free survivals (EFS) were observed in the IC-APL cohort, which was mainly due to a higher death rate during induction therapy.

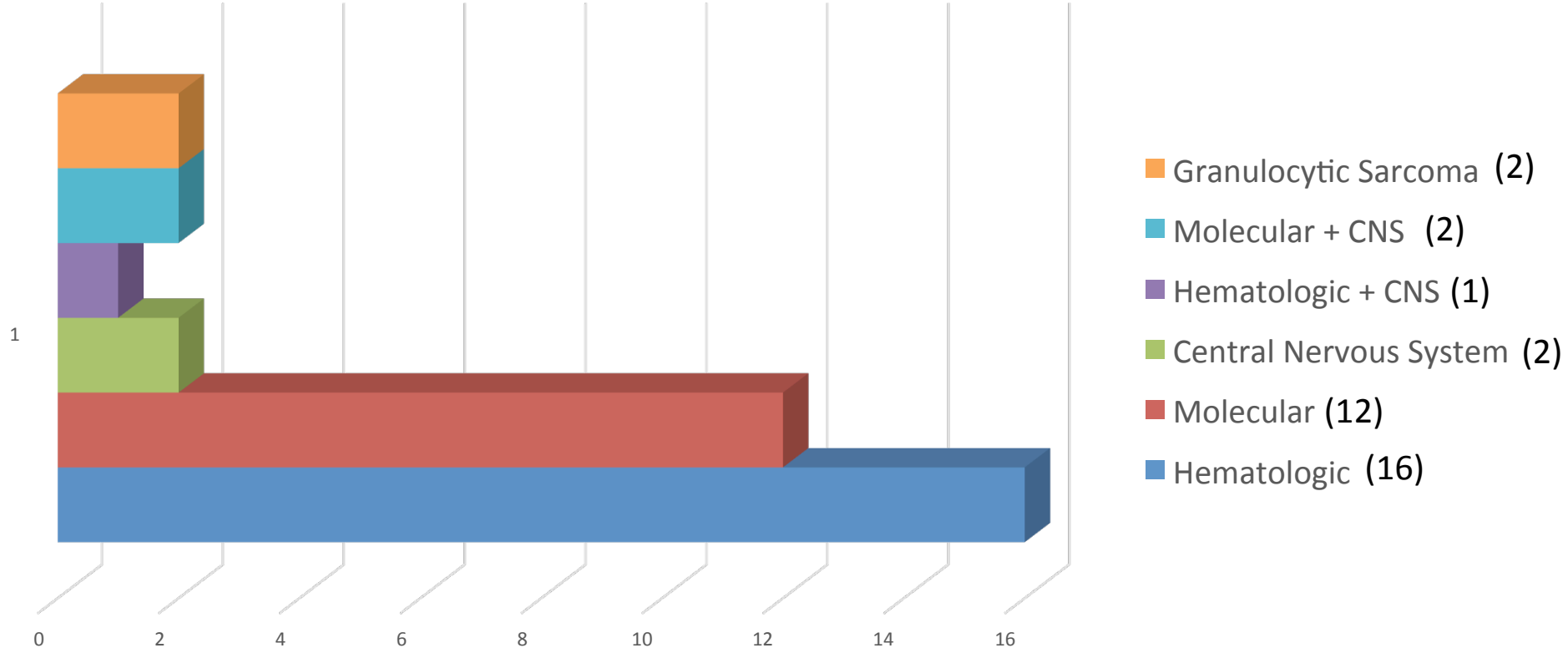
Consolidation and maintenance therapy



Relapses

ICAL

- Incidence of relapse in 11 years: 35/265 (13%)
  - Maintenance relapse: 21 pts
  - Off therapy relapse: 13 pts (Median 3.75y – Range: 2.25 - 7.67y)
  - After abandoned therapy: 1 pts
  - 16 deaths after relapse



Relapses II

- 5/16 of hematological relapses occurred in patients that were not compliant to serial monitoring
- 3/16 cases the hematological relapse occurred in the moment that the sample intended to confirm mol. relapse
- 4 were after monitoring was interrupted
- 4 were preceded by molecular relapse

Disease free survival

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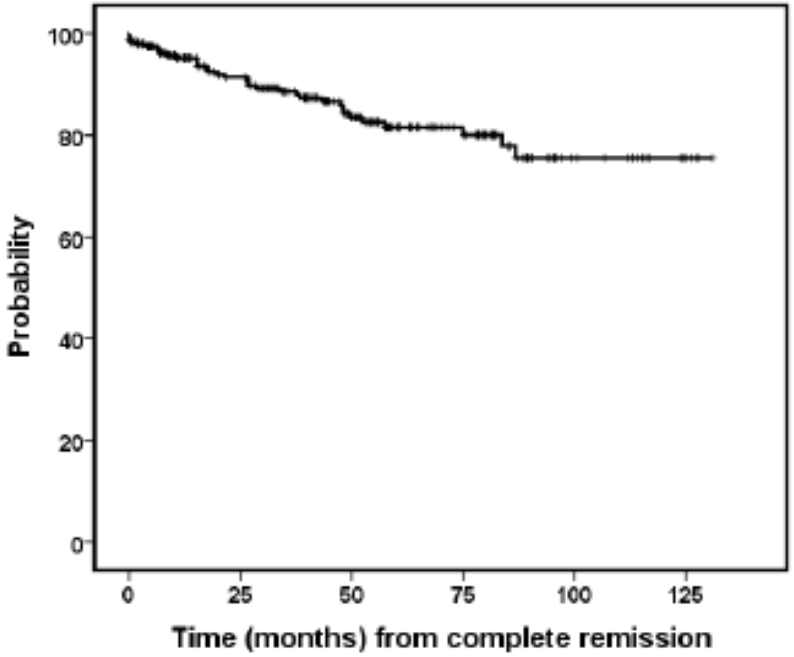
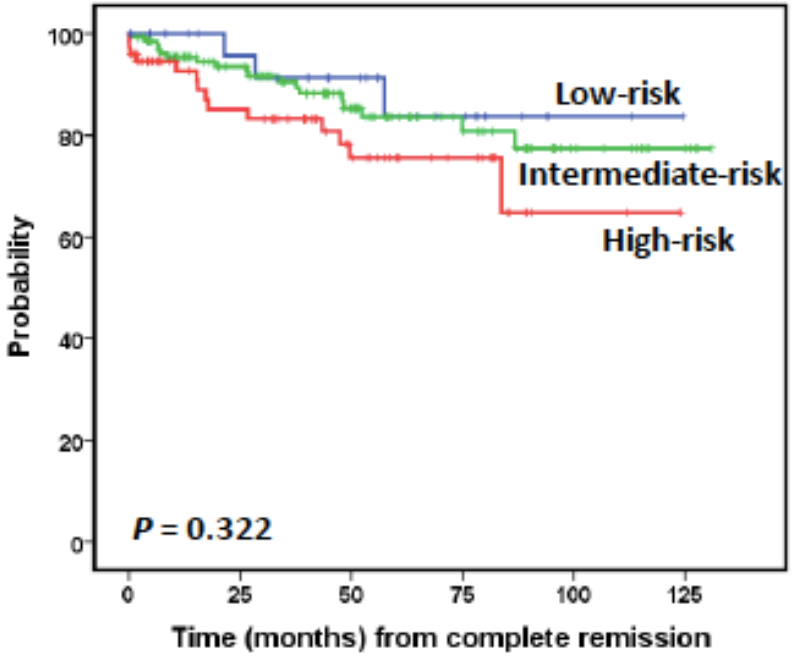
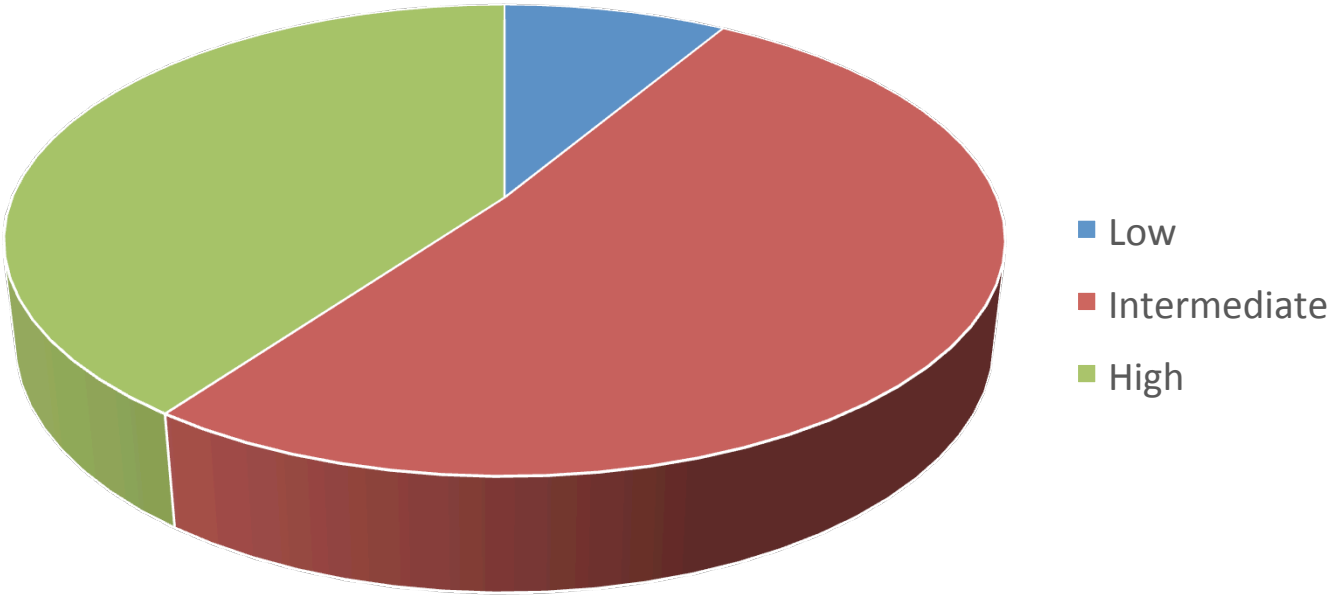




	All patients (n = 298)	Low-risk (n = 32)	Intermediate-risk (n = 161)	High-risk (n = 101)	*P*-value[3]
5-y DFS, % (95% CI)	82 (75 to 87)	83 (55 to 94)	83 (74 to 90)	76 (62 to 86)	0.322
5-y CIR, % (95% CI)	17 (11 to 23)	14 (0 to 28)	16 (8 to 23)	22 (11 to 33)	0.316

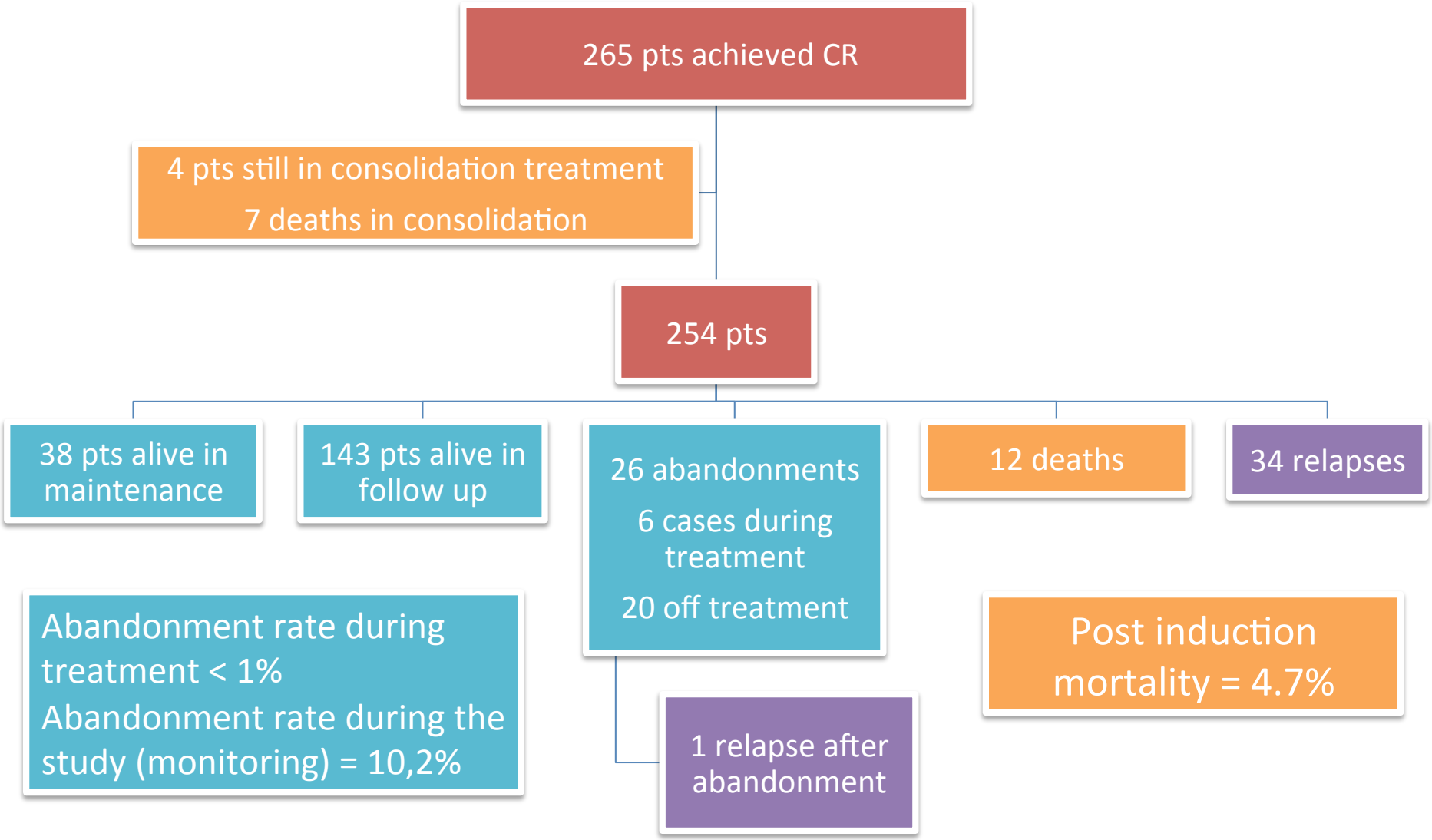
Distribution of relapsed cases according to risk category



	Relapse rate (%)
Low	3 (8.6%)
Intermediate	18 (51.4%)
High	14 (40%)
Total	**35**

Consolidation and maintenance therapy

ICAL



Deaths in consolidation, maintenance and follow up after treatment

During consolidation		
Infection	7 (fungal 5)	5 High / 1 Interm
During maintenance		
Secondary neoplasia	1 (breast cancer)	1 Low
Venous Thromboembolism	1	1 Interm
Infection	2 (fungal)	2 High
During Follow up (off treatment)		
Cardiovascular (MI)	1	1 Interm.
Secondary neoplasia	2 (AML) *	1 High / 1 Interm
Other causes	2	2 Low
Unknown	3	

Overall Survival

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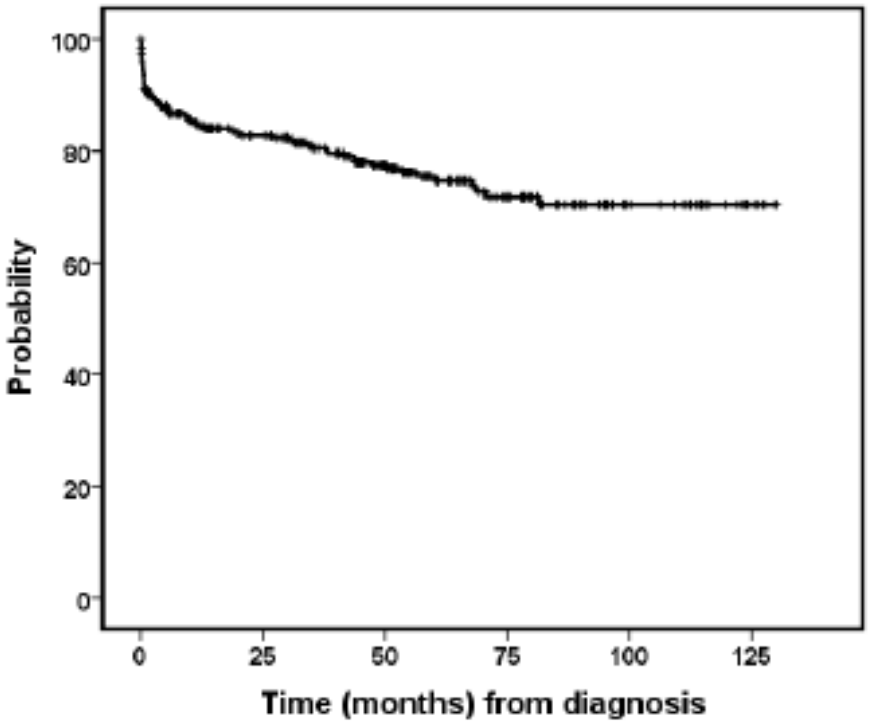

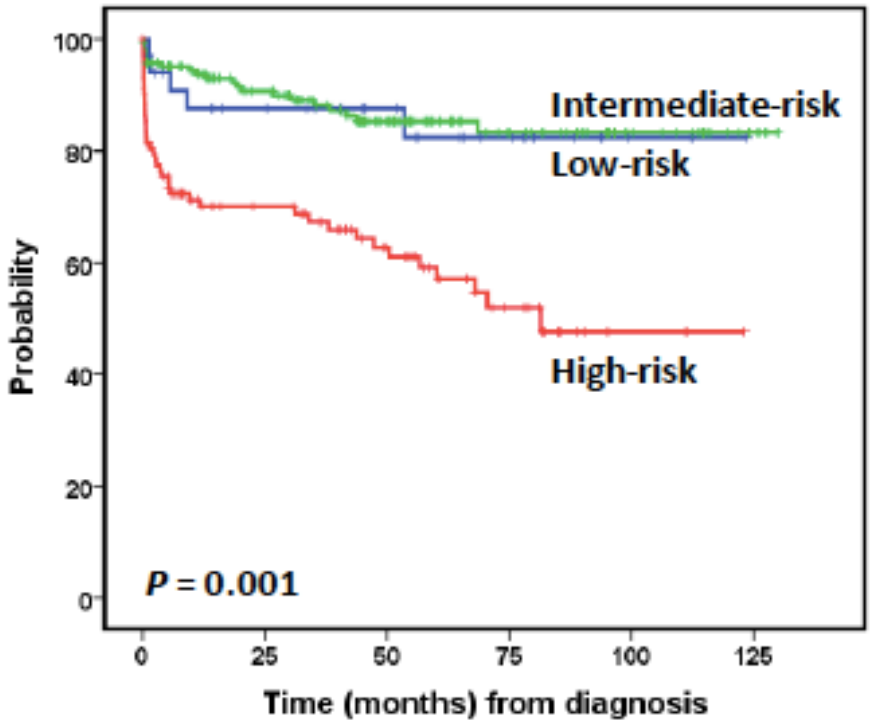

	All patients (n = 298)	Low-risk (n = 32)	Intermediate-risk (n = 161)	High-risk (n = 101)	*P*-value[3]
5-y OS, % (95% CI)	75 (69 to 80)	82 (62 to 92)	85 (78 tot 90)	59 (47 to 69)	< 0.001*

Infrastructure

- All countries have well established reference lab and master the diagnostic tools to make a fast diagnosis of APL. In the last two external Q.C. by UKNEQAS confirmed that the quality standards.
- Molecular testing was performed at diagnosis and at after 3rd cycle of consolidation cycle in all but one patient. Compliance to serial PML/RARA testing was close to 80%.

Infrastructure

ICAL

- Networking promoted by ICAL let to other multicentric studies in the region (AML; registries of lymphomas and AA). Thus improving clinical research in the region
- Add-on studies (molecular, coagulation) helped in the training and fostered the career of young investigators.

Achievements and Limitations I

ICAL

- Through networking ICAL succeeded in bringing continuous improvement of CR rates and a persistent reduction of early death rates in patients with APL from LA.
- Other therapeutic alternatives should address the issue of high mortality during induction in patients with WBC > 10,000/mm^3 at Dx.

Achievements and Limitations II

ICAL

- Continuous medical education is important to reassure that supportive measures and treatment of DS were promptly given to APL pts. CME was also essential to the compliance to MRD testing (molecular relapses)
- Obtaining bone marrow samples every 3 months after completion of the therapy is an obstacle to the compliance of MRD monitoring

Achievements and Limitations III

ICAL

- Post induction mortality was of about 5%, occurred mainly in high-risk patients and were due to infectious complications associated with myelosupression
- The role of antifungal prophylaxis with agents other than fluconazol should be tested in this subgroup of patients (or ATO will make this issue redundant??)

Achievements and Limitations IV

ICAL

- Networking was very effective to promote the development of regional infrastructure and training of specialized human resources
- Whether this is also true to other more challenging diseases remains to proven

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