Frontline therapy of acute promyelocytic leukemia: randomized comparison of ATRA and intensified chemotherapy including high dose cytosine-arabinoside versus ATRA and anthracyclines - A prospective multicenter randomized clinical trial of the German Acute Myeloid Leukemia Cooperative Group (AMLCG).

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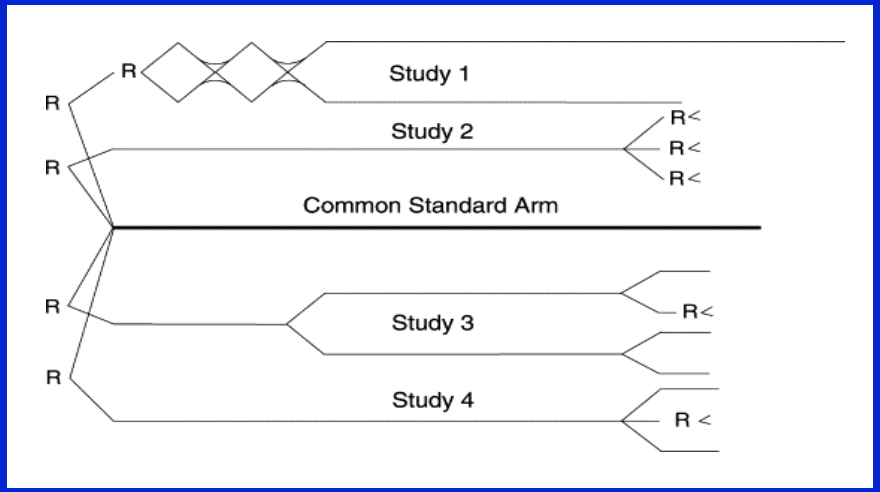
Background

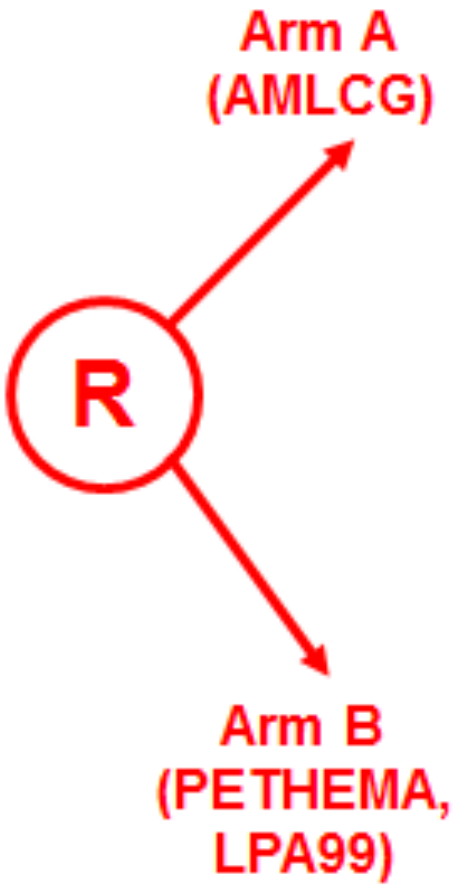
- The APL-2005 study was started as AMLCG trial with the intention to be part of an APL intergroup study with the PETHEMA (LPA99) protocol as common standard arm.



Büchner et al,
Leukemia Research
2002;12:1073-1075

- Method of comparing the outcome of different treatment regimens:
  → Cross trial networking:
  Up-front randomization on a common standard arm.

Study Design APL-2005 Study



Induction	ATRA plus TAD/HAM
Consolidation	TAD
Maintenance 2 years	AD + ATRA / AT + ATRA / AC + ATRA / AT + ATRA
Induction	ATRA plus Idarubicin (AIDA)
Consolidation 1	Idarubicin + ATRA
Consolidation 2	Mitoxantrone + ATRA
Consolidation 3	Idarubicin + ATRA
Maintenance 2 years	Methotrexat / Purinethol + ATRA

Objectives of APL-2005 Study

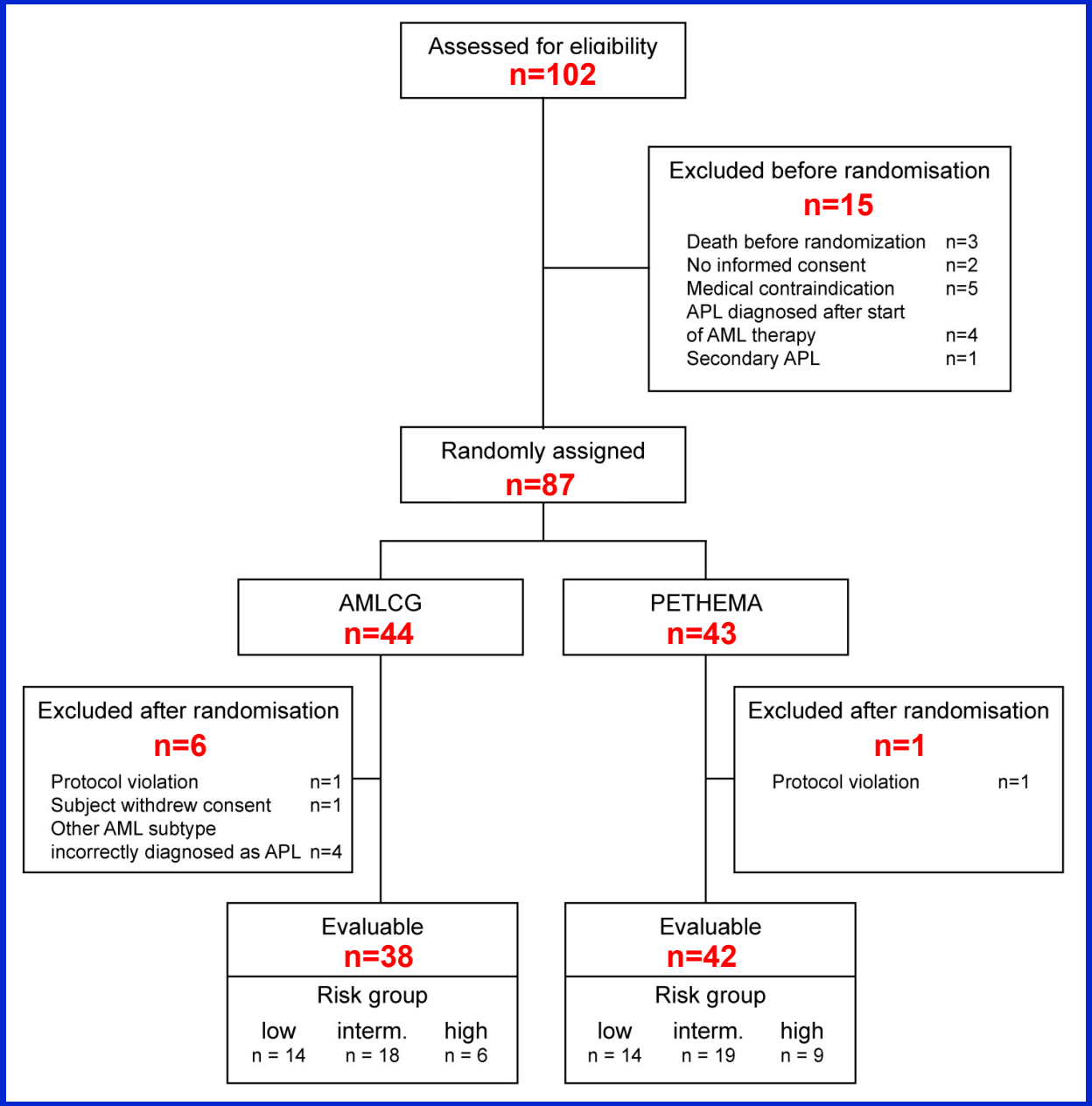
Recruitment of 100 pts with genetically confirmed newly diagnosed APL

First endpoint:	Comparison of the kinetics of MRD (primary endpoint: first negative RT-PCR of *PML/RARA* after induction or consolidation)
Second aims:	Comparison of the toxicities and outcomes of OS, EFS, RFS and CIR

First patient in:	November 2005
Last randomization:	May 2013
Last patient out:	December 2015
Data base closed:	August 2016

AMLCG
APL-2005 Study

Consort Diagram



Baseline Patients Characteristics

	AMLCG n=38	PETHEMA n=42	p-value
Age (Median, Range)	56 (23-83)	49.5 (20- 87)	**0.391**
<60	25 (66)	28 (67)	**1**
≥60	13 (34)	14 (33)	
Gender (n, %)			
male	22 (58)	21 (50)	**0.509**
female	16 (42)	21 (50)	
Blood counts (median)			
WBC $x10^9$/L	23	12	**0.583**
Platelets $x10^9$/L	33	34.5	**0.607**
Hb g%	9.3	9.5	**0.980**
Transcript type (n, %)			
L/V	19 (54)	29 (69)	**0.339**
S	15 (43)	13 (31)	
unknown	1 (2)	0	
Cytogenetics (n,%)			**1**
t(15;17)	23 (62)	24 (60)	
t(15;17) + others	14 (38)	15 (38)	
normal	0	1 (2)	
unknown	1	2	
Risk group (n,%)			
low	14 (37)	14 (33)	**0.875**
inter	18 (47)	19 (45)	
high	6 (16)	9 (22)	

Results of Induction Therapy

Results	AMLCG n (%)	PETHEMA n (%)	P
Complete hematological remission	33 (87)	35 (83)	0.76
Early death	5 (13)	7 (17)	
Suspected or manifest ADS (treated with steroids)	16 (42)	17 (40)	1
Toxicities WHO grade ≥ 3			
Bleeding	1 (3)	2 (5)	1
Infection/fever	21 (55) *	15 (36)	0.12
Hepatotoxicity	5 (13)	1 (2)	0.10
Cardiotoxicity	1 (3)	3 (7)	0.62
Mucositis	2 (5)	4 (10)	0.68
Median duration (range) of critical cytopenia (days)	32 (17 to 59)	27 (19 to 48)	0.02

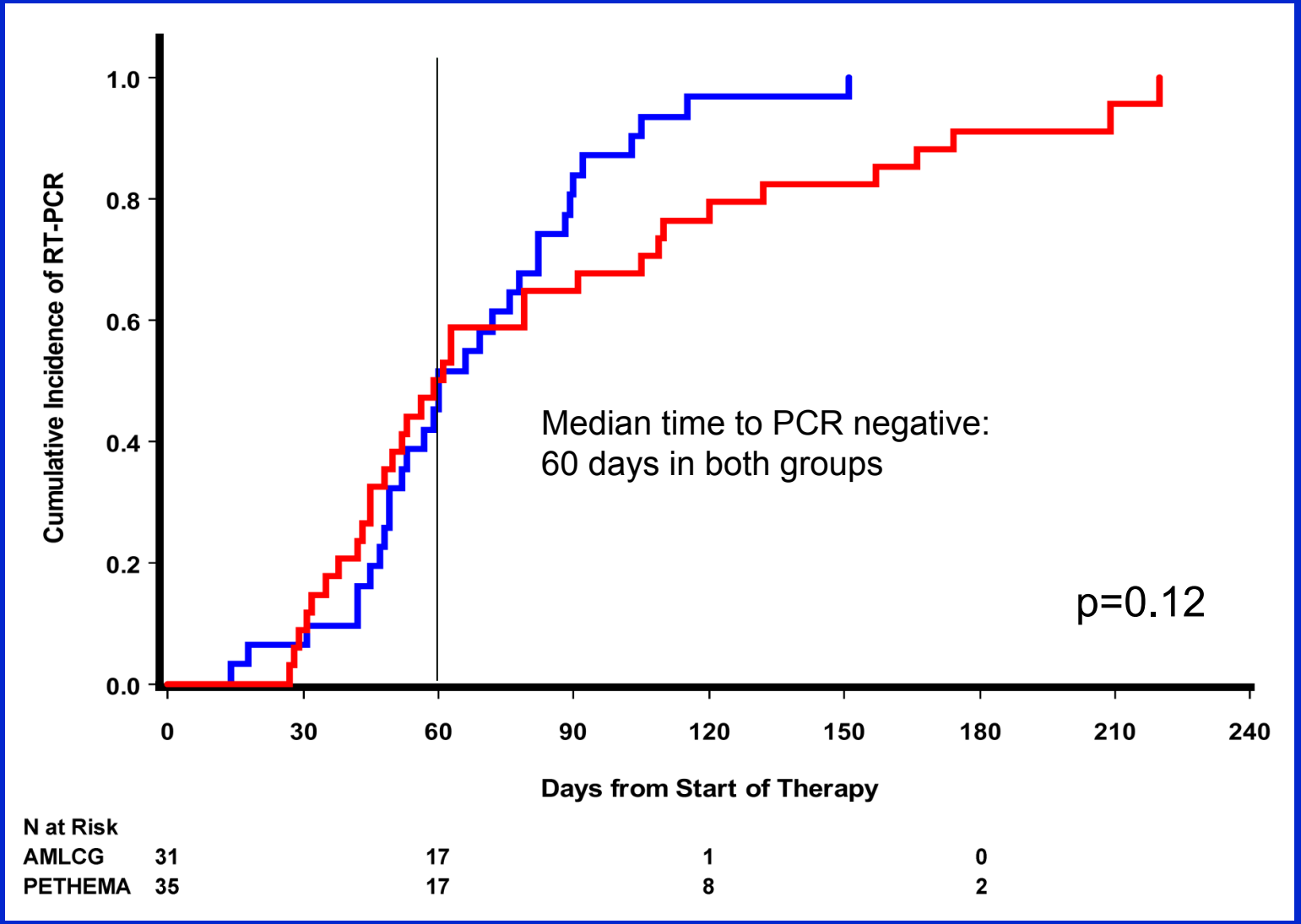
*10 patients had infections in both induction cycles

Infections during consolidation: AMLCG 31%, PETHEMA 19% (p=0.08)

RT-PCR Results

PCR results, CR patients	AMLCG	PETHEMA	P
After induction (n, %)			
Negative	29/31 (94)	23/34 (68)	0.0124
Positive	2/31 (6)	11/34 (32)	
Mean time until control after induction (days)	63 (±27)	47 (±25)	
After consolidation (n, %)			
Negative	24/25 (96)	27/29 (93)	1
Positive	1/25 (4)	2/29 (7)	

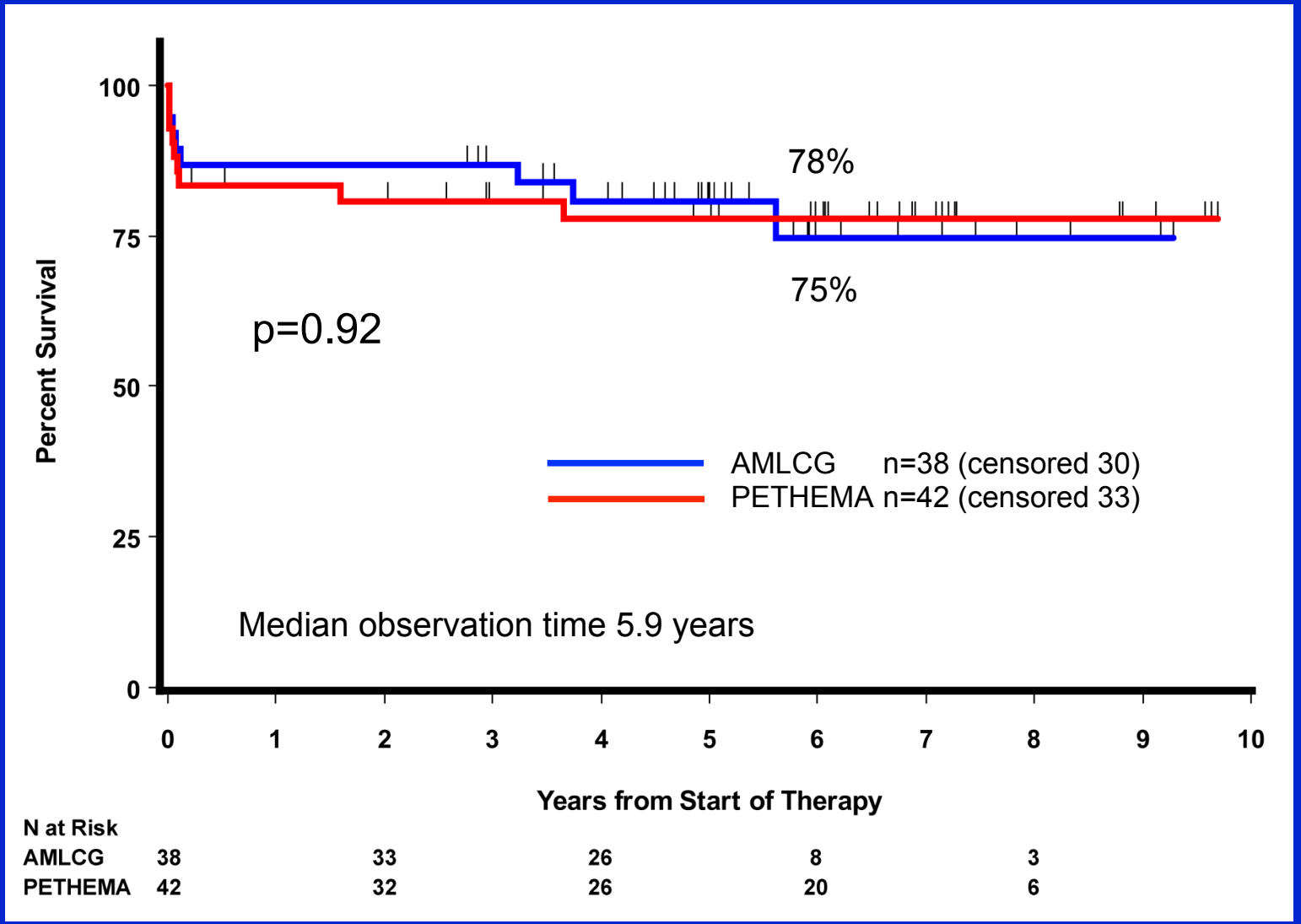
Cumulative incidence of RT-PCR conversion from positive to negative from start of induction until bone marrow control after consolidation



Long-term Outcome

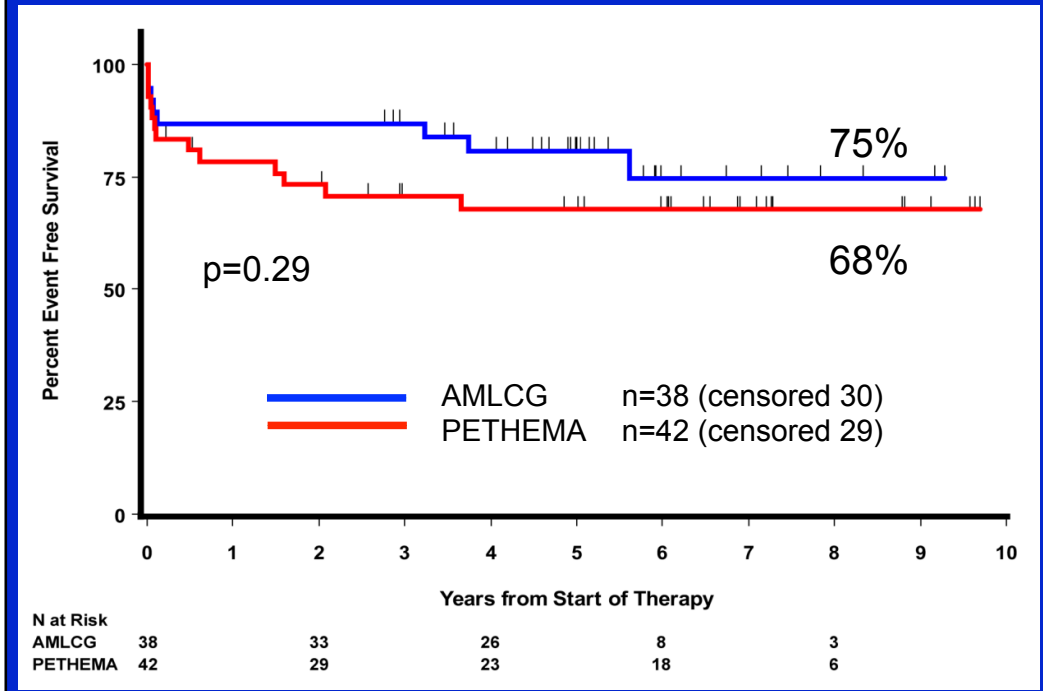
	AMLCG	PETHEMA	P
Outcome at 6 years (%)			
OS	75	78	0.92
EFS	75	68	0.29
RFS	86	81	0.28
CIR	0	12	0.04
Subgroups analysis			
Overall survival at 6 years (%)			
< 60 years	83	86	0.90
≥ 60 years	57	62	0.75
RFS at 6 years (%)			
low/ intermediate risk	87	92	0.98
high risk	65	43	0.28

APL-2005 Study: Overall Survival (n=80)

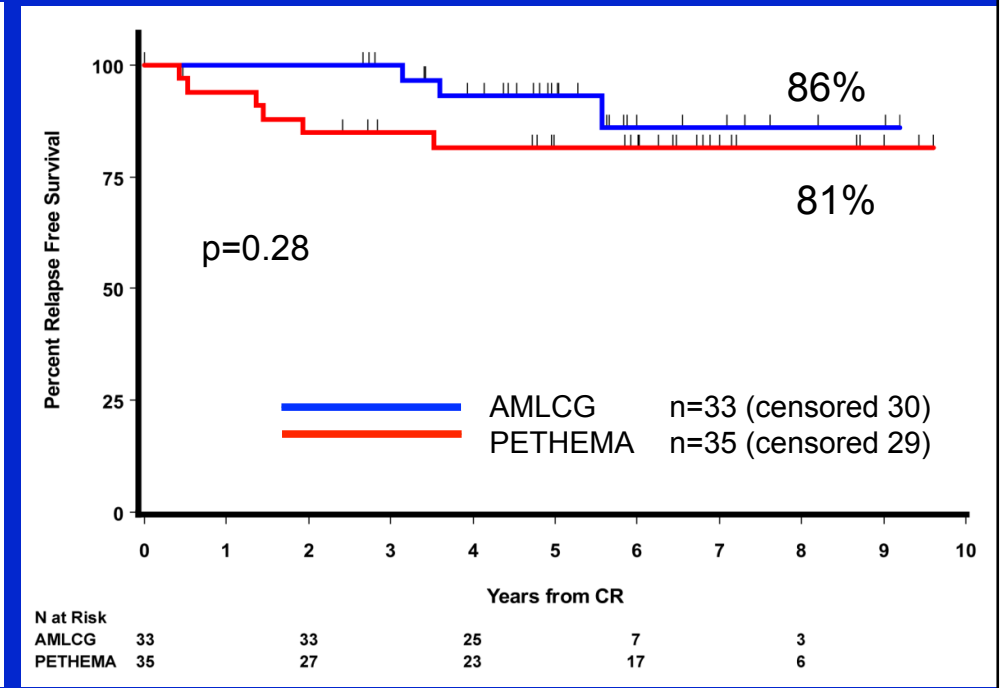


APL-2005 Study

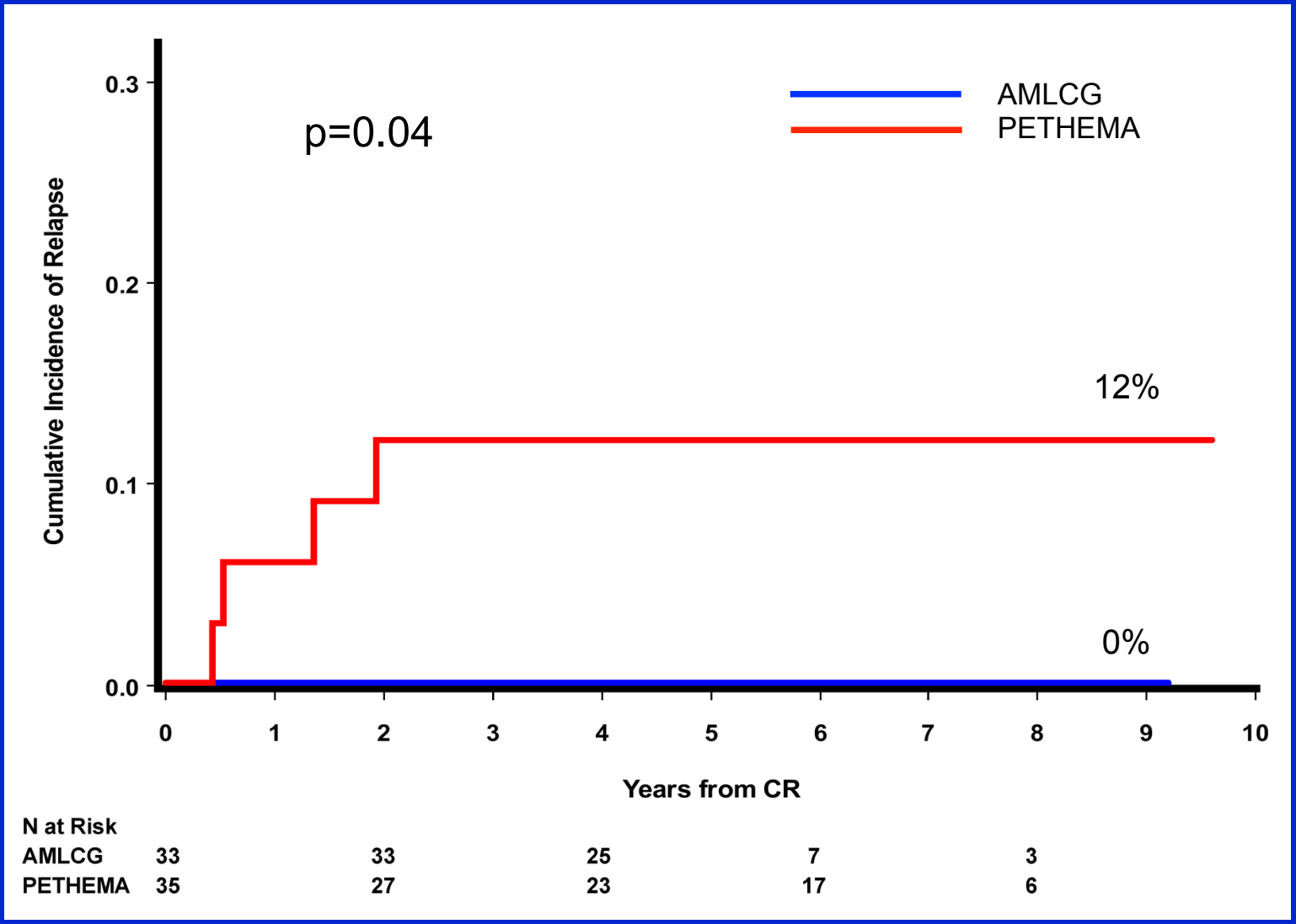
Event Free Survival (n=80)



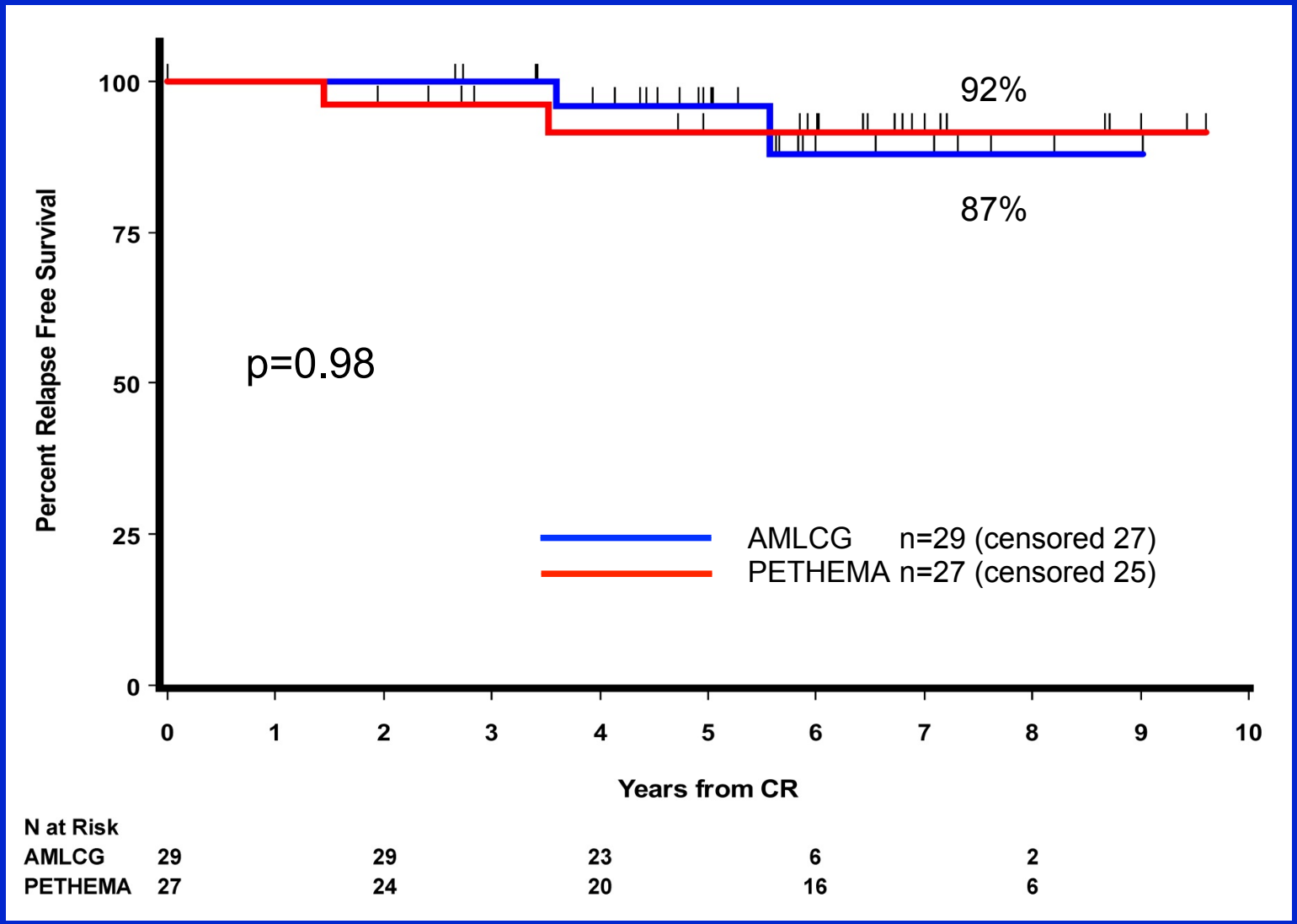
Relapse Free Survival (n=68)



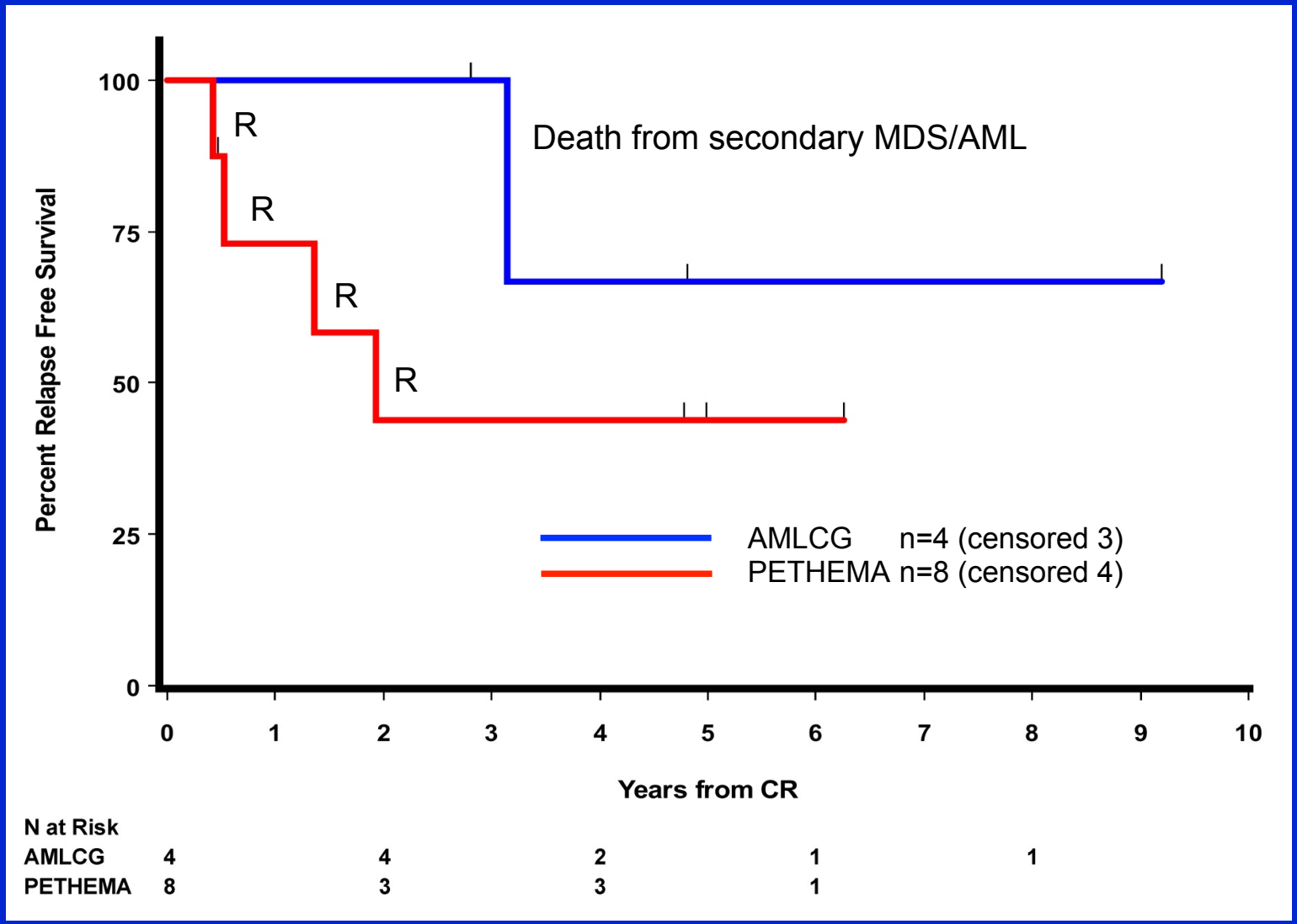
Cumulative Incidence of Relapse (n=68)



Relapse Free Survival, Low and Intermediate Risk



Relapse Free Survival High Risk



Events during Follow up

	AMLCG	PETHEMA
	n=38	**n=42**
Total deaths	**8 (21%)**	**9 (21%)**
Early death	**5 (13%)**	**7 (17%)**
Bleeding (n)	1	3
Infection (n)	3	3
Pulmonary embolism (n)	1	0
Multiorgan failure (n)	0	1
Death in CR	**3 (8%)** Pancreatic cancer 1, secondary AML/MDS 2	**2 (5%)** Secondary AML/MDS 1, liver cirrhosis 1
Relapse	**0**	**4 (10%)**
Secondary malignancy	**4 (11%)** MDS 2 solid tumor 1	**5 (12%)** MDS 3 solid tumor 2

Conclusions

With limitations due to the small patient number:

- The randomized comparison of AMLCG and PETHEMA regimens shows similar overall survival and indicates the limitations of ATRA and chemotherapy.
- With the more intensive regimen (AMLCG) a lower relapse rate was seen, but this was associated with more toxicity.
- In comparison with the literature, the results indirectly support the application of ATO+ATRA in standard risk APL.

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