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Integrating PET and MRD in follicular lymphoma

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Current concepts in FL

- The identification patients at high risk of relapse is a critical goal of modern research in oncohematology and FL.
- Individual risk of relapse is estimated:
  - Before therapy: Prognostic scores (FLIPI and FLIP2), biomarkers, SNPs, GEP mol. signatures
  - After therapy: FDG-PET, CT-scan, MRD

Response assessment in FL

PET:

- Has the highest prognostic impact on PFS and OS Trotman et al Lancet Hematol 2014 Vol1 n1 p1
- Is now recommended for staging and response assessment in updated criteria Cheson et al JCO 2014

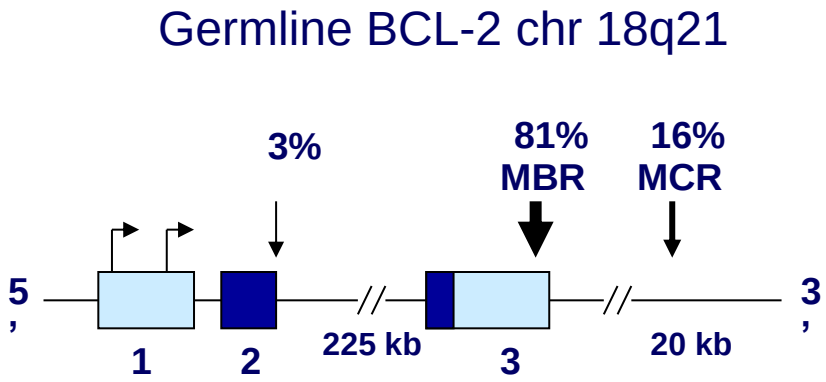
CT:

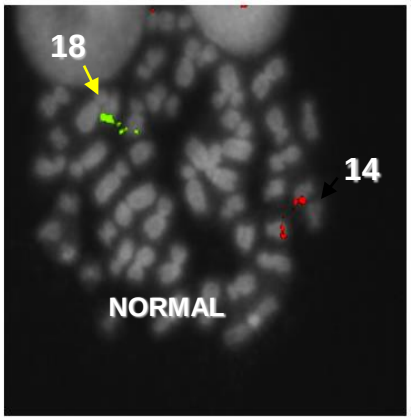
- Is difficult to assess (SPD) Cheson et al JCO 2007
- Has limited capacity to assess extranodal disease
- Has lower prognostic impact than FDG-PET for PFS and none for OS Trotman et al Lancet Hematol 2014 Vol1 p1 n1

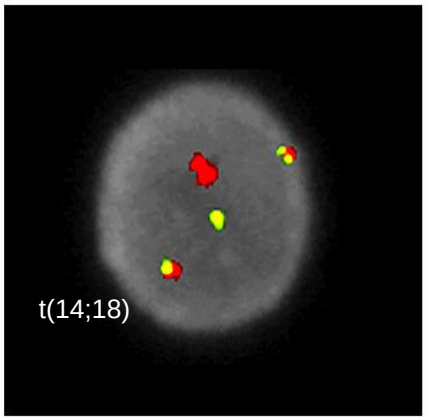
Molecular analysis:

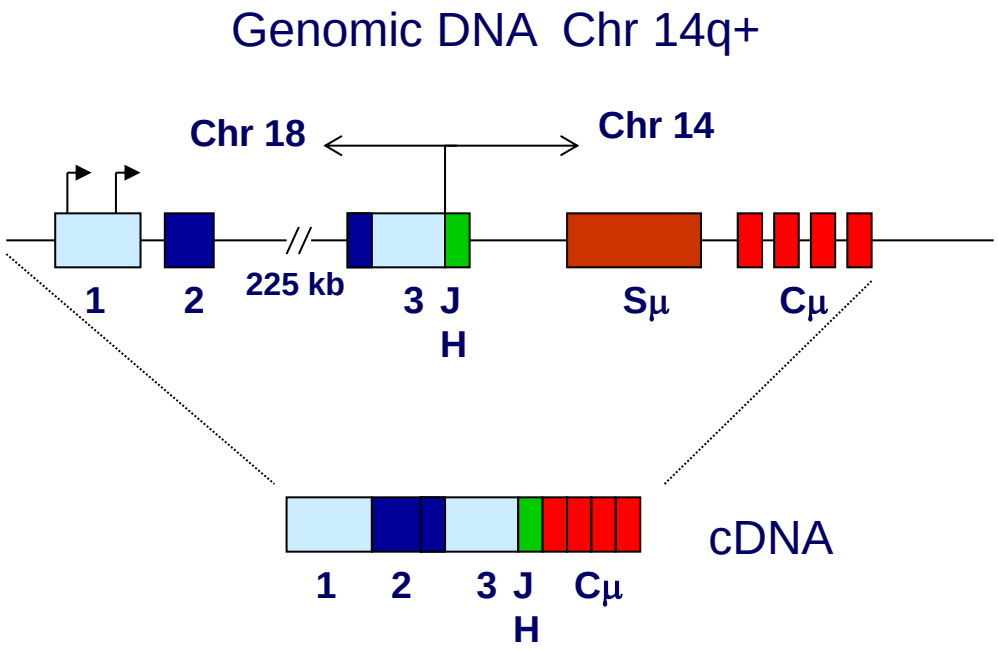
- Has the highest sensitivity among available methods in CLL and MCL
- FL are an excellent model due to t(14;18) chr. Translocation Gribben et al. Blood 1994

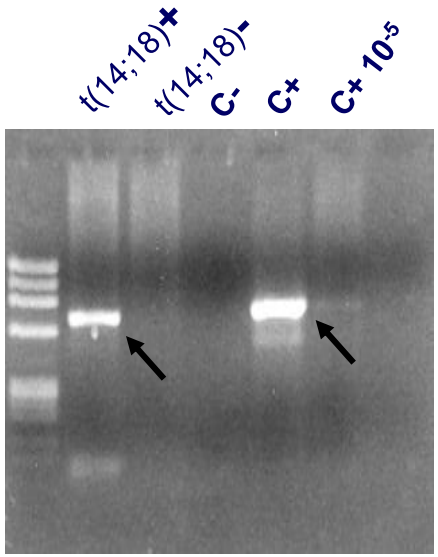
Schematic representation of t(14;18) chromosomal translocation



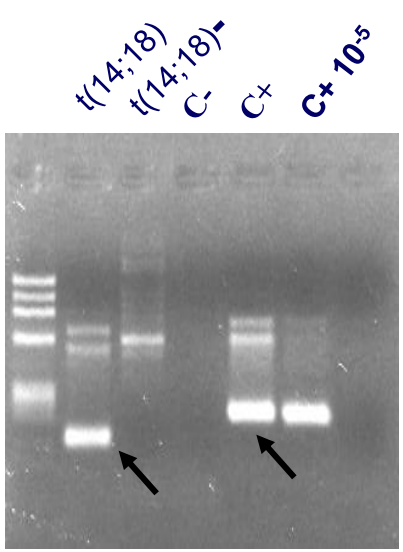






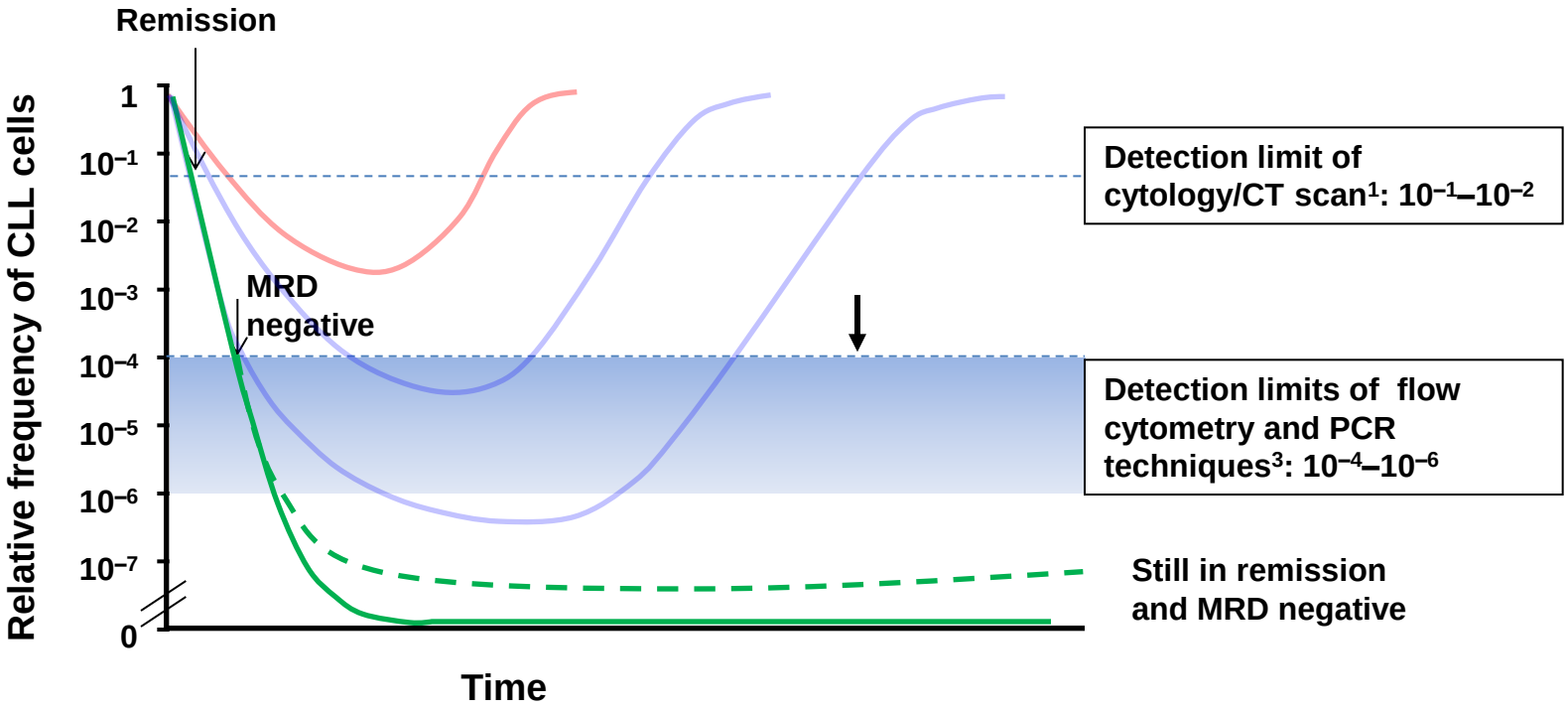


First PCR



Nested PCR

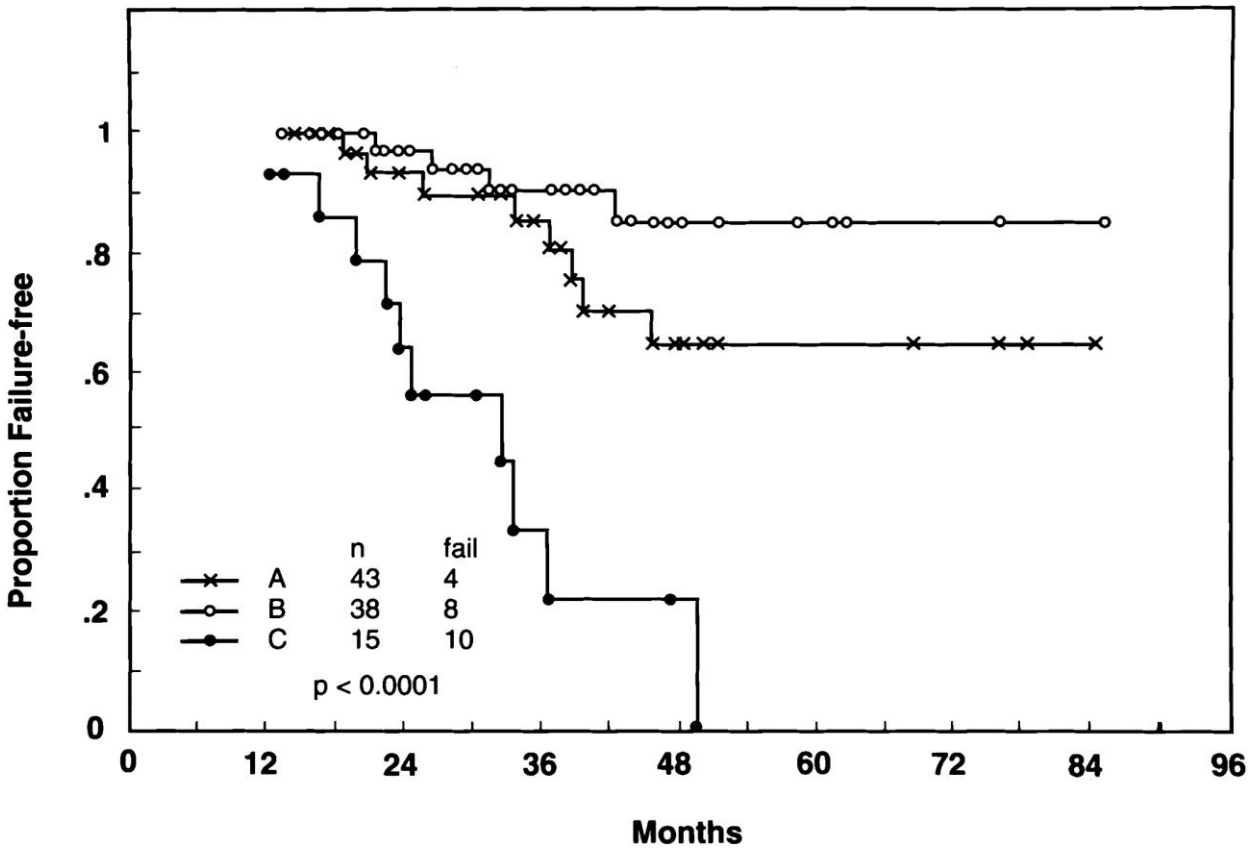
MRD may indicate depth of remission and predict relapse



1 Böttcher S, *et al*. *Hematol Clin N Am* 2013; 27:267–288;
2. Hallek M, *et al. Blood* 2008; 111:5446–5456;
3. Moreno C, *et al. Best Pract Res Clin Haematol* 2010; 23:97–107.

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Prognostic role of Minimal residual disease and beta2-microglobulin in patients with FL



Lopez-Guillermo, A. et al. Blood 1998;91:2955-2960

blood
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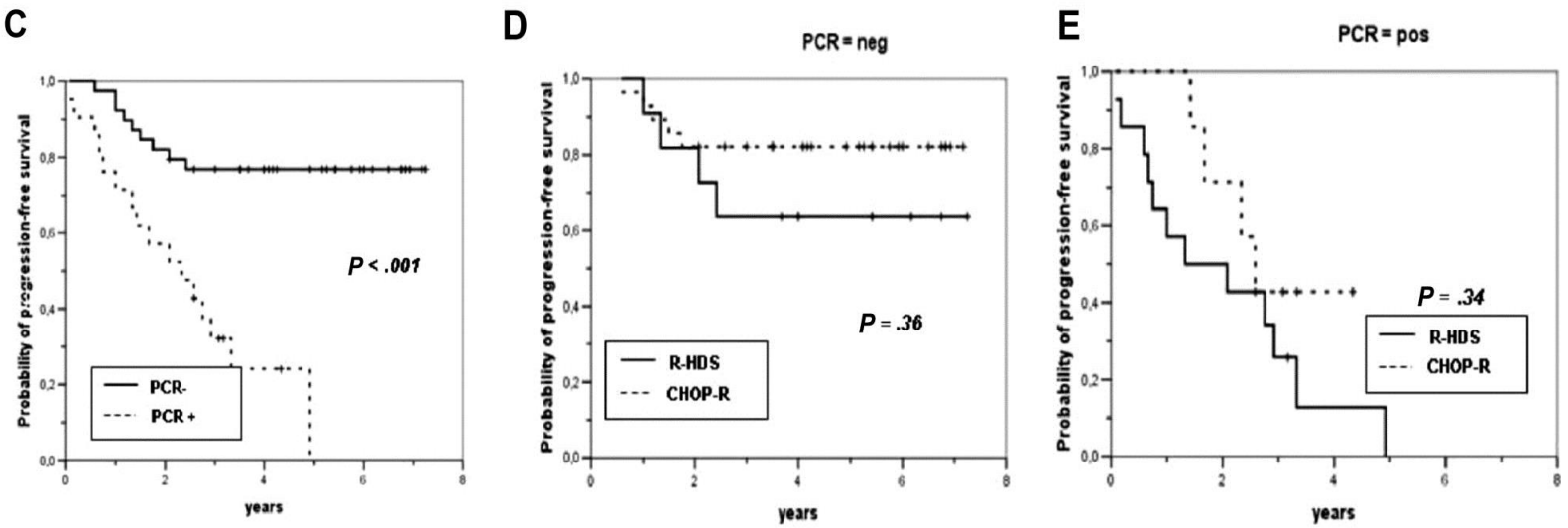
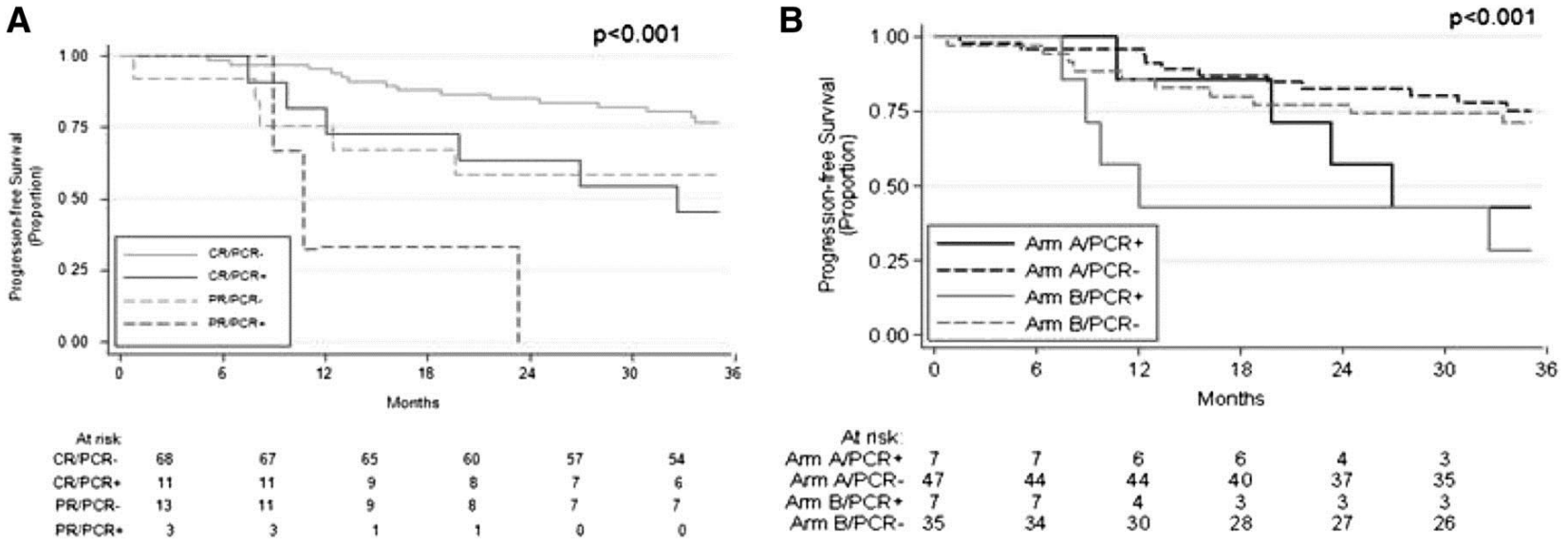
Minimal residual disease assessment of the GITMO randomized trial comparing R-CHOP vs R-HDS in high risk FL patients



Ladetto, M. et al. Blood 2008;111:4004-4013

Effect of MRD by response status and treatment group.



Ladetto M et al. Blood 2013;122:3759-3766

Current problems with MRD in FL

- No universal marker (t(14;18) available in~60%)
- Needs BM aspirate
- Compartment phenomenon (BM, PB and LN)
- Timing of MRD is uncertain
- No clear understanding of very low concentration of FL cells (false positives)
- No study has ever correlated MRD and FDG PET

PET response and Minimal Residual Disease impact on Progression-Free Survival in Patients with Follicular Lymphoma

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Poster B10

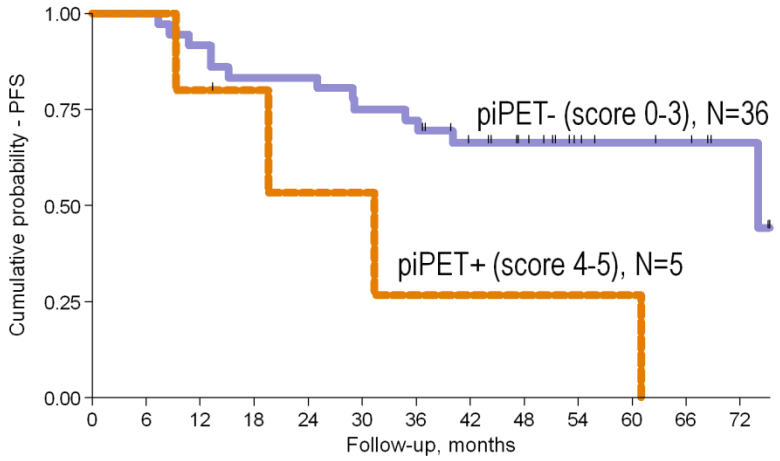
- Pts with centrally reviewed PET(5PS x3 with liver cutoff) (FOLL05; N=79)
- Baseline search for t(14;18)*(N=68)
- MRD analysis* on postinduction BM sample (N=41)

Table 1. Distribution of cases according to piPET and MRD

	MRD -	MRD+
piPET-	28 (68%)	8 (20%)
piPET+	2 (5%)	3 (7%)

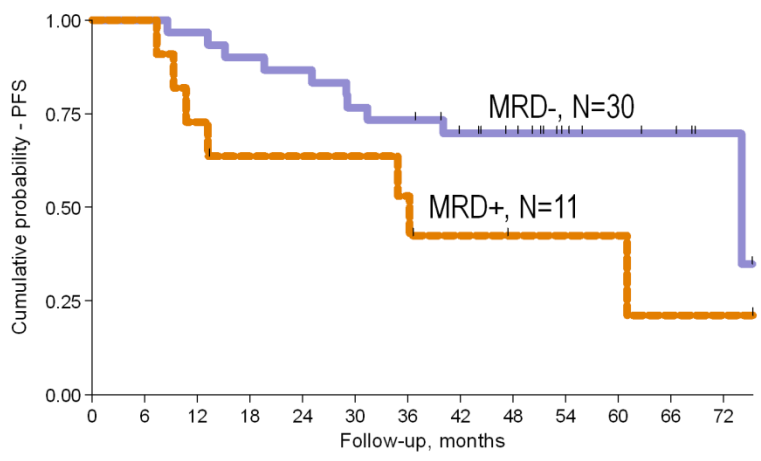
P = 0.110 K=.249(FAIR)

Figure 1.
PFS according to piPET



	HR	95%CI	P
piPET +	3.62	1.15-11.4	.028

Figure 2.
PFS according to MRD



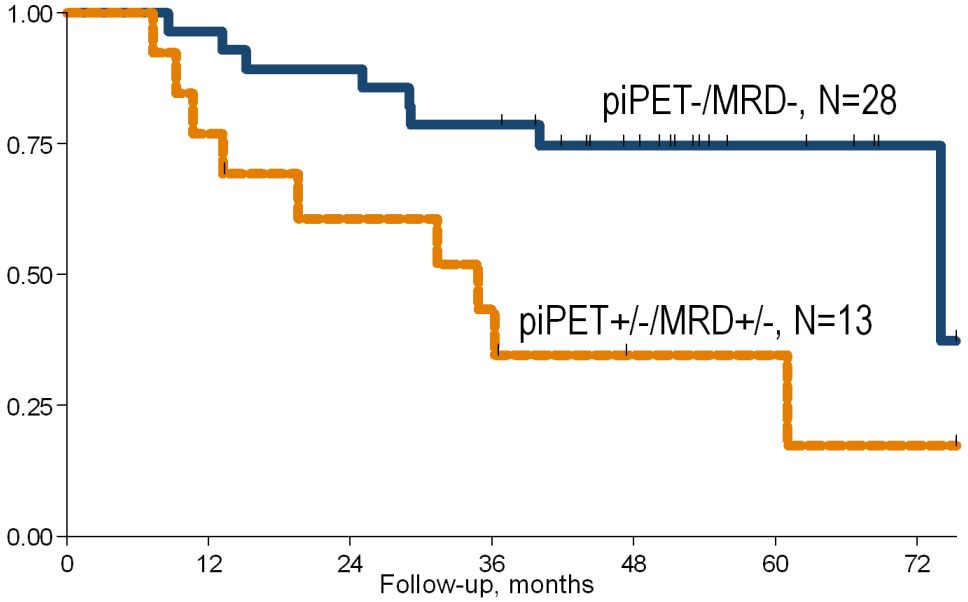
	HR	95%CI	P
MRD +	2.54	0.96-6.72	.060

(*) nested PCR for t(14;18) ch. translocation. All testS were performed within the FIL MRD network (Galimberti et al. Submitted)

PET response and Minimal Residual Disease impact on Progression-Free Survival in Patients with Follicular Lymphoma

Poster B10

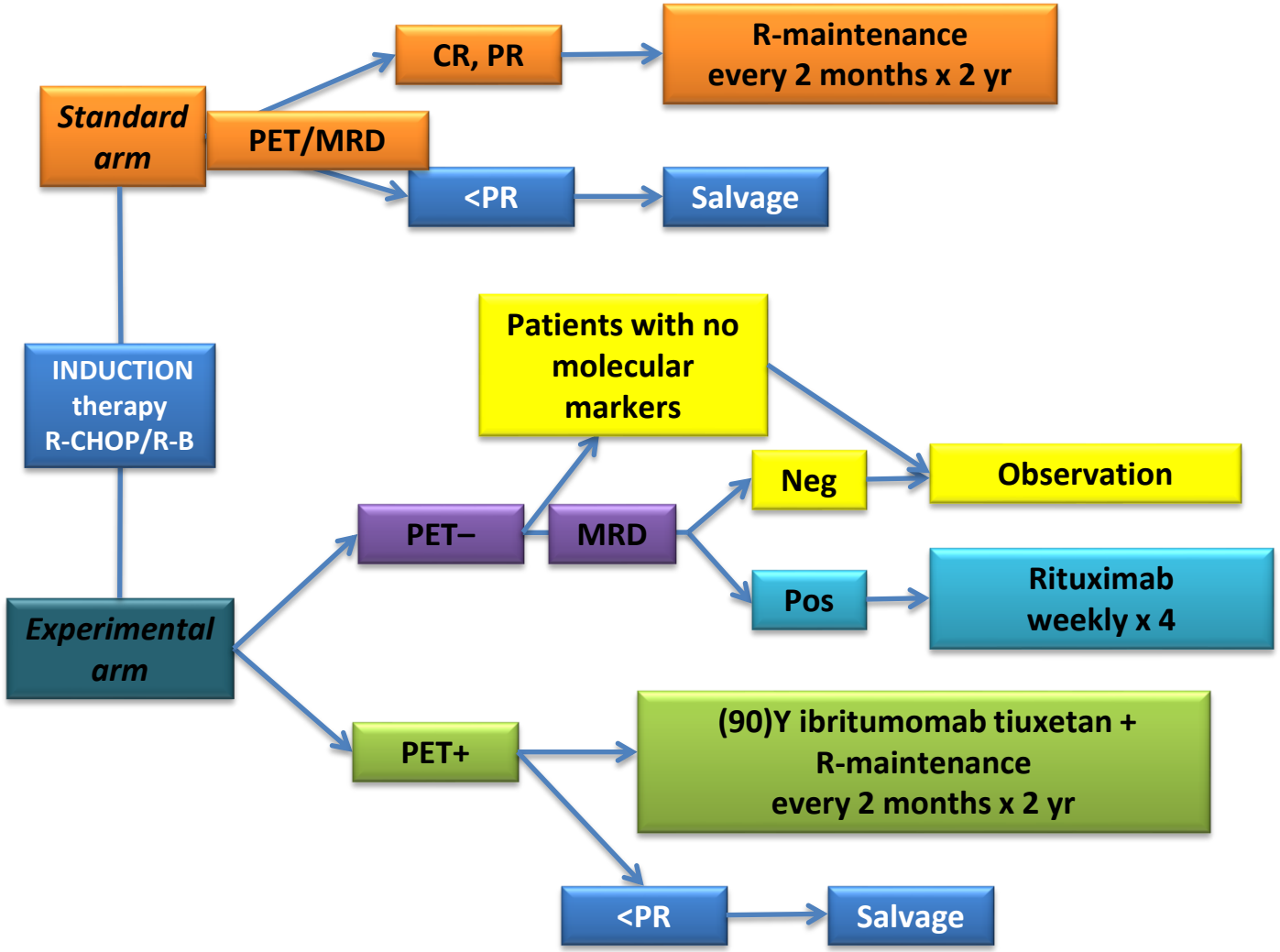
Figure 4.
PFS according to piPET and MRD *(2 subgroups)*



	HR	95%CI	P
piPET+/-/MRD+/-	3.42	1.31-8.95	.012

FOLL12 TRIAL DESIGN (EudraCT Number: 2012-003170-60)
1° line, stage II–IV, FL (P.I. M. Federico)

FOLLICULAR NHL
Grade I–II–IIIa
Age 18–75
Stage II–IV
Active disease
FLIPI2≥1



Preliminary analysis of PET and t(14;18) from the FOLL12 clinical trial

- 193 patients enrolled at 8/2014
- All baseline and restaging PET were centralized and reviewed at the end of induction therapy (Widen)
- Molecular analysis was performed timely at registration and at the end of therapy* by FIL MRD network.
- 118 FL had a detectable t(14;18)(61%) at time of diagnosis (LN, BM or PB)
- Preliminary results are available for
  - Staging PET and qualitative molecular analysys (N=118)*
  - Staging PET and quantitative molecular analysys (N=83)*
  - Not enough data for restaging PET and MRD analysis

(*) nested PCR for t(14;18) ch. translocation. All test were performed within the FIL MRD network

Baseline characteristics (n=118)

Variable	N	%pend.	n (%)
BM (IHC) +	118	-	67 (57)
PET bone +	118	-	40 (34)
t(14;18) BM qual +	118	-	77 (65)
t(14;18) PB qual +	111	6	66 (59)
t(14;18) + (BM or PB +)	*118*	-	*79 (67)*
			Median (2.5-97.5°)
t(14;18) BM quant *	83	30	-2.30 (-8; 0.270)
t(14;18) PB quant *	75	36	-2.40 (-8; 0.130)

* Quantitative bcl2 MRD in Log10

PET and t(14;18) qualitative test as surrogates for BM involvement in FL

	Sens	Spec	PPV	NPV	ACC.
FDG-PET (bone)	0.45	0.8	0.75	0.53	0.6
t(14;18) (BM)	0.72	0.39	0.61	0.51	0.58
PET and t(14;18)	0.62	0.58	0.81	0.35	0.61

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Conclusions

- Both FDG-PET and t(14;18) analysis are good techniques to study FL and there is a rationale to combine them.
- Very preliminary results suggest that it is useful to integrate PET and MRD analysis (staging and restaging)
- FOLL12 trial will provide new data on PET and MRD correlation
- In the future new molecular techniques (NGS) will probably overcome some of the current limitations of MRD analysis in FL and other NHL.

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