15-ICML International Conference on Malignant Lymphoma

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- PROGNOSTIC FACTORS

- CHEMOTHERAPY-FREE STRATEGIES

- TRIALS

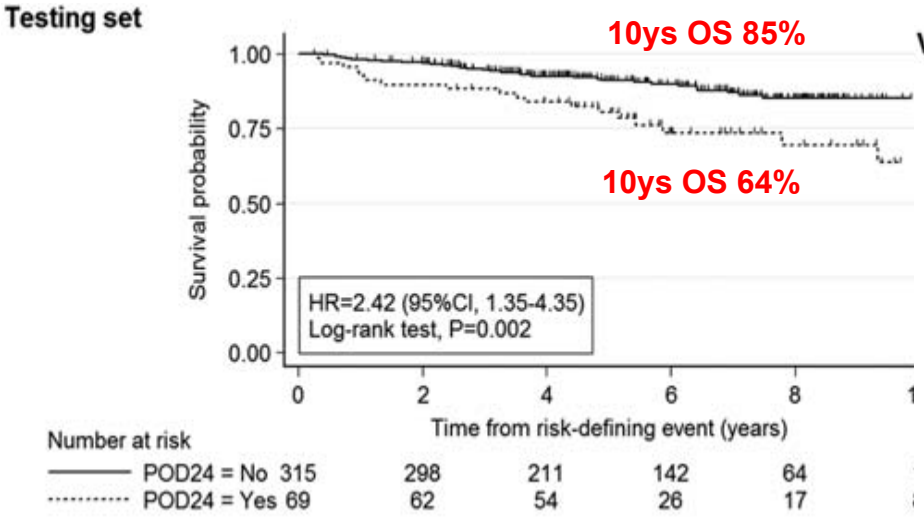
- FUTURE DIRECTIONS

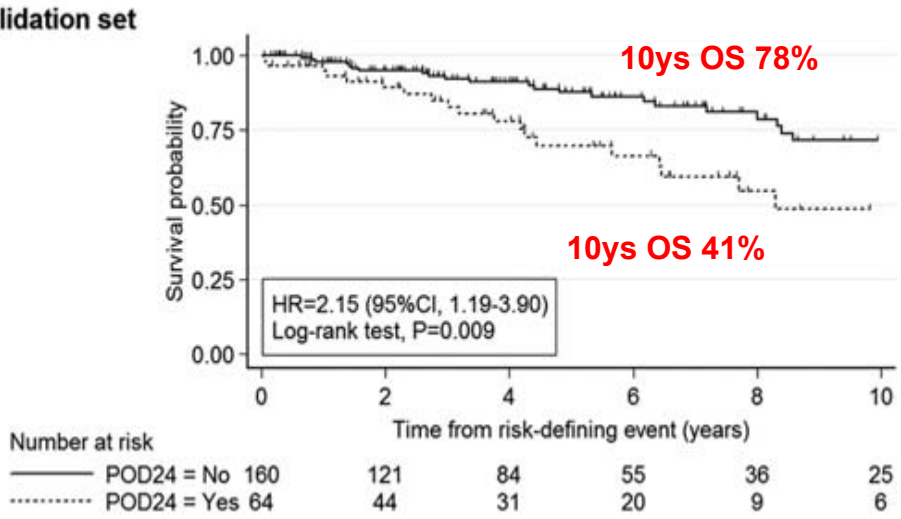
PROGNOSTIC FACTORS

EARLY PROGRESSION OF DISEASE (POD24) PREDICTS SHORTER SURVIVAL IN MALT LYMPHOMA PATIENTS RECEIVING SYSTEMIC TREATMENT

A. Conconi et al.

- TESTING SET: from IELSG19: 401 EMZL patients (131 randomly assigned to chlorambucil treatment, 138 to rituximab and 132 to chlorambucil plus rituximab), VALIDATION SET: from MALT-IPI study: 287 patients who received systemic treatment (chemotherapy, immunotherapy or both)



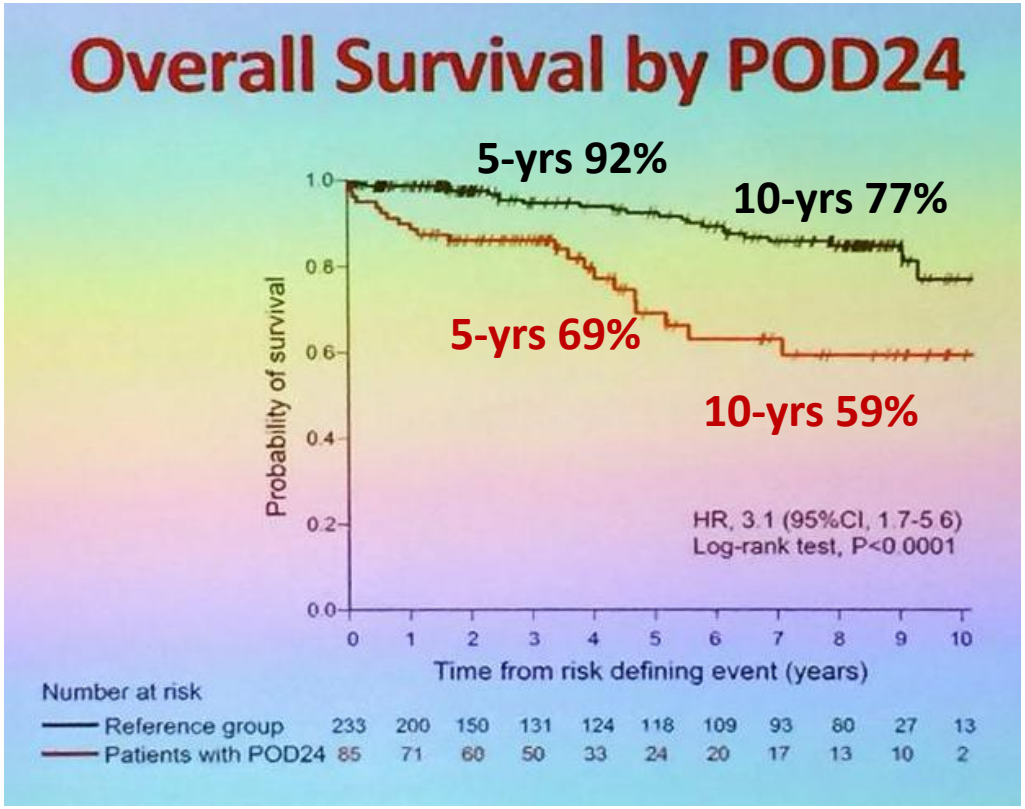


FIRST VALIDATED EVIDENCE OF THE PROGNOSTIC IMPACT OF POD24 IN EMZL

PREDICTIVE VALUE OF POD24 VALIDATION IN FOLLICULAR LYMPHOMA PATIENTS INITIALLY TREATED WITH CHEMOTHERAPY-FREE REGIMENS IN A POOLED ANALYSIS OF THREE RANDOMIZED TRIALS OF THE SWISS GROUP FOR CLINICAL CANCER RESEARCH (SAKK).

Moccia A, et al.

- Enrollment: 1998-2016
- 318 evaluable pts, pts with advanced and symptomatic disease
- Pooled dataset of 3 randomized trials (2 trials evaluating different durations of Rituximab therapy alone and 1 randomized trial R-Lenalidomide vs Rituximab)



FIRST VALIDATION THAT POD24 RETAINS ITS PROGNOSTIC VALUE IN PTS TREATED WITHOUT CHEMOTHERAPY

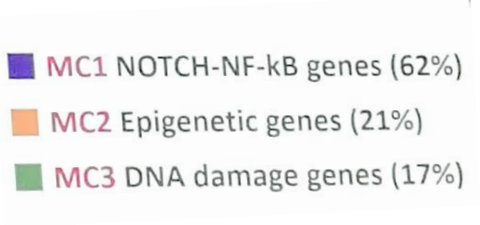
MULTI-OMICS LANDSCAPE OF SPLENIC MARGINAL ZONE LYMPHOMA (SMZL) - INTERIM ANALYSIS OF IELSG46 STUDY *A. Bruscaggin et al.*

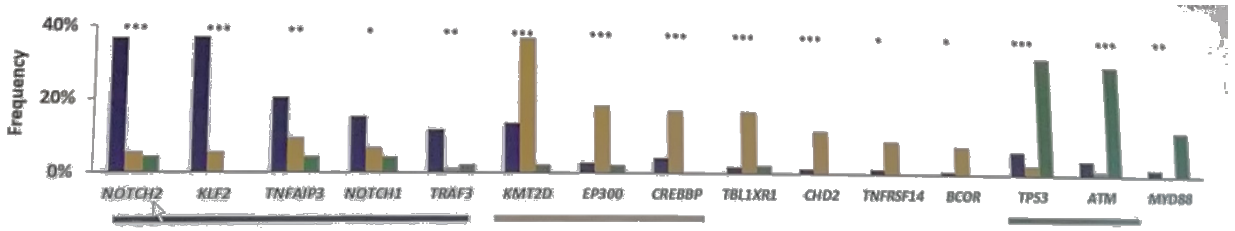
- Retrospective, observational
- 382 spleen sample of SMZL
- Pathology revision, NGS, GEP, IgVH sequencing

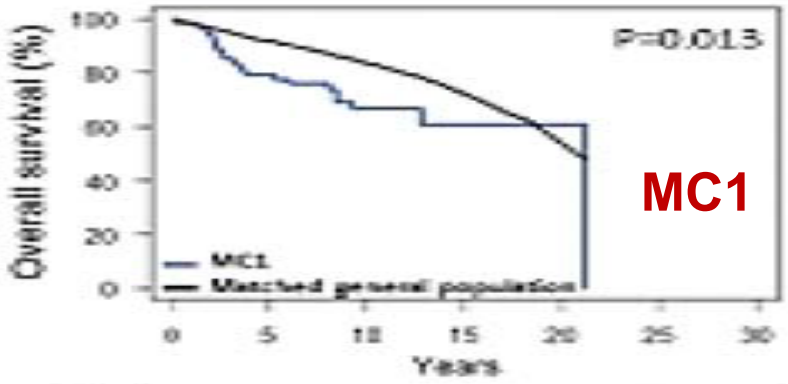
Genes recurrently mutated in >10%
SMZL:
- KLF2
- NOTCH2
- KMT2D
- TNFAIP3
- NOTCH1.

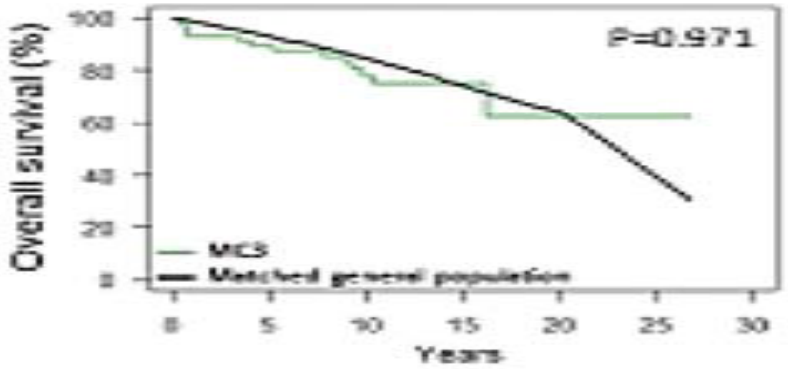
Deletion 7q occurred in 24% SMZL

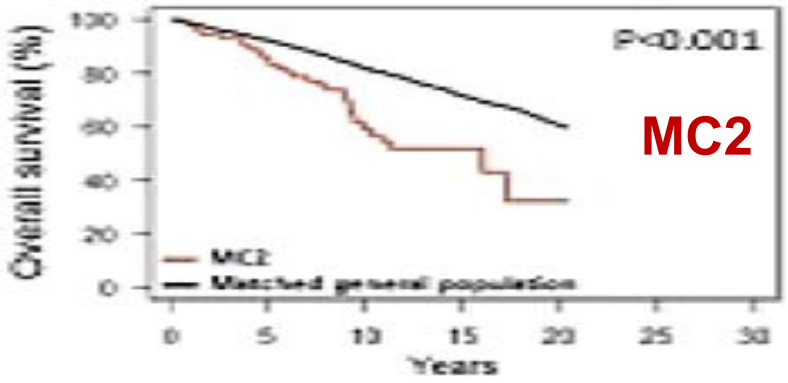
Discovery of unexpected molecular clusters (MC) in SMZL with distinct clinical outcome :
MC1(NF-κB pathway) and MC2 (NOTCH pathway), driven by KLF2 mutations and NOTCH2 mutations respectively, were enriched 7q deletion.
MC3 was defined by epigenetic mutated genes and was enriched in KMT2D mutations.
MC4 was enriched in TP53 and ATM mutations, and in 17p Deletions

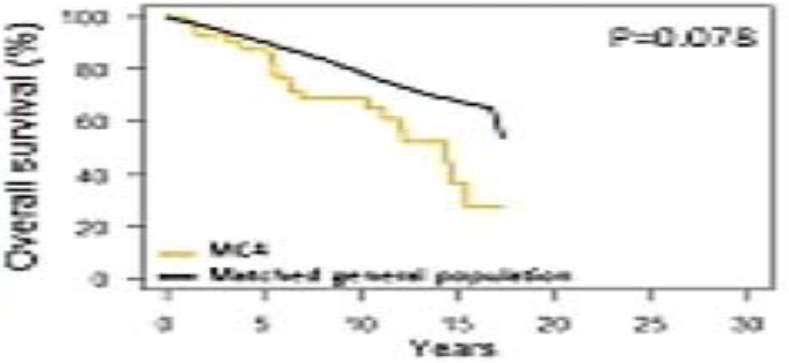












MC1 and MC2: lower relative survival compared to the general population

PROGNOSTIC VALUE OF PRE-TREATMENT PET SCAN IN PATIENTS WITH FOLLICULAR LYMPHOMA RECEIVING FRONTLINE THERAPY

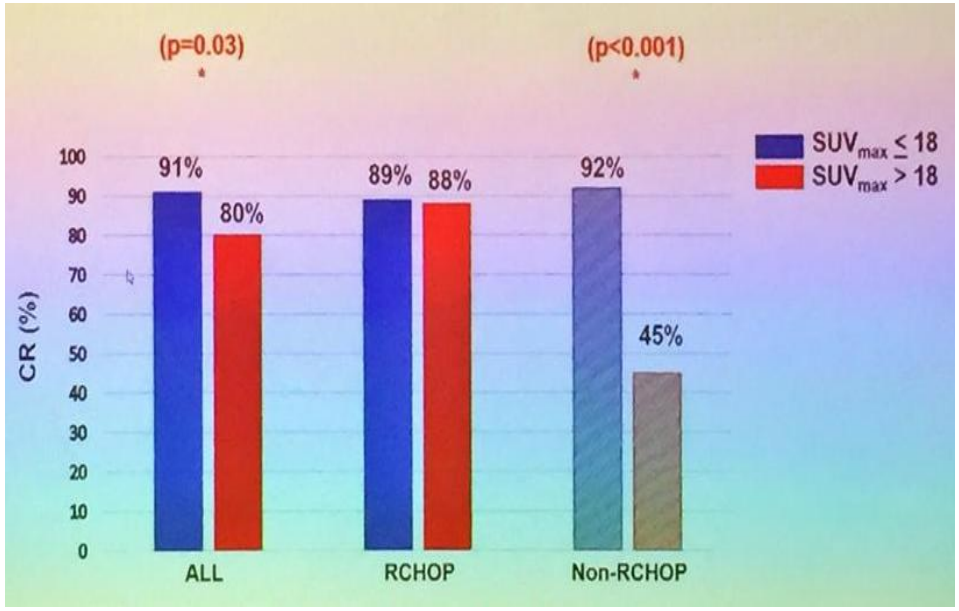
Strati P, et al.

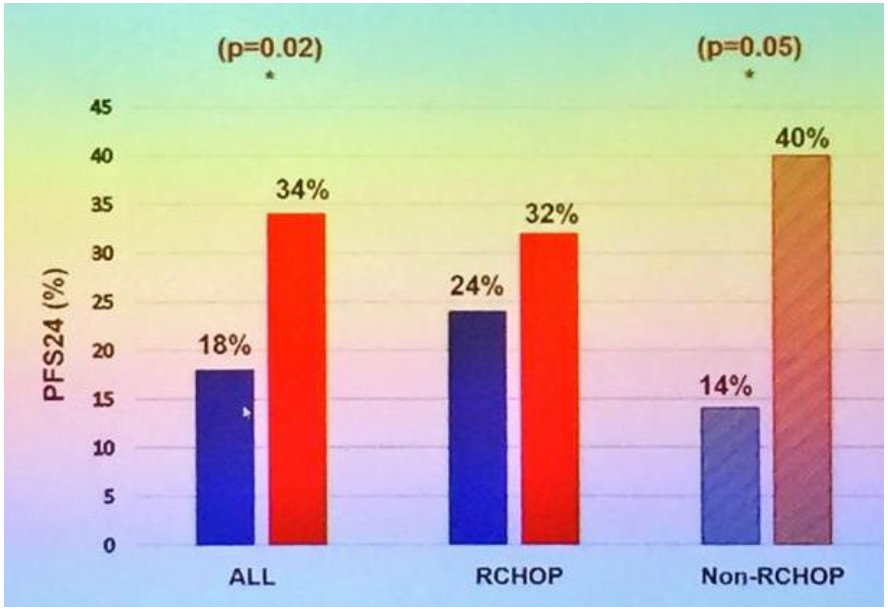
- Single institution (MDACC) retrospective analysis of advanced stage low grade FL pts treated with front-line Rituximab-based therapy
- Aim: Prognostic significance of SUVmax of pre-treatment PET scan
- 346 pts
- Median pre-treatment SUV max 11 (range 1.5-42)
- A value of SUVmax 18 showed strongest association with PFS
- Treatment: R-CHOP 44%, BR 16%, R2 18%, R-FND 7% and 15% Rituximab alone
- Enrollment: 08/2001-04/2014
- Median follow-up: 94 months

SUVmax >18 significantly associated with:

lower CR rate in non-R-CHOP regimens (45% vs 88%)

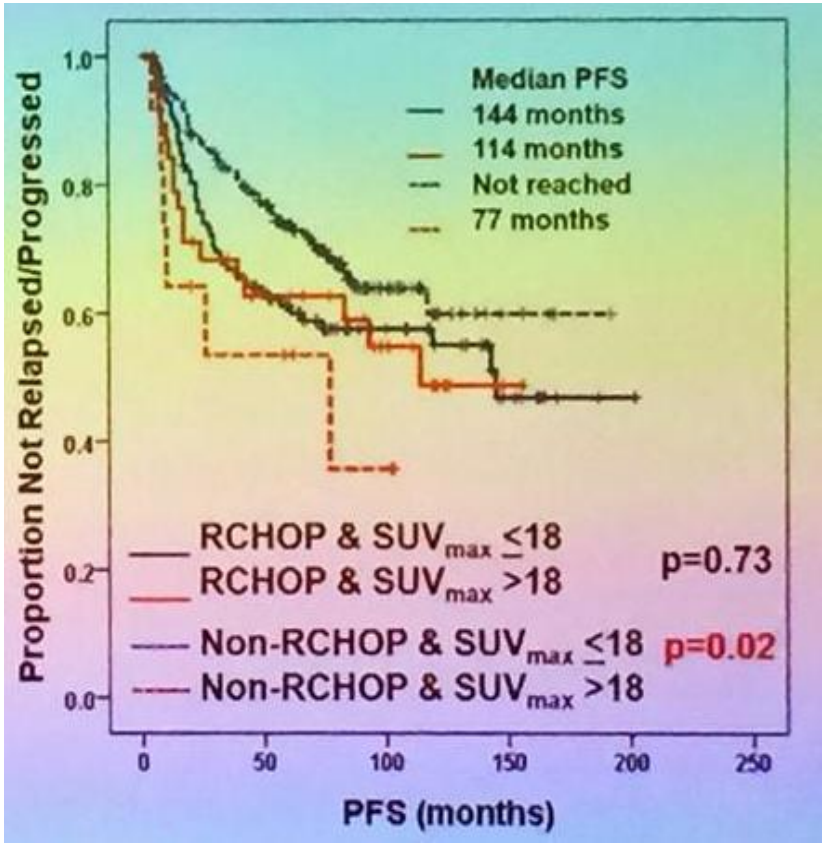
higher rates of progression within 2 years among pts treated with non-R-CHOP regimens (40% vs 32%)



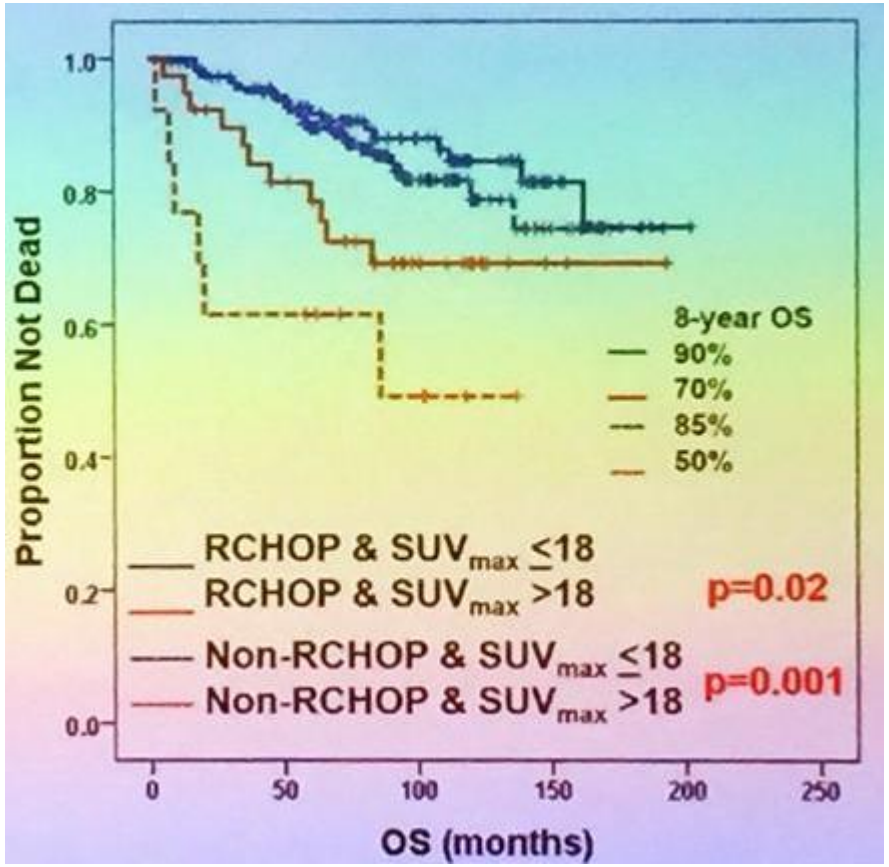


SUVmax >18 significantly associated with:

shorter PFS among pts treated with non-R-CHOP regimens (77 months vs not reached)



shorter 5-yrs OS both in pts treated with R-CHOP (70% vs 75%) and non-R-CHOP regimens (50% vs 75%)



CHEMOTHERAPY-FREE STRATEGIES

RITUXIMAB PLUS LENALIDOMIDE IS AS EFFECTIVE AS IMMUNOCHEMOTHERAPY IN THE ERADICATION OF MOLECULAR DISEASE IN UNTREATED FOLLICULAR LYMPHOMA: RELEVANCE LYSA ANCILLARY STUDY

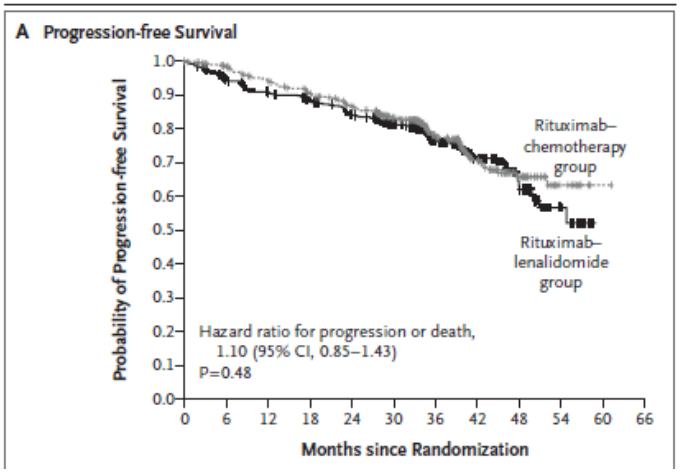
Delfau-Larue MH, et al.

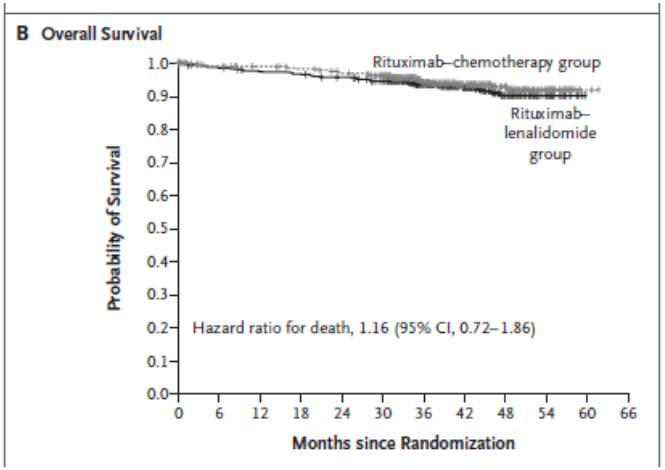
F. Morschhauser **N Engl J Med 2018;379:934-47.**

ORIGINAL ARTICLE

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma

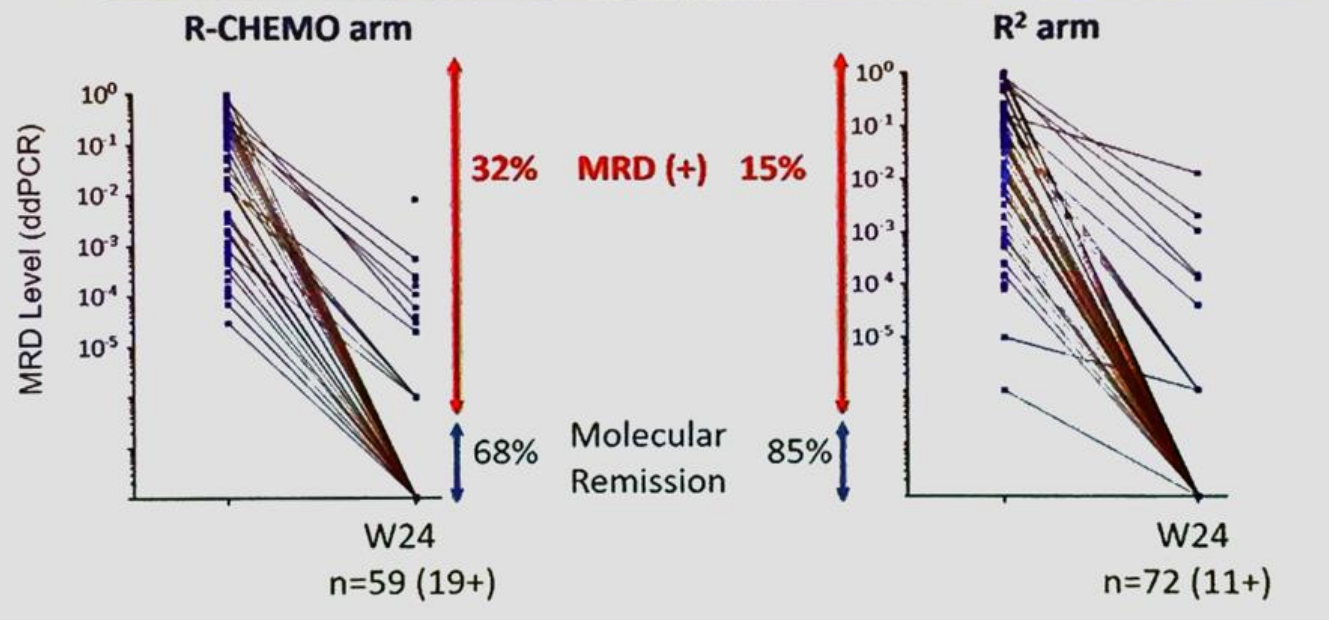
- Phase III, multicentric, international for untreated FL
- R2 vs Rchemio + rituximab maintenance
- 1030 pts





- Predictive value of molecular response after first-line immunochemotherapy
- To evaluate the ability of a chemofree regimen to eradicate MRD
- 440 pts form RELEVANCE TRIAL – 222 pts evaluable for MRD response at baseline, week 24 and week 120

- In multivariate analysis only R-chemo arm and B2M >3 were associated with increased risk of MRD+ at W24
- Achievement of MRD- was significantly associated with improved PFS: 3-yr PFS 85.3% in MRD- vs 54.4% in MRD+



- **An immunomodulatory induction treatment can achieves high rate of molecular response**
- **Confirmation that achieving a complete molecular response at the end of induction predicts a more favourable PFS**

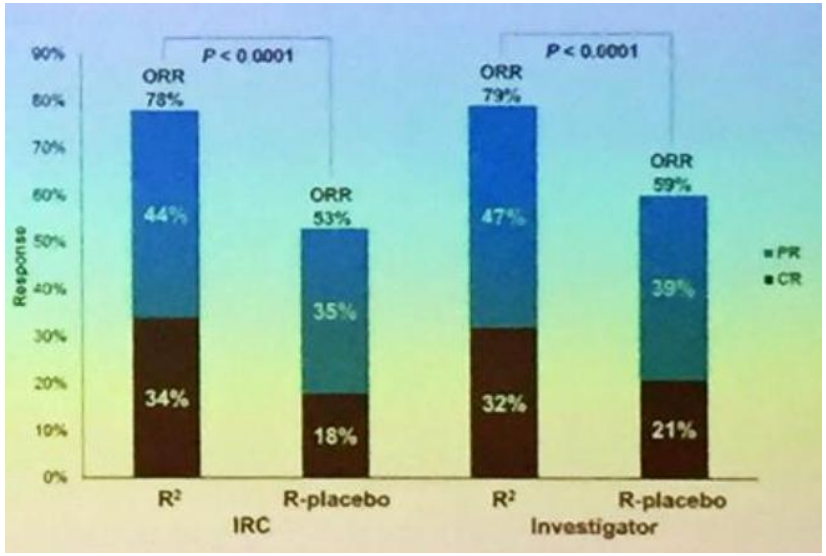
AUGMENT PHASE III STUDY: LENALIDOMIDE/RITUXIMAB (R^2) IMPROVED EFFICACY OVER RITUXIMAB/PLACEBO IN RELAPSED/REFRACTORY FOLLICULAR PATIENTS IRRESPECTIVE OF POD24 STATUS

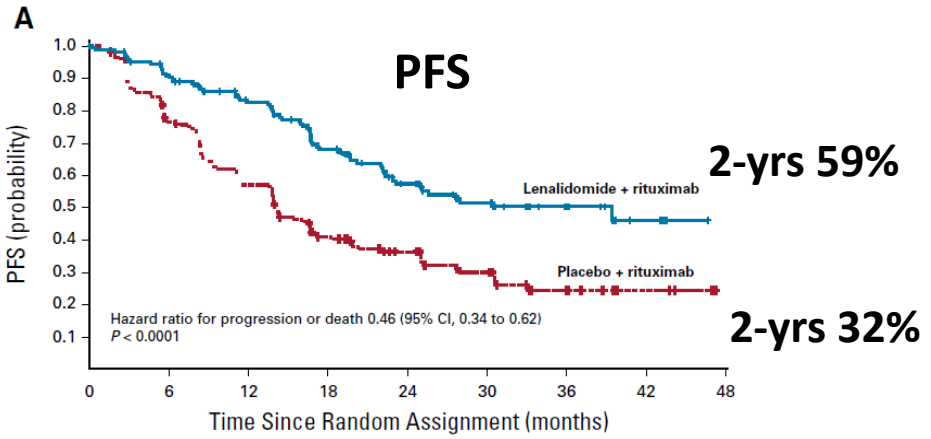
Leonard JP, et al.

Leonard JP et al J Clin Oncol 37:1188-1199.

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

- Phase III, multicenter, randomized trial of lenalidomide plus rituximab versus placebo plus rituximab in patients with relapsed and/or refractory follicular or marginal zone lymphoma
- 358 pts
- Treatment: Rituximab standard dose cycle 1 d1-8-15-22 and d1 cycles 2-5 ± Lenalidomide 20 mg/day d1-21/28 x 12 cycles



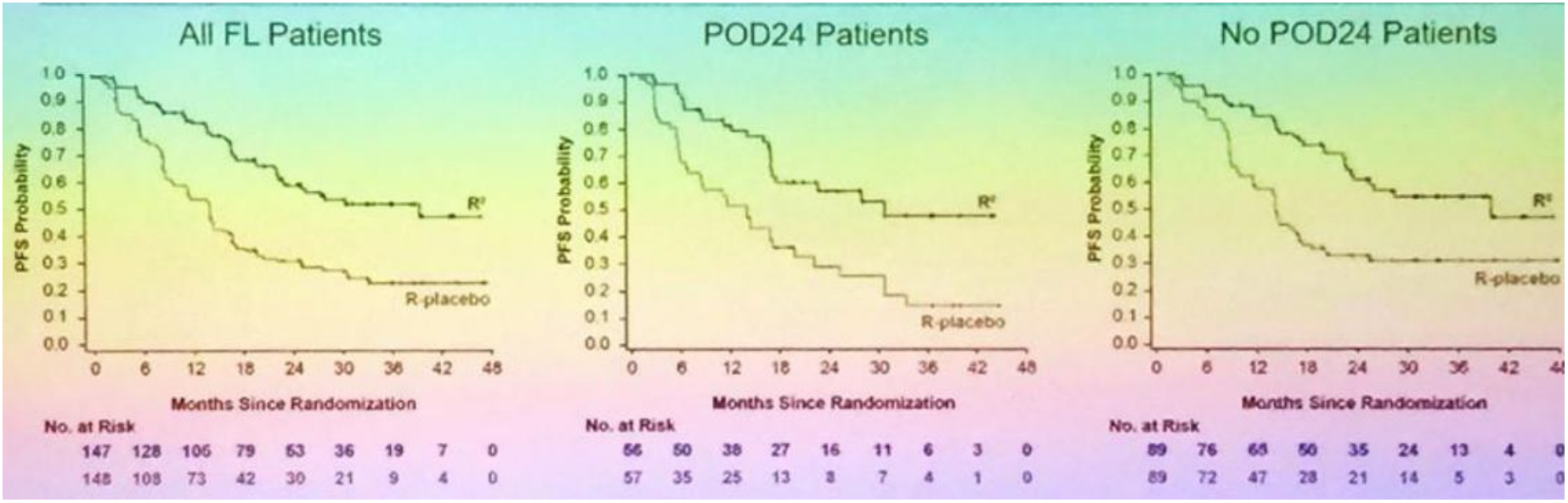


Median follow up 28.3 m

ORR ,CRR and PFS significantly improved for R2 vs R/placebo

- To examine the potential impact of POD24 in relapsed/refractory FL pts receiving Lenalidomide + Rituximab (R2) vs Rituximab + placebo
- 295 pts

- For all pts and subgroups based on POD24 status, median PFS was improved in the R2 vs R/placebo arm
- Treatment with R2 (vs R/placebo) reduced the risk of relapse/progression by 59% in patients with POD24, and improved both ORR and CR
- **R2 demonstrated superior efficacy over R/placebo, including those with POD24**



INTERIM ANALYSIS OF PHASE IIIB MAGNIFY STUDY OF INDUCTION R^2 FOLLOWED BY MAINTENANCE IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA

Sharman J, et al.

- Multicenter phase III trial in pts with relapsed/refractory FL and MZL
- To determine the optimal duration of Lenalidomide
- **Treatment: Rituximab standard dose cycle 1 d1-8-15-22 and q8wk cycles 3+ plus Lenalidomide 20 mg/day d1-21/28 x 12 cycles**
- Post induction phase: random 1:1 to continue R2 vs Rituximab maintenance
- 370 pts with median 2 prior therapies

	ORR, %	CR, %	Median TTR, mo (range)	Median DOR, mo (95% CI)*	Median PFS, mo (95% CI)*
Overall	73	45	2.7 (1.6-12.0)	36.8 (35.8-NR)	36.0 (26.5-NR)
By histology					
FL gr 1-3a	74	46	2.8 (1.6-12.0)	NR (27.7-NR)	30.2 (23.0-NR)
MZL	65	38	2.7 (1.9-11.1)	35.8 (NR-NR)	38.4 (26.5-38.4)
Rituximab-refractory status					
Yes	63	40	2.8 (1.6-12.0)	35.8 (19.2-NR)	18.1 (15.5-26.5)
No	78	47	2.7 (1.6-11.6)	NR (36.8-NR)	NR (36.0-NR)

INTERIM ANALYSIS OF PHASE IIIB MAGNIFY STUDY OF INDUCTION R^2 FOLLOWED BY MAINTENANCE IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA

Sharman J, et al.

	ORR, %	CR, %	Median TTR, mo (range)	Median DOR, mo (95% CI)*	Median PFS, mo (95% CI)*
Overall	73	45	2.7 (1.6-12.0)	36.8 (35.8-NR)	36.0 (26.5-NR)
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No	78	47	2.7 (1.6-11.6)	NR (36.8-NR)	NR (36.0-NR)

- ORR was 73% with CR 45%, similar by histology
- Median DOR was 36.8 months and PFS was 37 months
- Most common AEs: fatigue (48%), neutropenia (40%), diarrhea (35%), nausea (30%) and constipation (29%)
- **R2 therapy is an active treatment regimen also in pts refractory to Rituximab, and with a tolerable safety profile**

UMBRALISIB MONOTHERAPY DEMONSTRATES EFFICACY AND SAFETY IN PATIENTS WITH RELAPSED/REFRACTORY MARGINAL ZONE LYMPHOMA: A MULTICENTER, OPEN-LABEL, REGISTRATION DIRECTED PHASE 2 STUDY

P. Zinzani et al.

- next-generation PI3K-delta inhibitor with unique inhibition of casein kinase-1ε (CK1ε)
- different tolerability (low rate of immune-mediated toxicity)

- 72 patients enrolled between July 2017 and august 2018, 42 pts eligible for interim analysis
- Inclusion criteria: MZL, ECOG PS ≤2, and ≥1 prior therapy including at least one CD20 mAb-containing regimen.
- Umbralisib 800 mg orally once daily until progression or unacceptable toxicity.
- Primary endpoint: ORR. Secondary endpoints: DOR, PFS and safety.

	Interim Efficacy Population*
N	42
MZL Subtype, n (%)	
Extranodal	23 (55%)
Nodal	12 (29%)
Splenic	7 (17%)
Median Age, median (range)	67 (34 - 81)
Female, n (%)	25 (60%)
Male, n (%)	17 (40%)
ECOG 0/1/2, n	23/19/0
Prior Therapies, median (range)	2 (1 - 6)
1 prior line	19 (45%)
2 or more prior lines	23 (55%)
rituximab monotherapy only	7 (17%)
rituximab-based chemoimmunotherapy	32 (76%)
radiation	3 (7%)
stem cell transplant	1 (2%)
lenalidomide	2 (5%)
ibrutinib	2 (5%)
Refractory to most recent therapy, n (%)	8 (19%)
Refractory to prior anti-CD20, n (%)	6 (14%)
Lactate dehydrogenase (LDH), ≥350 unit/L, n (%)	12 (29%)

ADVERSE EVENTS (69 pts)

- Well tollerated, no colitis, no deaths
- AE's leading to dose reduction in 6 pts (9%)
- 10 pts (14%) discontinued due to an AE considered at least possibly related to Umbralisib
- AST/ALT elevation: time related
- Diarrea g3-4: NO time related

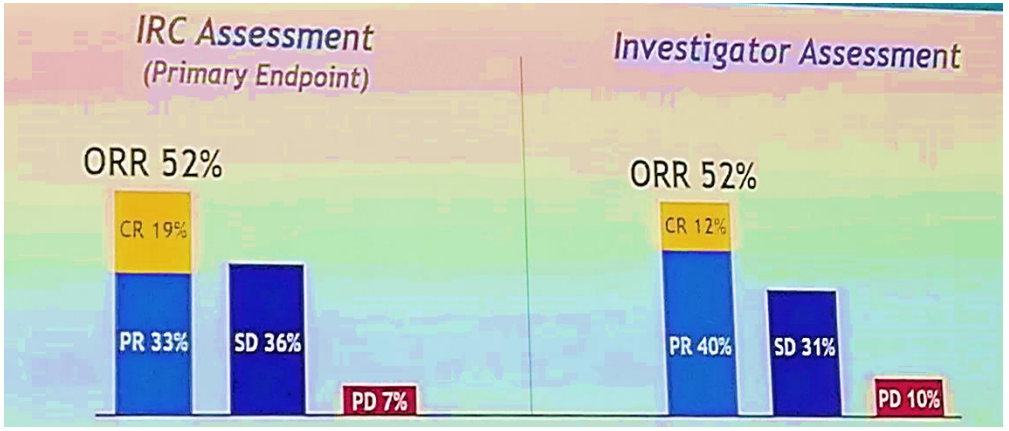
	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	33%	19%	10%	-
Nausea	17%	14%	-	-
Fatigue	19%	9%	3%	-
AST increased	17%	3%	9%	-
ALT increased	6%	9%	9%	1%
Headache	16%	6%	3%	-
Cough	17%	4%	-	-
Decreased appetite	14%	7%	1%	-
Vomiting	12%	9%	-	-
Rash	12%	3%	3%	
Dysgeusia	14%	3%	-	-
Edema peripheral	12%	4%	-	-
Dizziness	7%	7%	-	-
Neutropenia	1%	-	7%	6%
Insomnia	9%	4%	-	-
Upper respiratory tract infection	1%	12%	-	-
Back pain	6%	3%	3%	-
Hyperuricemia	10%	-	-	-
Pyrexia	6%	4%	-	-

AE AFTER 6 MONTHS

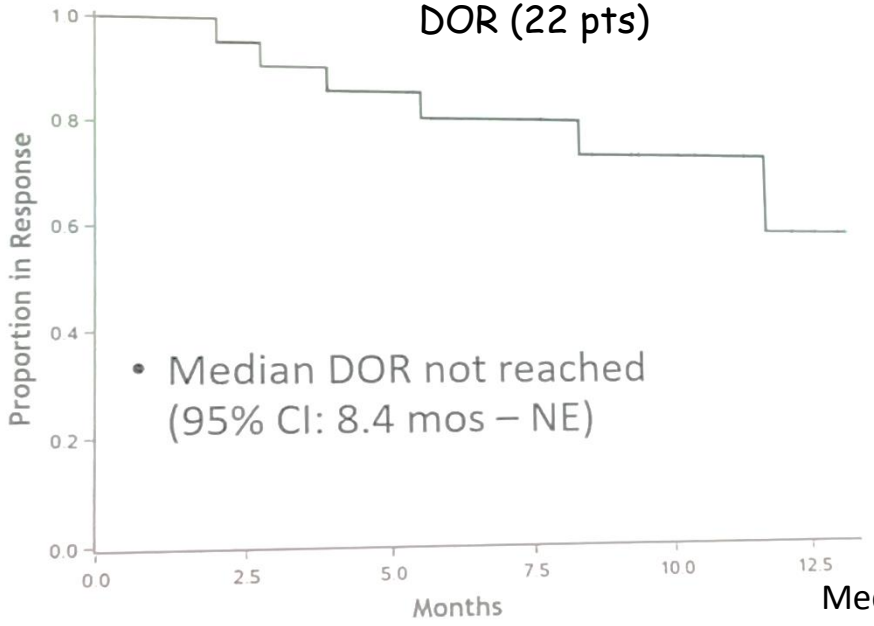
	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	10	24%	2	5%
ALT increased	1	2%	-	-
AST increased	-	-	-	-
Pneumonitis	1	2%	1	2%
Pneumonia	-	-	-	-

Median time to response 2,7 months

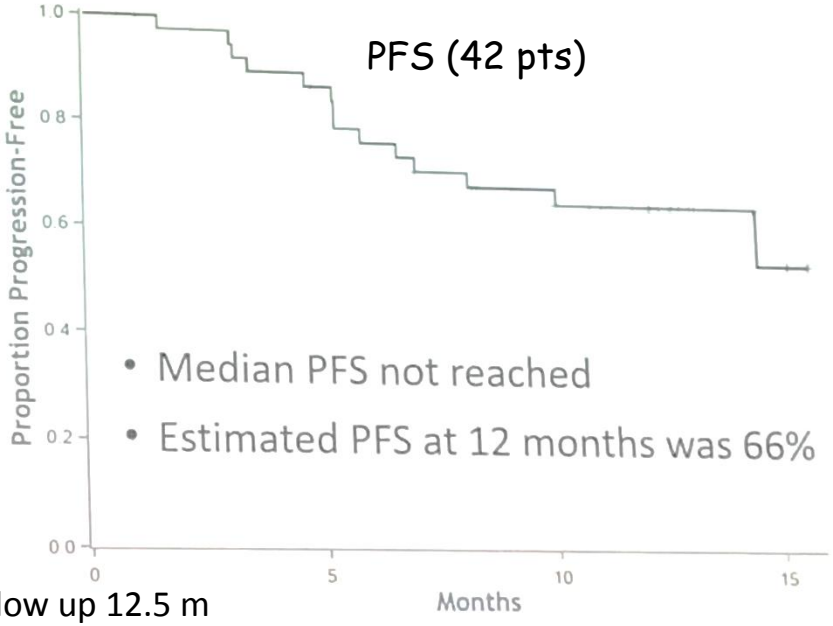
Clinical benefit rate 88% (CR + PR + SD)



DOR (22 pts)



PFS (42 pts)



Median follow up 12.5 m

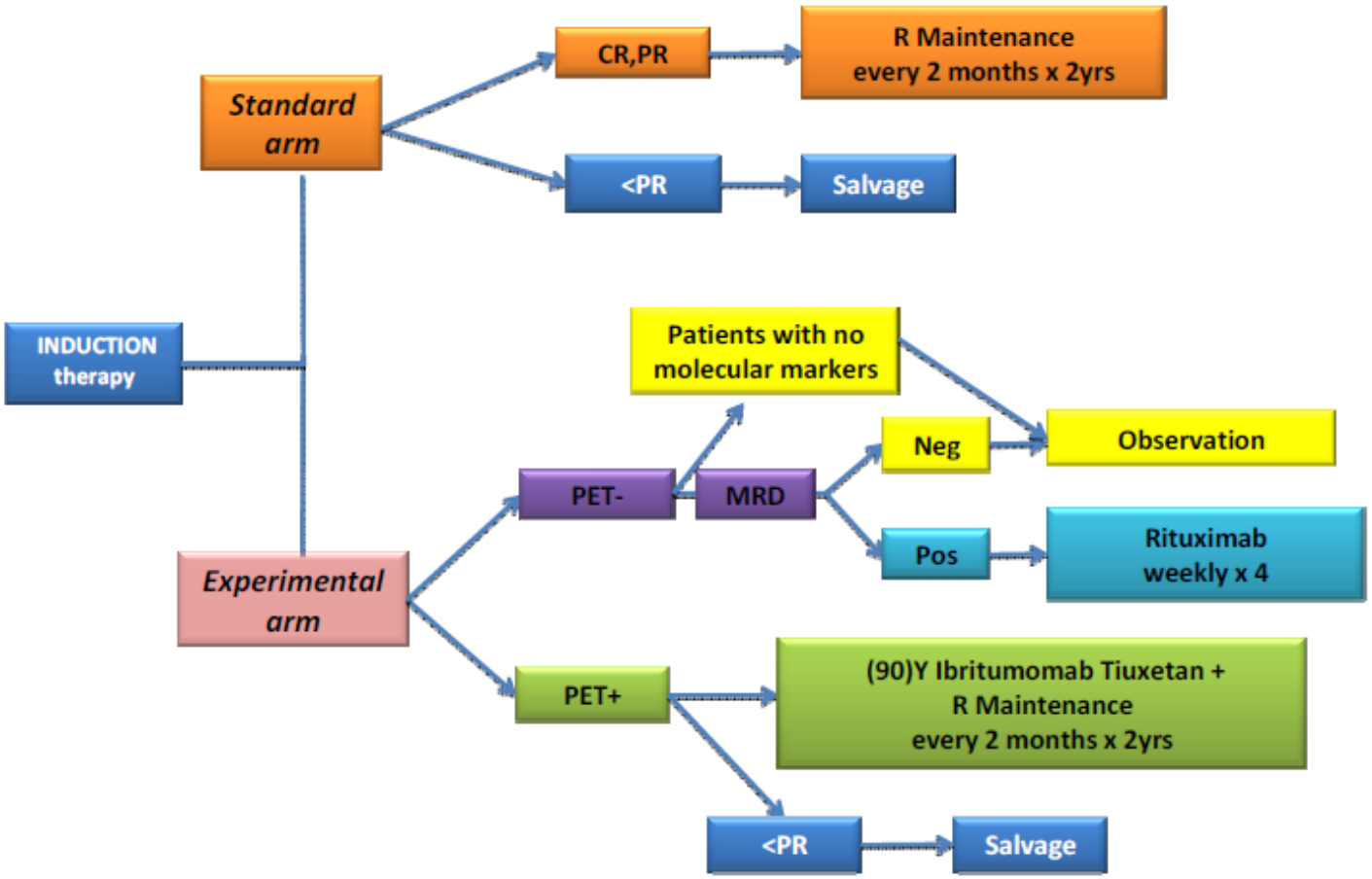
- **Highly active, active across subtypes**
- **Tolerable side effects**
- **Durable response**

TRIALS


Scientific
Government
CLINICAL
TRIALS
Research
Safety
Laboratories
Medical
Drugs
Studies
Companies
Data
Cost

RESPONSE ORIENTED MAINTENANCE THERAPY IN ADVANCED FOLLICULAR LYMPHOMA. RESULTS OF THE INTERIM ANALYSIS OF THE FOLL12 TRIAL CONDUCTED BY THE FONDAZIONE ITALIANA LINFOMI.

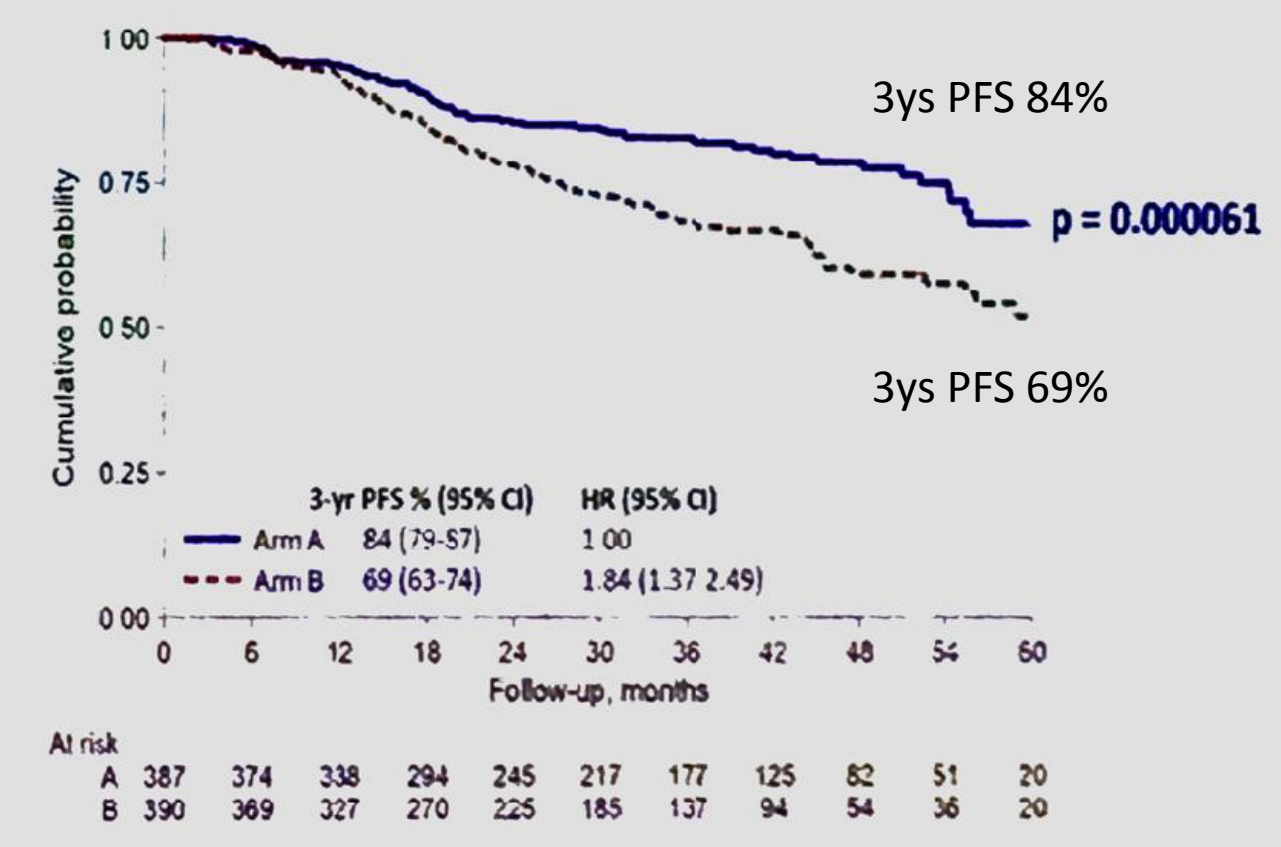
Federico M, et al.



- 790 enrolled pts randomized to standard arm (394 pts) or experimental arm (396 pts)
- Median FU 37 months
- **3-yrs OS 96% and 3-yrs PFS 76%**

- ORR 89-95%
- **CR 76-79%**

Factor	Overall N (%)	R-CHOP Pre-amendment	Post-amendment R-CHOP	R-B
CR	589 (78)	174 (79)	156 (76)	259 (79)
PR	102 (14)	32 (14)	37 (18)	33 (10)
ORR	691 (92)	206 (93)	193 (95)	292 (89)
SD/PD	29 (4)	7 (3)	5 (2)	17 (5)
Early withdrawal	34 (5)	8 (4)	6 (3)	20 (6)
Total	754	221	204	329
EoT PET positive	82 (12)	26 (13)	23 (12)	33 (11)

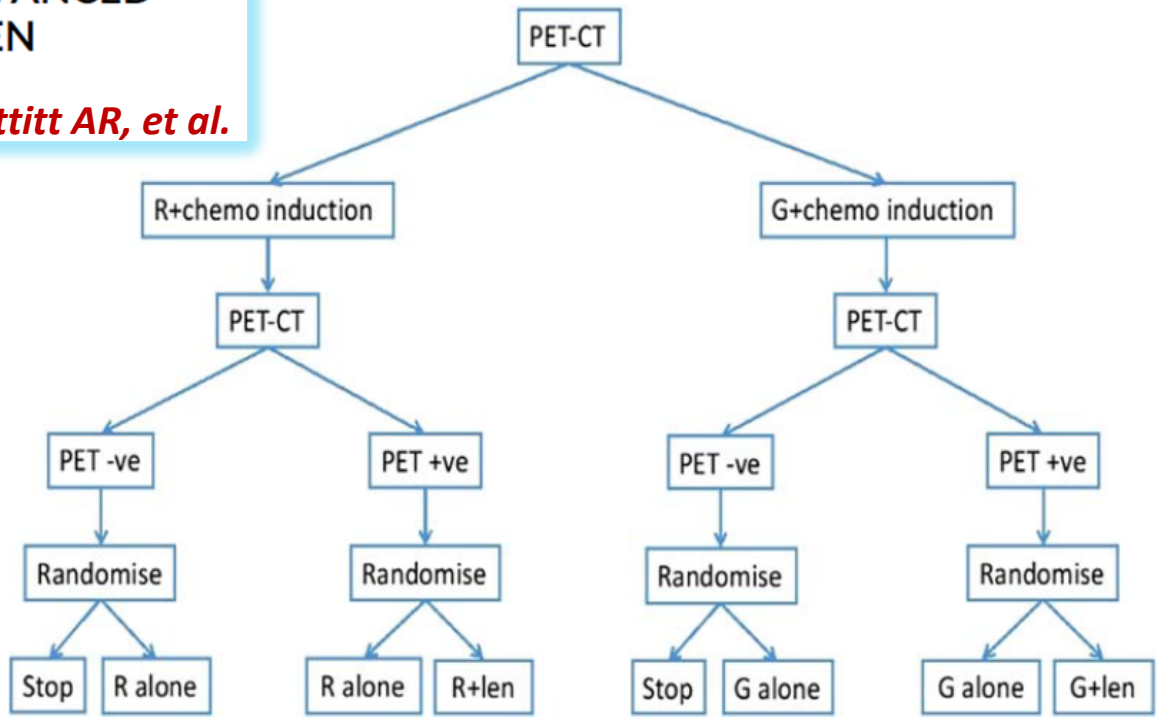


Response oriented experimental arm resulted significantly inferior to standard maintenance arm (estimated 3-yrs PFS 68% vs 84%), despite the atteinment of a post-induction complete metabolic response

ONGOING TRIAL

NCRI PETREA TRIAL: A PHASE 3 EVALUATION OF PET-GUIDED, RESPONSE-ADAPTED THERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED, ADVANCED-STAGE, HIGH-TUMOUR-BURDEN FOLLICULAR LYMPHOMA

Pettitt AR, et al.



- Prognostic value of PET negativity
- Hypothesis: PFS benefit of maintenance largely confined in responders pts who remain PET+
- Investigate treatment intensification in PET+ pts by adding Lenalidomide to anti-CD20 maintenance

FUTURE DIRECTIONS

EFFICACY AND SAFETY OF OBINUTUZUMAB + LENALIDOMIDE + ATEZOLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA: PRIMARY ANALYSIS OF A PHASE 1B/2 TRIAL

Morschhauser F, et al.

SAKK 35/15: A PHASE I TRIAL OF OBINUTUZUMAB IN COMBINATION WITH VENETOCLAX IN PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA PATIENTS

Stathis A, et al.

POLATUZUMAB VEDOTIN (POLA) + OBINUTUZUMAB (G) + LENALIDOMIDE (LEN) IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): PHASE IB/II INTERIM ANALYSIS

Diefenbach C, et al.

HIGH RATE OF DURABLE COMPLETE REMISSION IN FOLLICULAR LYMPHOMA AFTER CD19 CAR-T CELL IMMUNOTHERAPY *Hirayama AV, et al.*

CLINICAL ACTIVITY OF REGN1979, AN ANTI-CD20 X ANTI-CD3 BISPECIFIC ANTIBODY (AB) IN PATIENTS (PTS) WITH (W/) RELAPSED/REFRACTORY (R/R) B-CELL NON-HODGKIN LYMPHOMA (B-NHL) *M.S. Topp et al*

THE FIRST-IN-CLASS ANTI-CD47 ANTIBODY HU5F9-G4 + RITUXIMAB INDUCES DURABLE RESPONSES IN RELAPSED/REFRACTORY DLBCL AND INDOLENT LYMPHOMA: INTERIM PHASE 1B/2 RESULTS *R.Advani et al*

CD20-TCB (RG6026), A NOVEL "2:1" FORMAT T-CELL-ENGAGING BISPECIFIC ANTIBODY, INDUCES COMPLETE REMISSIONS IN RELAPSED/REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA

M.J. Dickinson et al