U.S. Management of First Relapse Follicular Lymphoma

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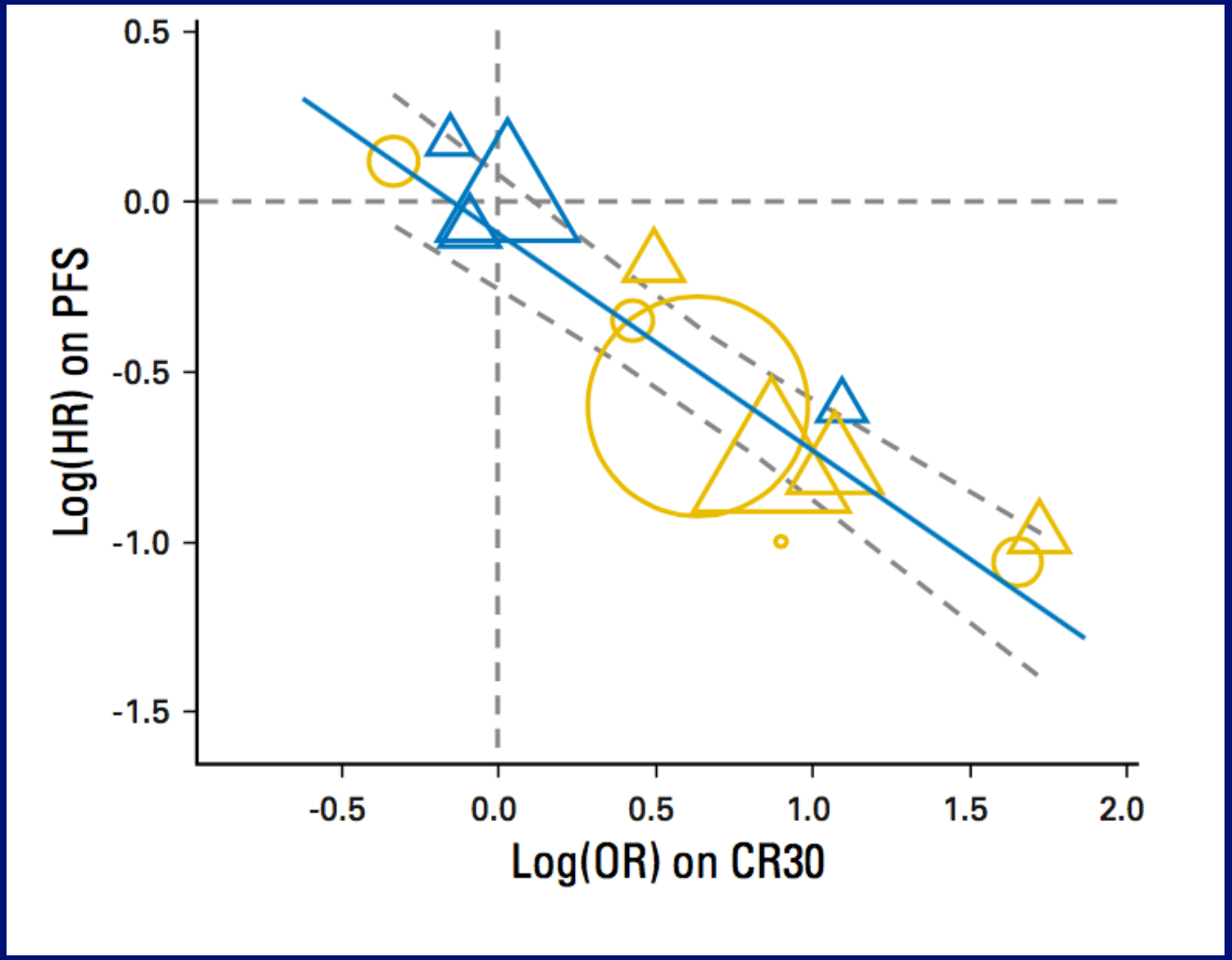
FLASH Analysis Dataset

- The current analyses included 13 studies:
  - Total of 26 arms, 4,177 patients
  - Total of 3,830 patients with non-missing 30mCR status
  - 9 studies (N=2,845) with at least one arm with Rituximab and 4 studies (N=985) with no Rituximab
  - 8 induction trials (N=2,206) and 5 maintenance trials (N=1,624)

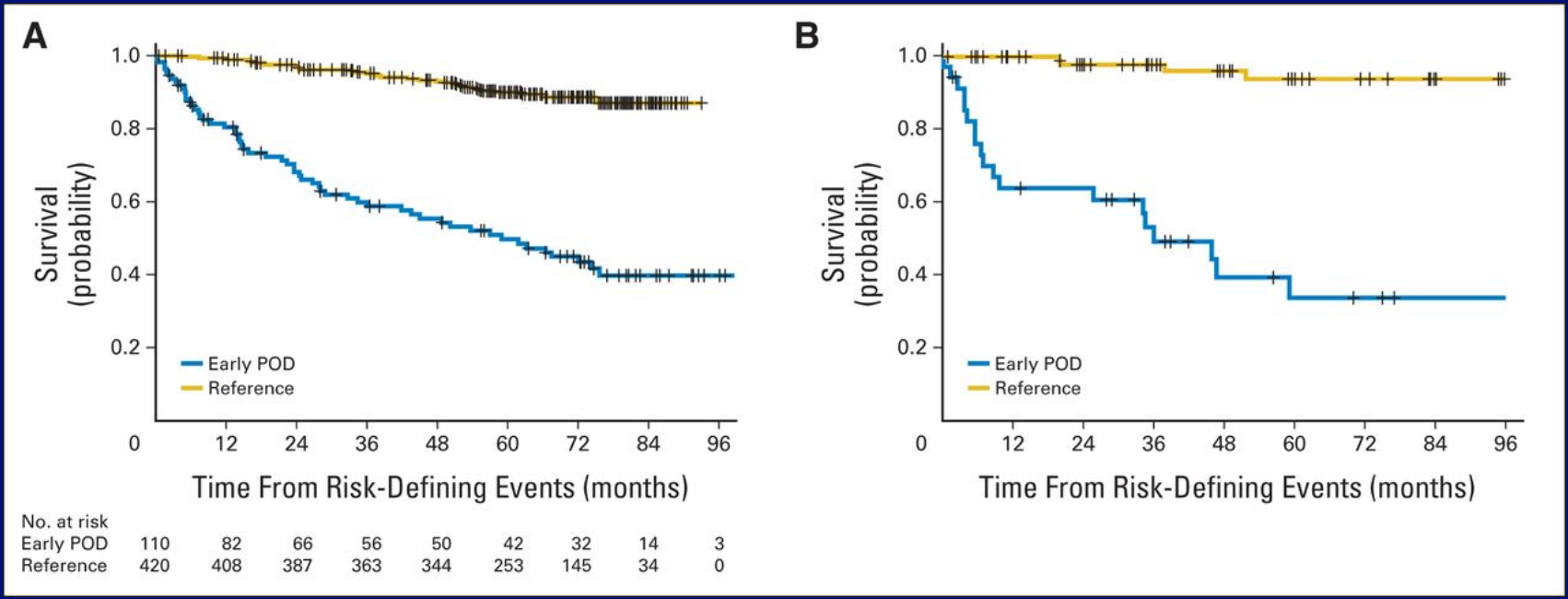
Shi et al, JCO e-pub on line 2017

Correlation Between CR30 and PFS



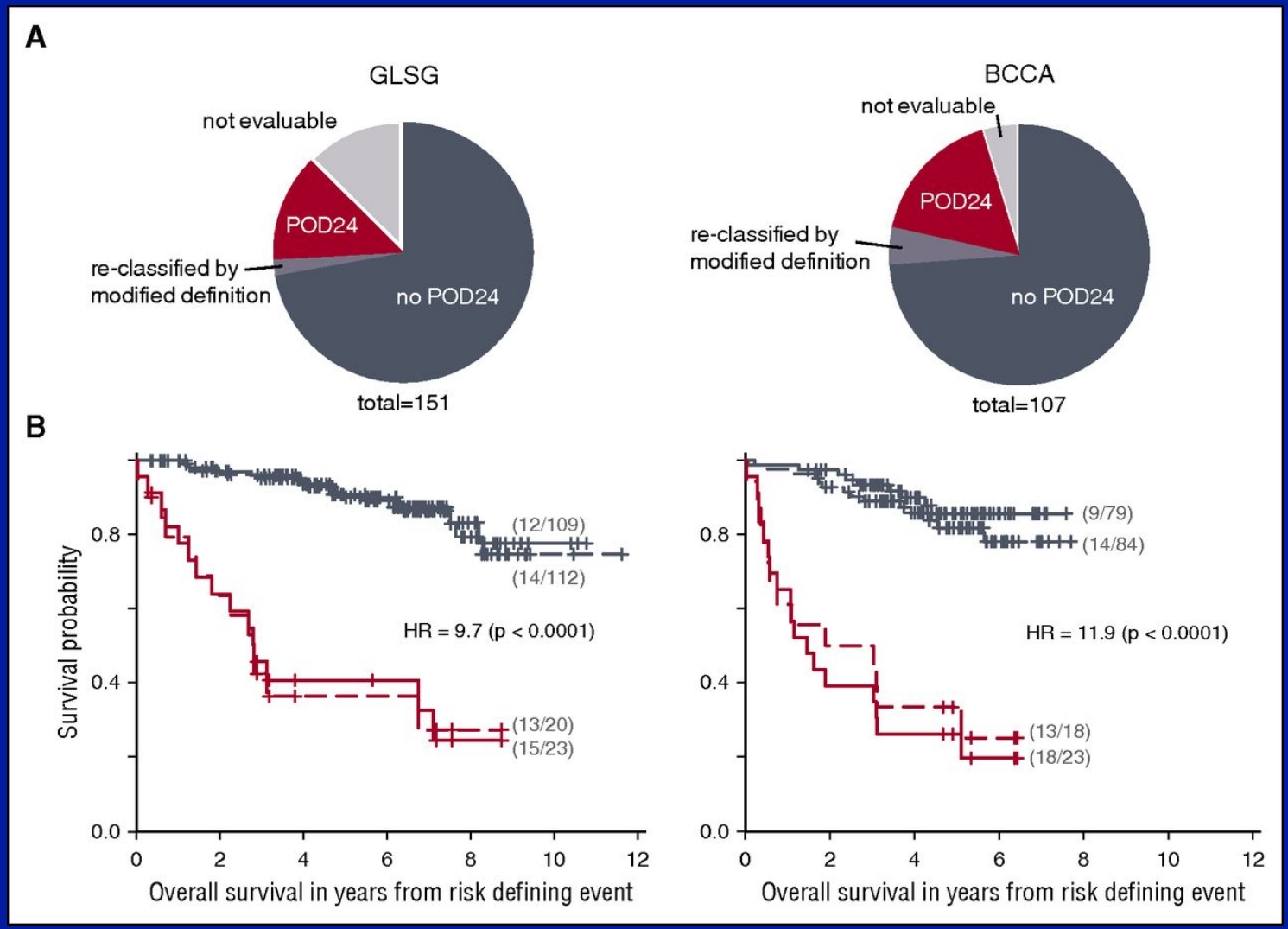
Shi et al, JCO e-pub on line 2017

OS from a risk-defining event after diagnosis in FL patients who received R-CHOP chemotherapy in the National LymphoCare Study group.



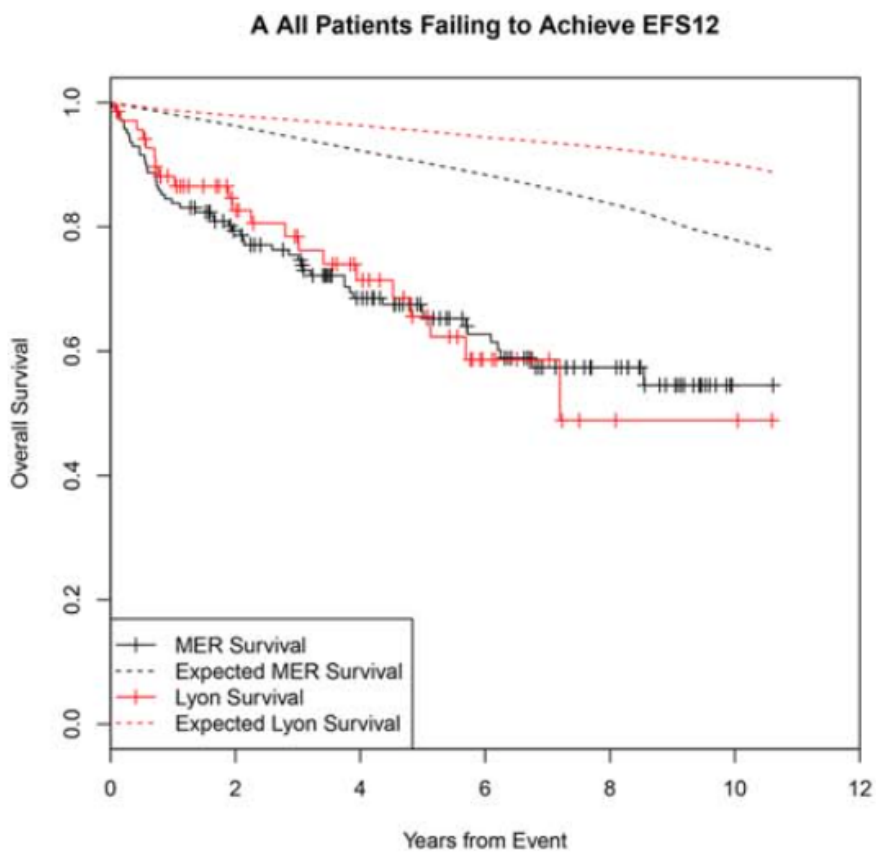
Carla Casulo et al. JCO 2015;33:2516-2522

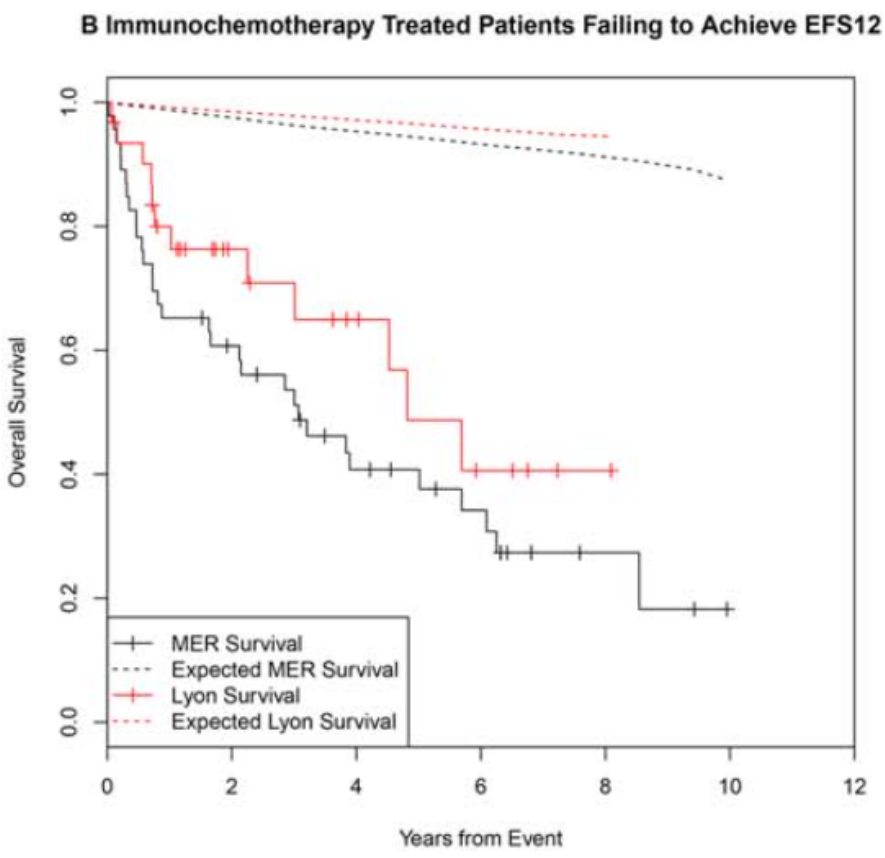
Progression of disease within 24 months (POD24) is an accurate predictor of poor overall survival (OS).



Vindi Jurinovic et al. Blood 2016;128:1112-1120

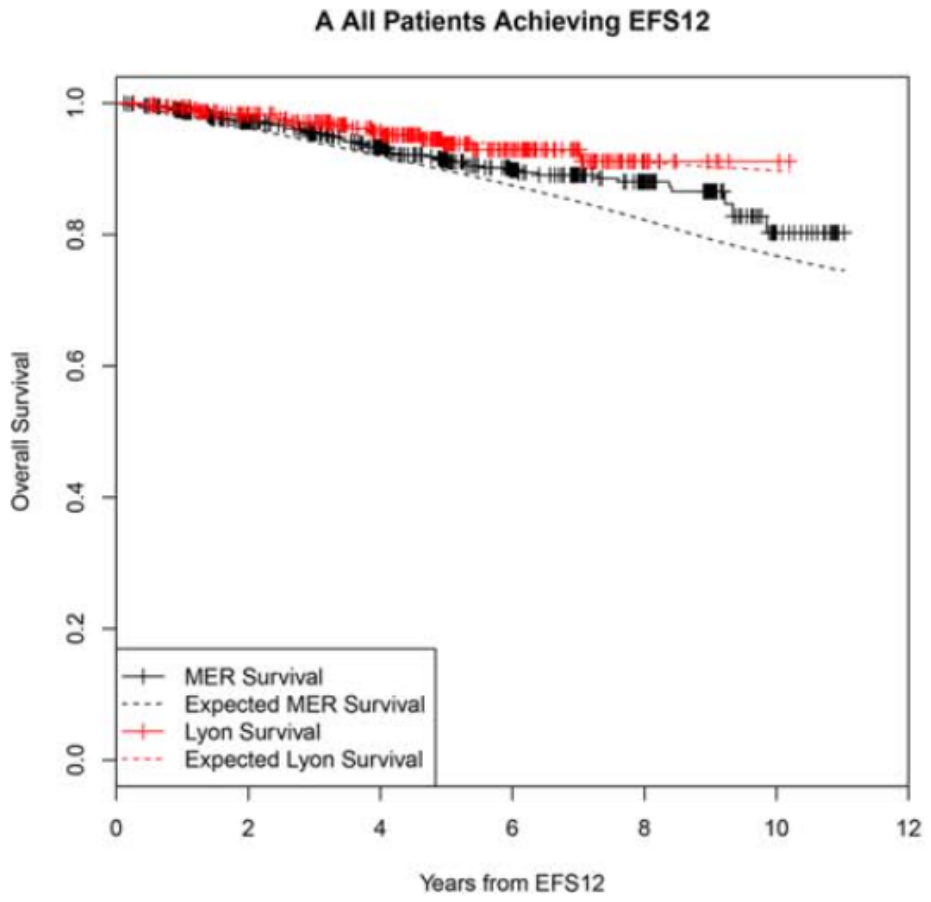
EFS 12 in FL

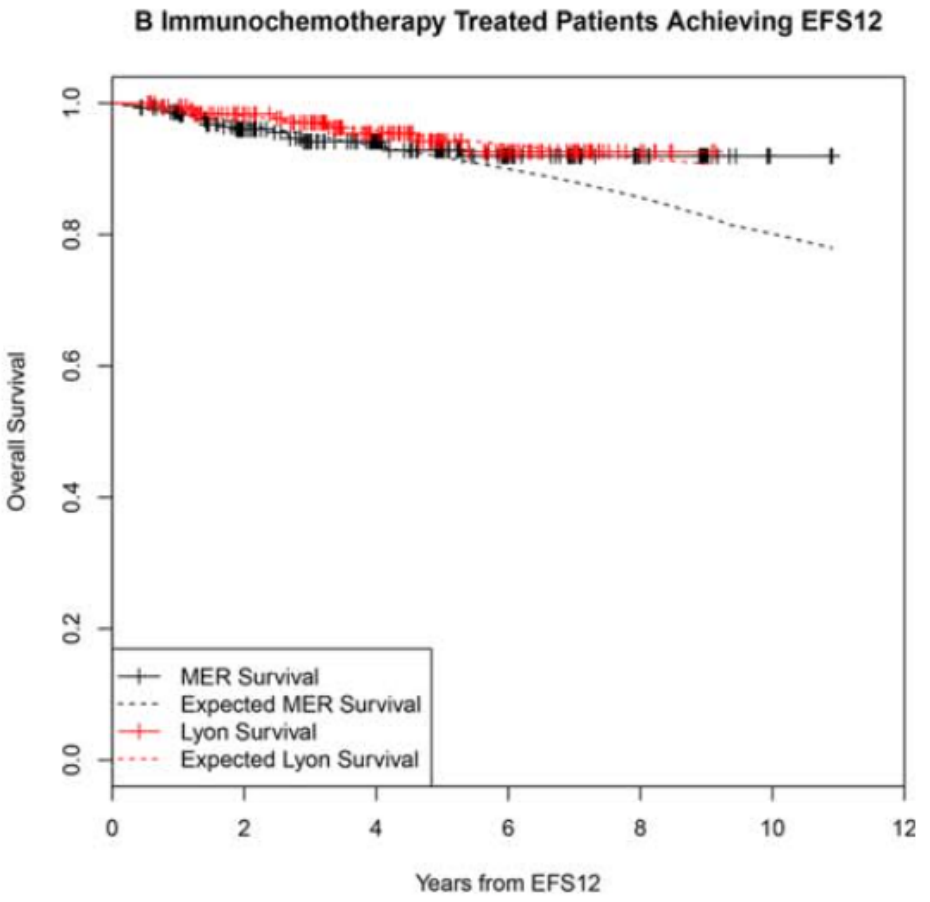




Maurer et al, Am J Hematol 91:1096, 2016

No EFS12 in FL

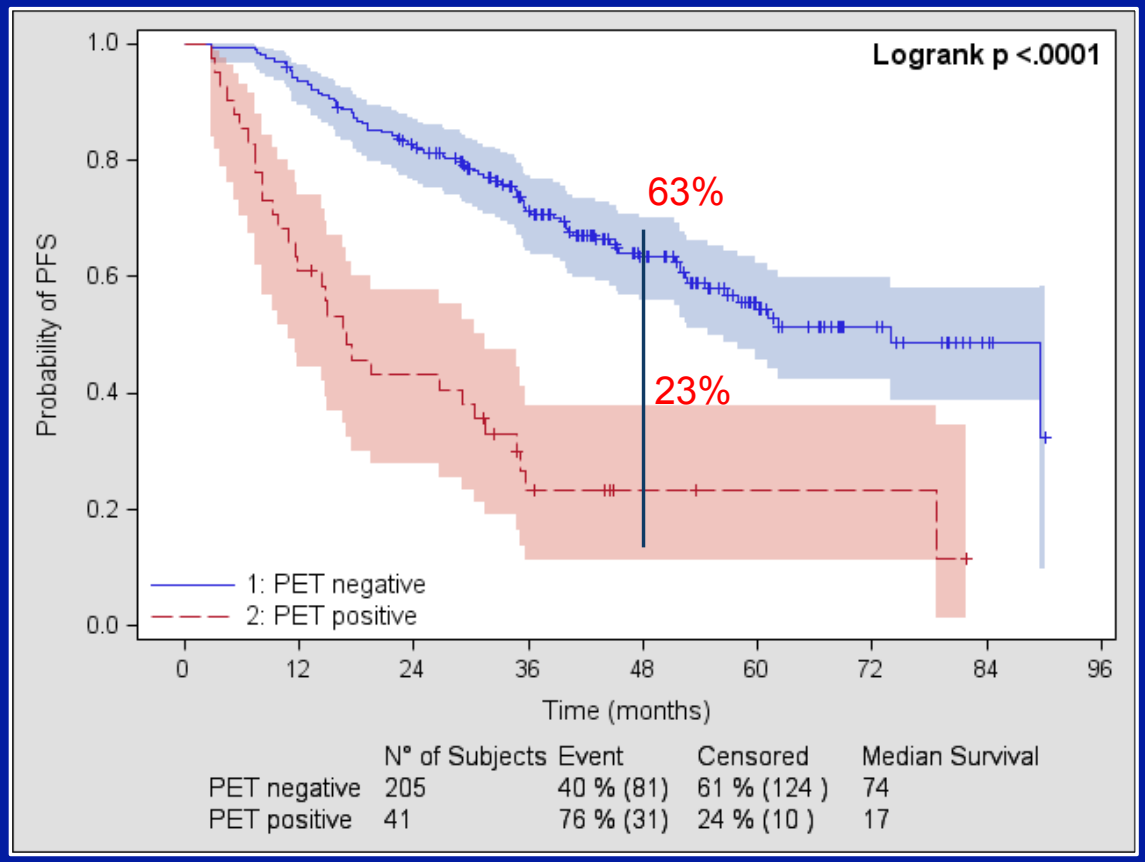




Maurer et al, Am J Hematol 91:1096, 2016

Post-treatment PET predicts PFS

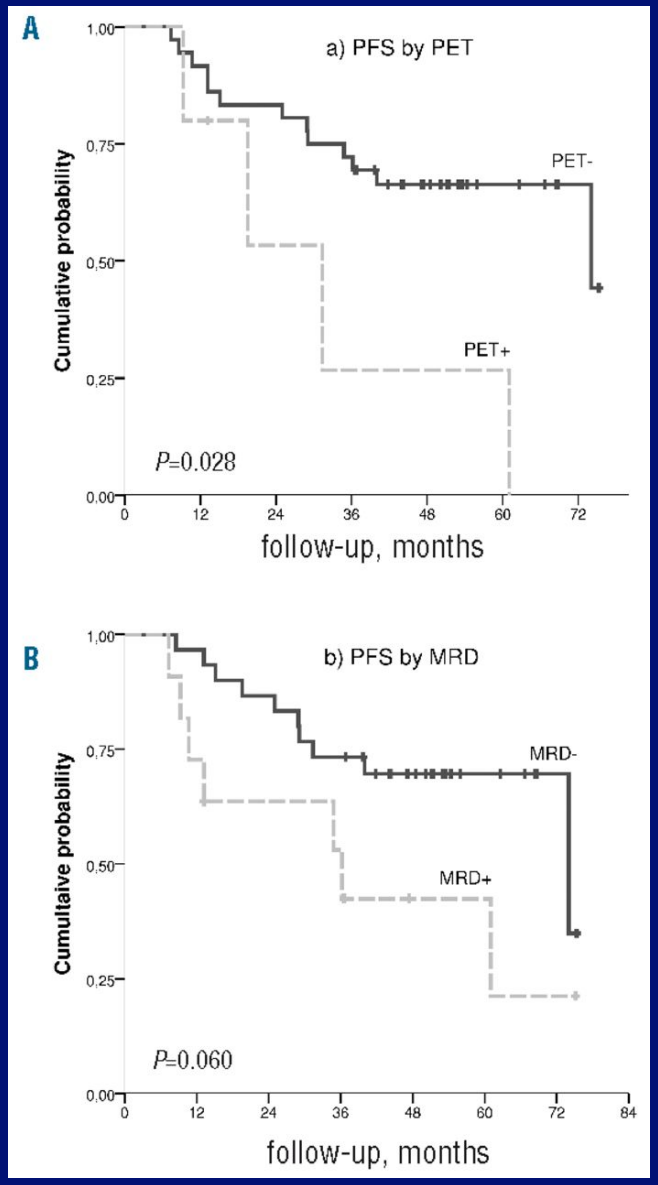
Score ≥4



HR 3.9 (95% CI 2.5-5.9, p<.0001)
Median PFS:
16.9 (10.8-31.4) vs. 74.0 mo (54.7-NR)

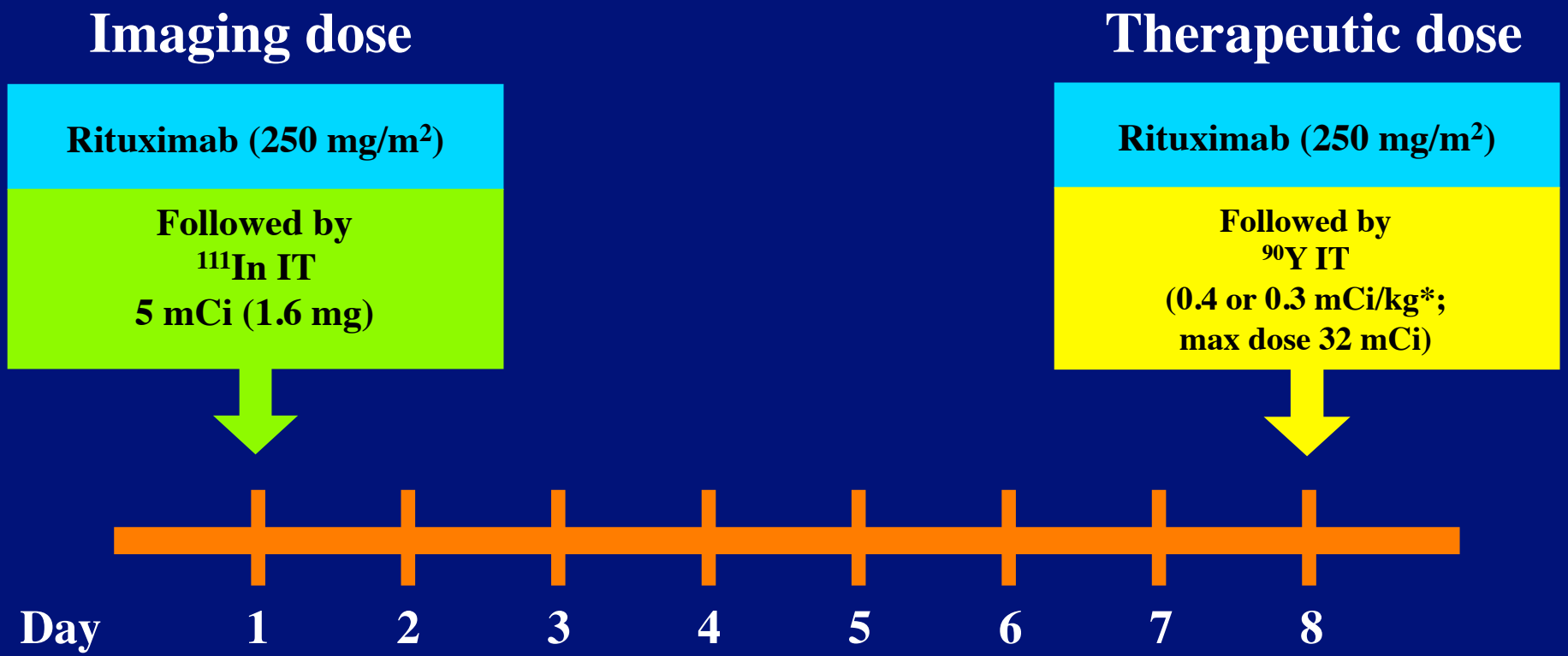
Trotman et al, Lancet Haematol, 2014

(A) PFS by PET. (B) PFS by MRD.



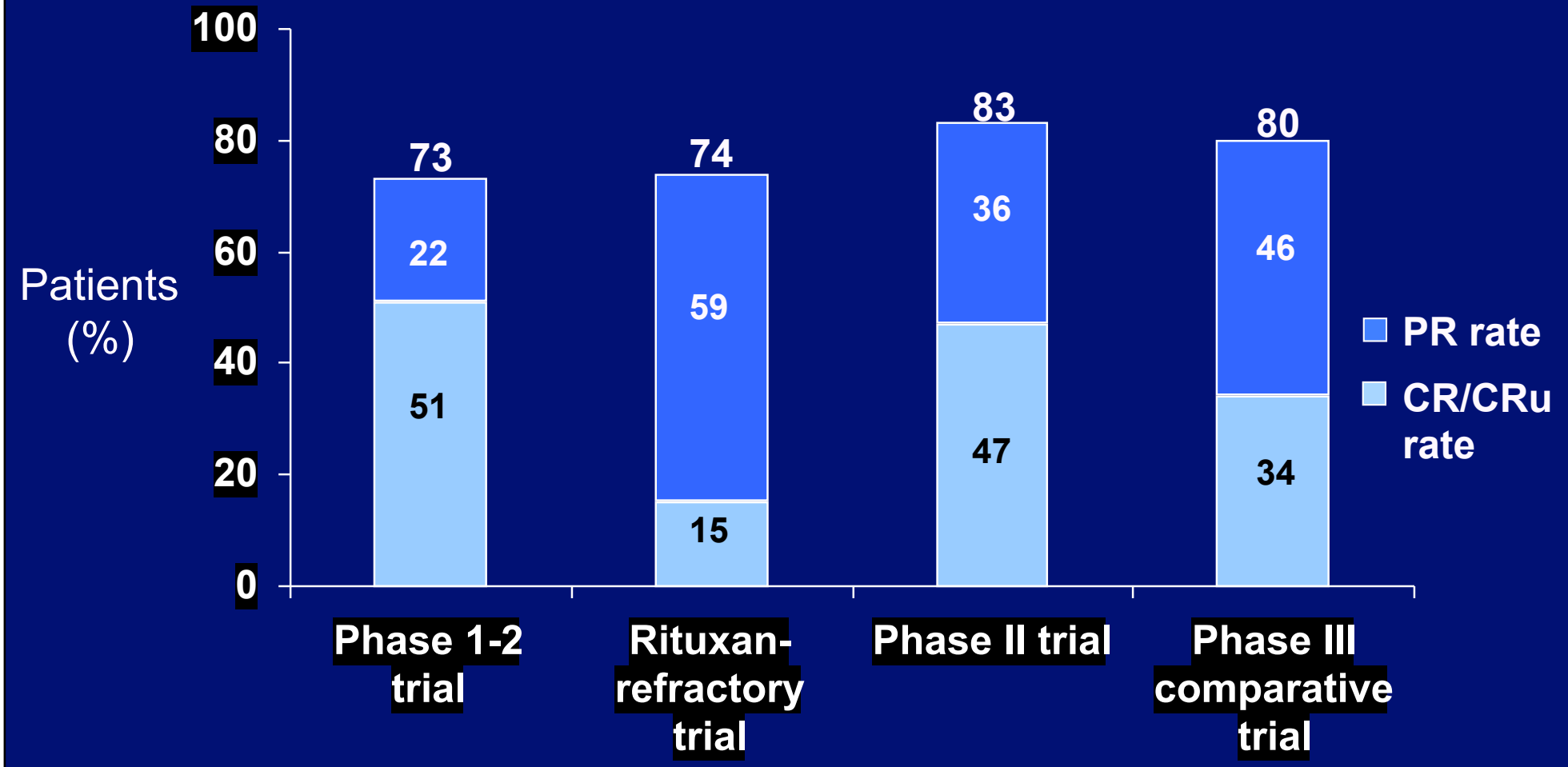
Stefano Luminari et al. Haematologica 2016;101:e66-e68

Y90 Ibritumomab Tiuxetan (Zevalin) Treatment Schema



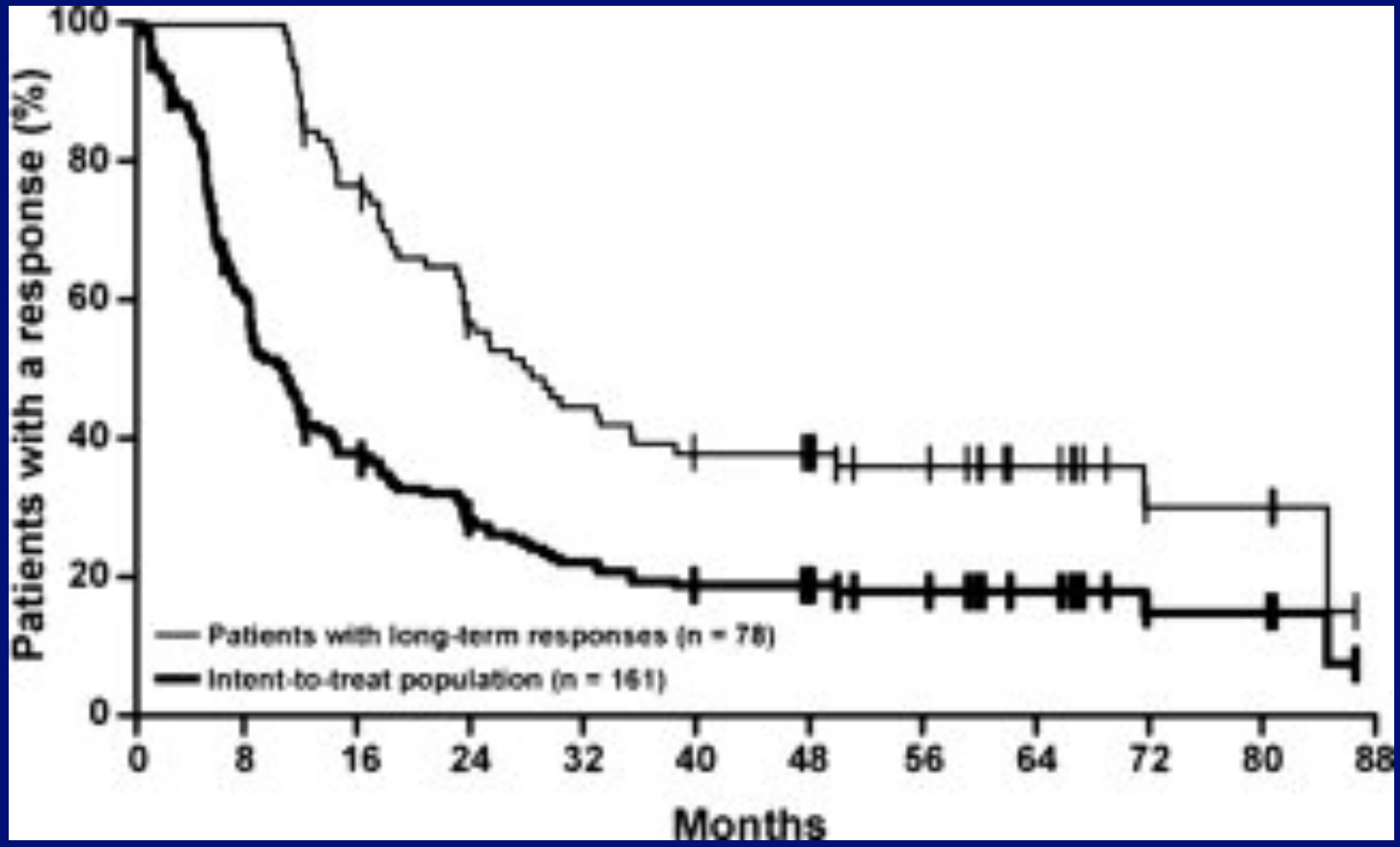
*0.4 mCi/kg in patients with a platelet count ≥150,000/μL or 0.3 mCi/kg with a platelet count 100,000–149,000/μL.

Overview of Y-90 Ibritumomab Tiuxetan Experience in Relapsed/Refractory B-Cell NHL



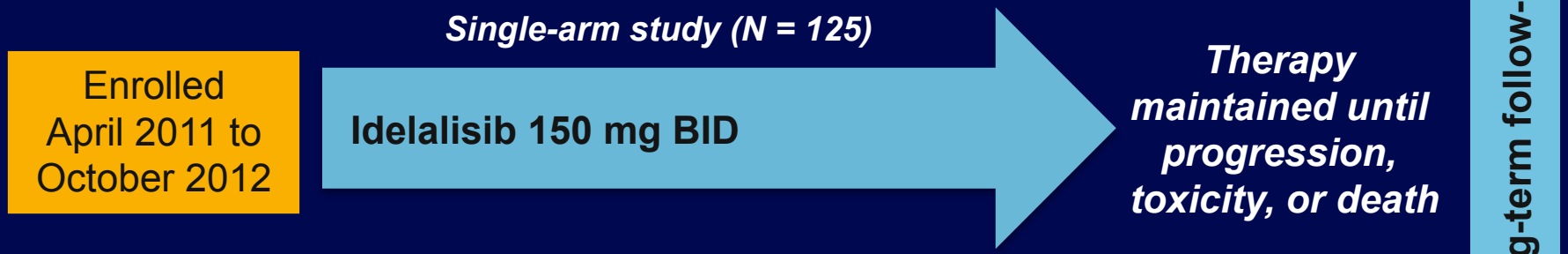
Gordon et al. *Blood*. 2004;103:4429–4431. Witzig et al. J Clin Oncol. 20:3262–3269. Wiseman et al. *Blood*. 2002;99:4336–4342. Witzig et al. J Clin Oncol. 2002;20:2453–2463.

Long-term responses in patients with recurring or refractory B-cell NHL treated with yttrium 90 ibritumomab tiuxetan



Witzig et al, Cancer 109, I 1804-,2007

Phase II Study 101-09: Idelalisib Monotherapy in Refractory iNHL



- Key eligibility criteria:
  - Previously treated iNHL (FL, MZL, SLL, WM)
- Refractory to BOTH rituximab and an alkylating agent
  - Defined as less than PR or progressive disease (PD) within 6 months
  - Documented radiologically

- Primary endpoint:
  - ORR
- Secondary endpoints:
  - DOR
  - PFS
  - OS
  - Time to response
  - Safety
  - Quality of life

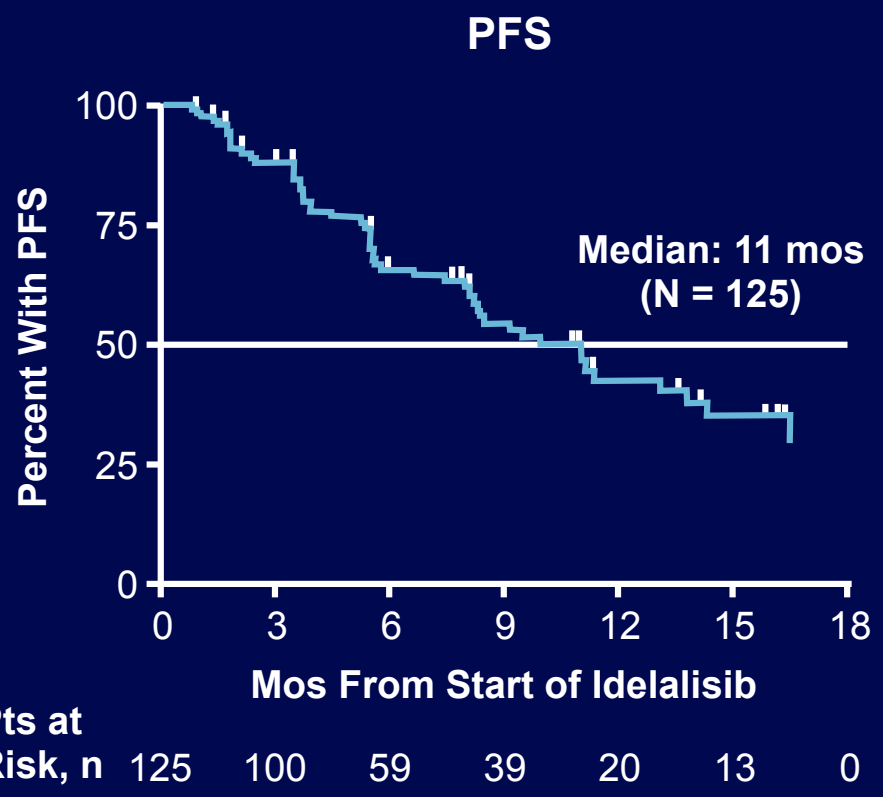
Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

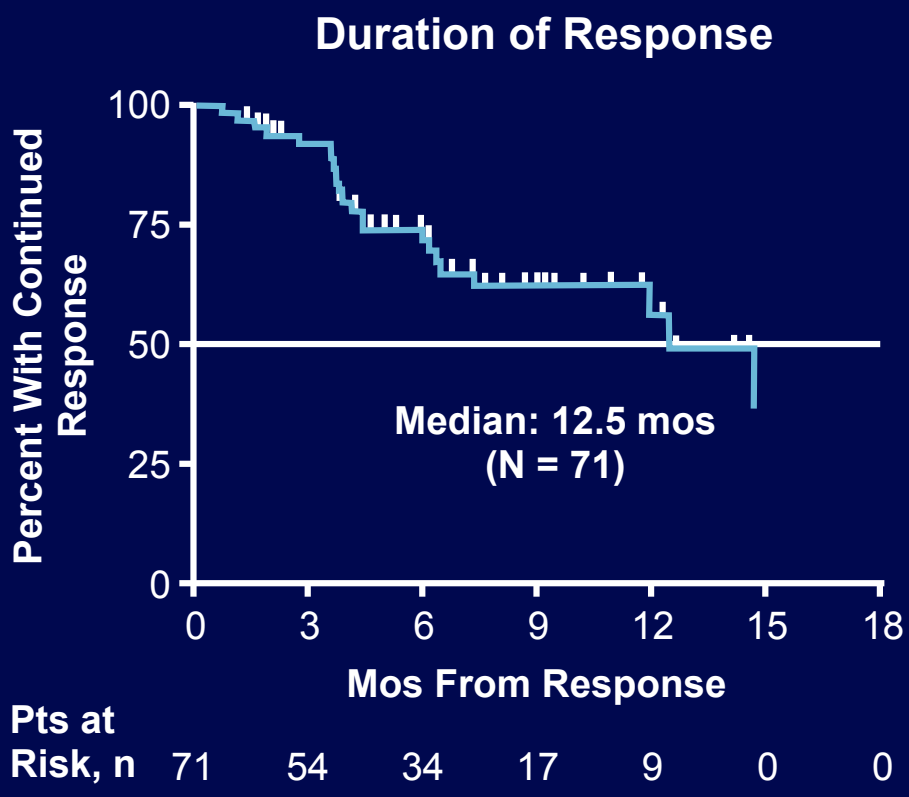
Idelalisib Monotherapy in Refractory iNHL (Phase II): Responses

Characteristic	Patients, n (%) (N = 125)
ORR, n (%)	71 (57)
CR	7 (6)
PR	63 (50)
Minor response*	1 (1)
SD	42 (34)
PD	10 (8)
Not evaluated	2 (2)
Time to response, mos (n = 71)	
Median (interquartile range)	1.9 (1.8-3.7)

Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

Phase II Study of Idelalisib Monotherapy in Refractory iNHL: PFS and DOR





Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

Idelalisib Monotherapy in Refractory iNHL (Phase II): Adverse Events

AE, n (%)	Any Grade	Grade ≥3
Diarrhea	54 (43)	16 (13)
Fatigue	37 (30)	2 (2)
Nausea	37 (30)	2 (2)

Transaminases, n (%)	Any Grade	Grade 3/4
ALT elevated	59 (47%)	16 (13%)
AST elevated	44 (35%)	10 (8%)

Gopal A, et al. N Engl J Med. 2014;370:1008-1018.

BloombergBusiness | News | Markets | Insights | Video

Gilead Cancer Drug Reviewed After Deaths in Combo Trials

by Doni Bloomfield
DoniBloomfield

March 11, 2016 – 6:39 PM CET *Updated on* March 11, 2016 – 11:50 PM CET

- FDA, European drug regulators are reviewing Gilead treatments
- Deaths, side effects reported after drug used in combination

U.S. and European regulators are reviewing Gilead Sciences Inc.'s cancer drug Zydelig after some patients died or suffered other side effects while taking it with other drugs in

Gilead Sciences Halts Drug Studies Over Side Effects, Death

By THE ASSOCIATED PRESS ·
FOSTER CITY, Calif. — Mar 15, 2016, 5:37 PM ET

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3
SHARES

Biologic drugmaker Gilead Sciences Inc. has halted several patient studies of its cancer drug, Zydelig, because of increased risk of death and serious side effects.

The company told The Associated Press the "adverse events" were spotted during an ongoing review of late-stage testing in patients with chronic lymphocytic leukemia, a blood cancer, and patients with relapsed non-Hodgkin's lymphoma, a cancer of the infection-fighting lymphatic system.

Nathan Kaiser, a spokesman for the Foster City, California, company, wouldn't disclose details, including how many patients died or suffered serious side effects.

"We are conducting a comprehensive review of all ongoing studies and are consulting with regulatory authorities," Kaiser wrote in an email Tuesday.

CALGB 50401: Response and event-free survival

	L (N=45)	L + R (N=44)
Overall (ORR)	51.1% 95% CI (35.8-66.3)	72.7% 95% CI (52.2-85.0)
Complete (CR)	13.3%	36.4%
Partial (PR)	37.8%	36.4%
Median EFS	1.2 yrs	2.0 yrs
2 year EFS	27%	44%

Median F/U 1.7 years (0.1 – 4.1)

Unadjusted EFS HR of L vs L+R is 2.1 (p=0.010)

Adjusted (for FLIPI) EFS HR of L vs L+R is 1.9 (p=0.061)

Leonard et al, JCO 33:3635, 2015

Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: updated results of the GADOLIN study

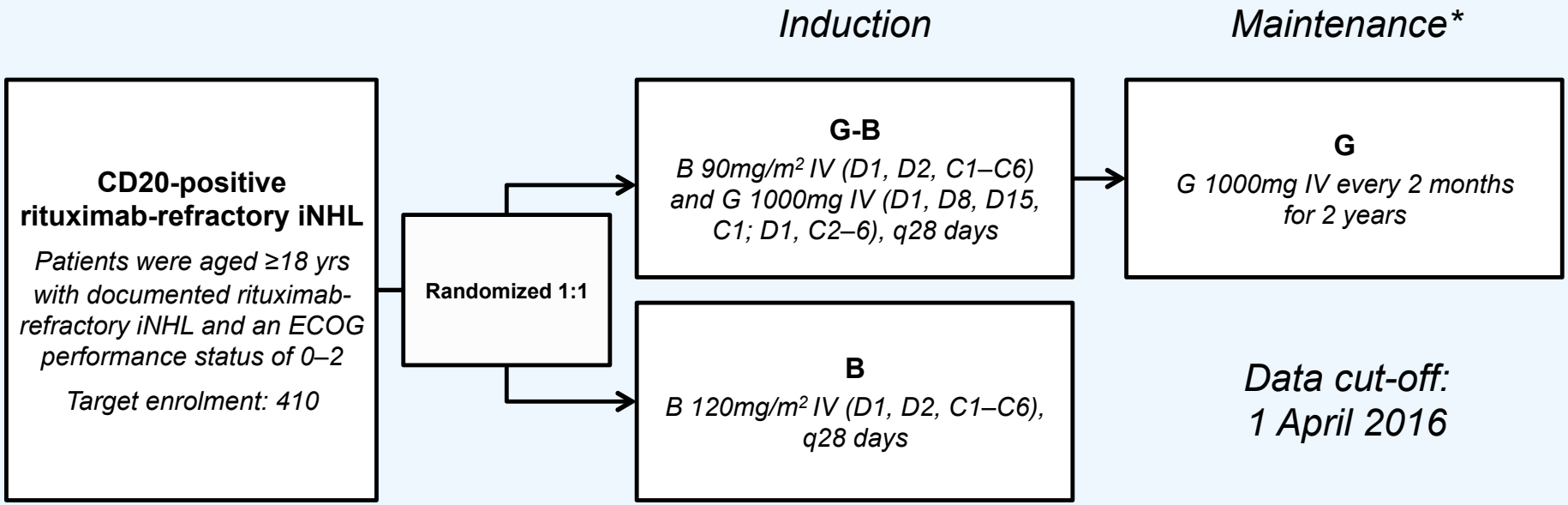
Bruce D Cheson,[1] Marek Trněný,[2] Kamal Bouabdallah,[3] Greg Dueck,[4] John Gribben,[5] Pieternella J Lugtenburg,[6] Oliver Press,[7] Gilles Salles,[8] Günter Fingerle-Rowson,[9] Federico Mattiello,[9] Elisabeth Wassner-Fritsch,[9] Laurie H Sehn[10]

[1]Georgetown University Hospital, Washington, DC, USA; [2]Charles University, Prague, Czech Republic; [3]University Hospital of Bordeaux, CHU Haut-Leveque, Bordeaux, France; [4]British Columbia Cancer Agency, Kelowna, BC, Canada; [5]Queen Mary University of London, London, United Kingdom; [6]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]Hospices Civils de Lyon, Université Claude Bernard Lyon-1, Lyon, France; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [10]British Columbia Cancer Agency and the University of British Columbia, Vancouver, BC, Canada

ASH 2016, abstr 615

Study design

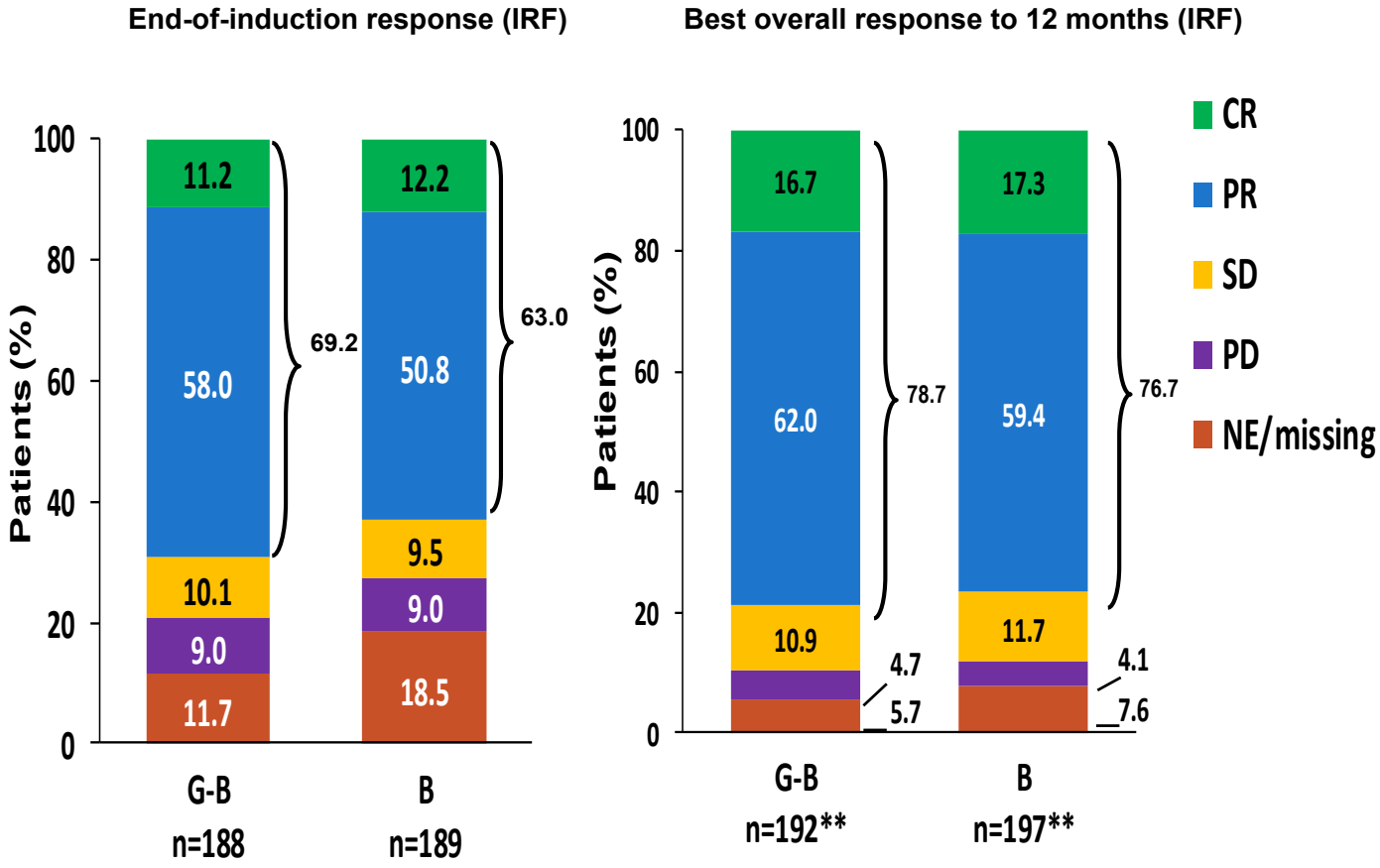
Open-label, multicenter, randomized, Phase III study in rituximab-refractory iNHL patients



- **Rituximab-refractory definition:** Failure to respond to, or progression during any prior rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance settings
- **Endpoints considered in current analysis:** PFS (INV), OS, TTNT, safety

*Patients in the G-B arm without evidence of progression following induction received G maintenance

GADOLIN: Response to therapy



- 19 patients still in induction (G-B, n=6; B, n=13)*

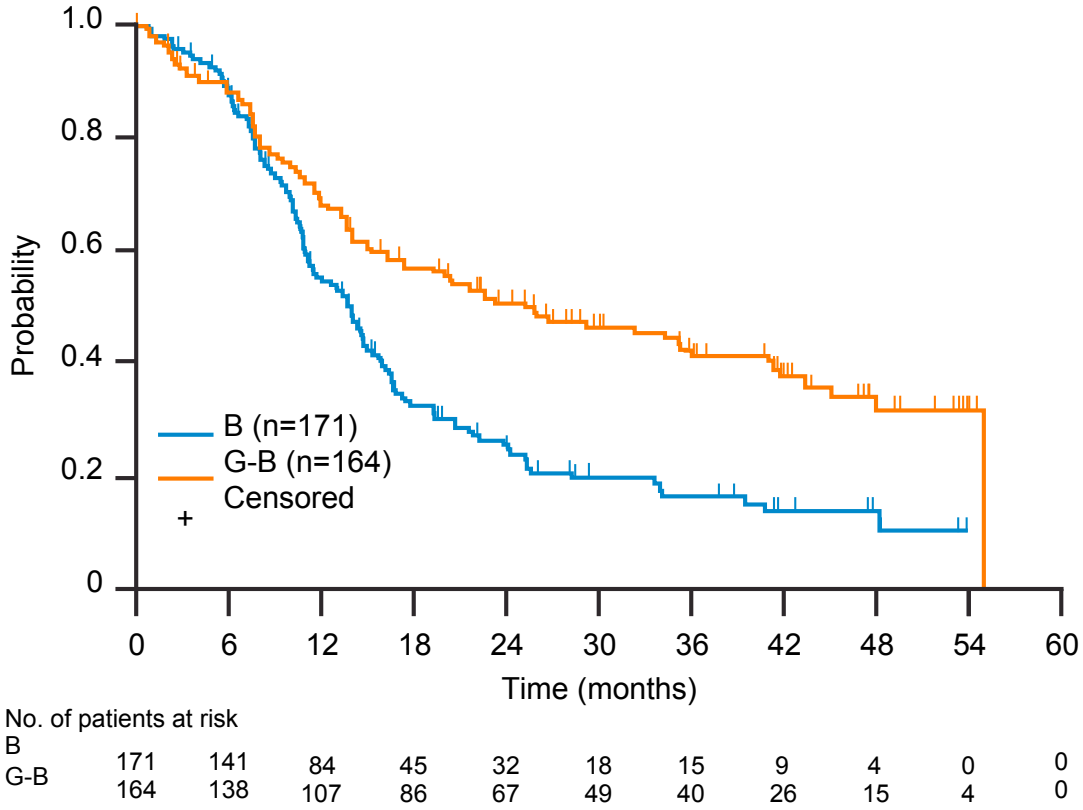
* Patients ongoing in induction therapy are excluded from analysis. Patients with end of induction response assessment performed >60 days after last induction dose shown as missing.

** Best overall response excludes ongoing patients who have not yet reached the first response assessment.

IRF, independent radiology facility

INV-assessed PFS in the FL population

Kaplan-Meier plot of INV-assessed PFS by treatment arm (FL)



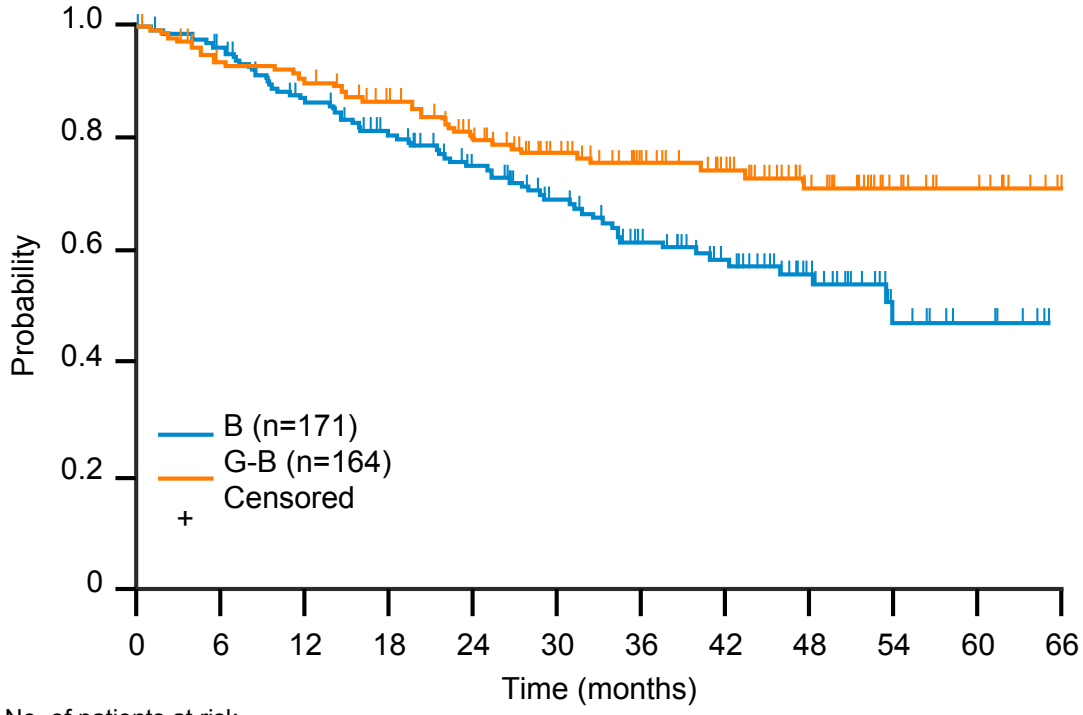
	G-B, n=164	B, n=171
Pts with event, n (%)	93 (56.7)	125 (73.1)
Median PFS (95% CI), mo	25.3 (17.4, 36.0)	14.0 (11.3, 15.3)
HR (95% CI), p-value*	0.52 (0.39, 0.69), p<0.0001	

Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

OS in the FL population

Kaplan-Meier plot of OS by treatment arm (FL)



No. of patients at risk

B	171	159	137	122	103	84	65	49	32	13	7	0
G-B	164	147	141	129	111	90	71	56	38	20	12	0

	G-B, n=164	B, n=171
Pts with event, n (%)	39 (23.8)	64 (37.4)
Median OS (95% CI), mo	NR (NR, NR)	53.9 (40.9, NR)
HR (95% CI), p-value*	0.58 (0.39, 0.86), p=0.0061	

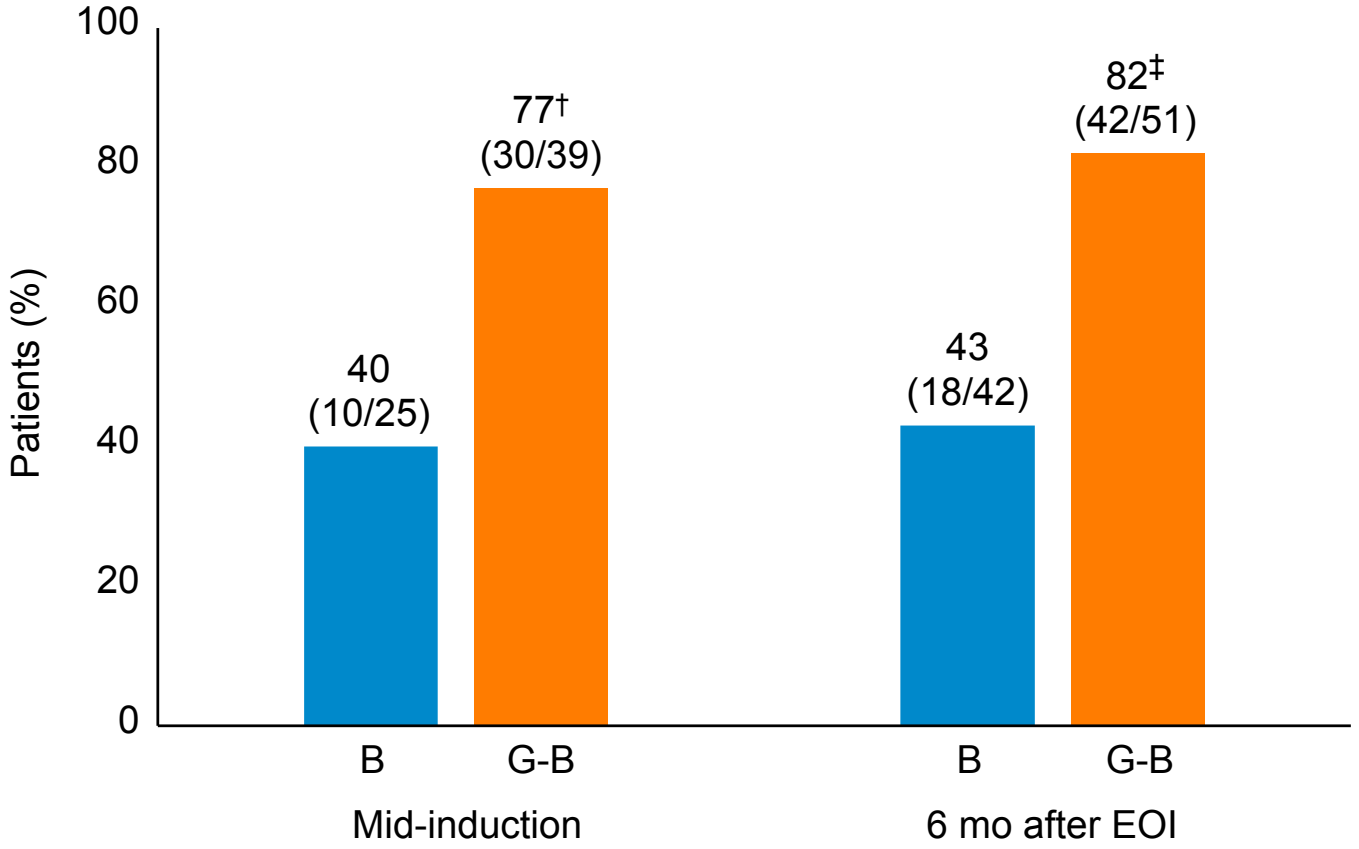
Median follow-up (FL): 31.2 months
(vs 21.1 months in primary analysis)

NR, not reached

*Stratified analysis; stratification factors: prior therapies, refractory type, geographical region

MRD-negative response in the FL population[1]

FL patients (%) achieving MRD-negative status in PB at mid-induction (Cycle 5 Day 1) and 6 months after EOI by treatment arm[*1]*

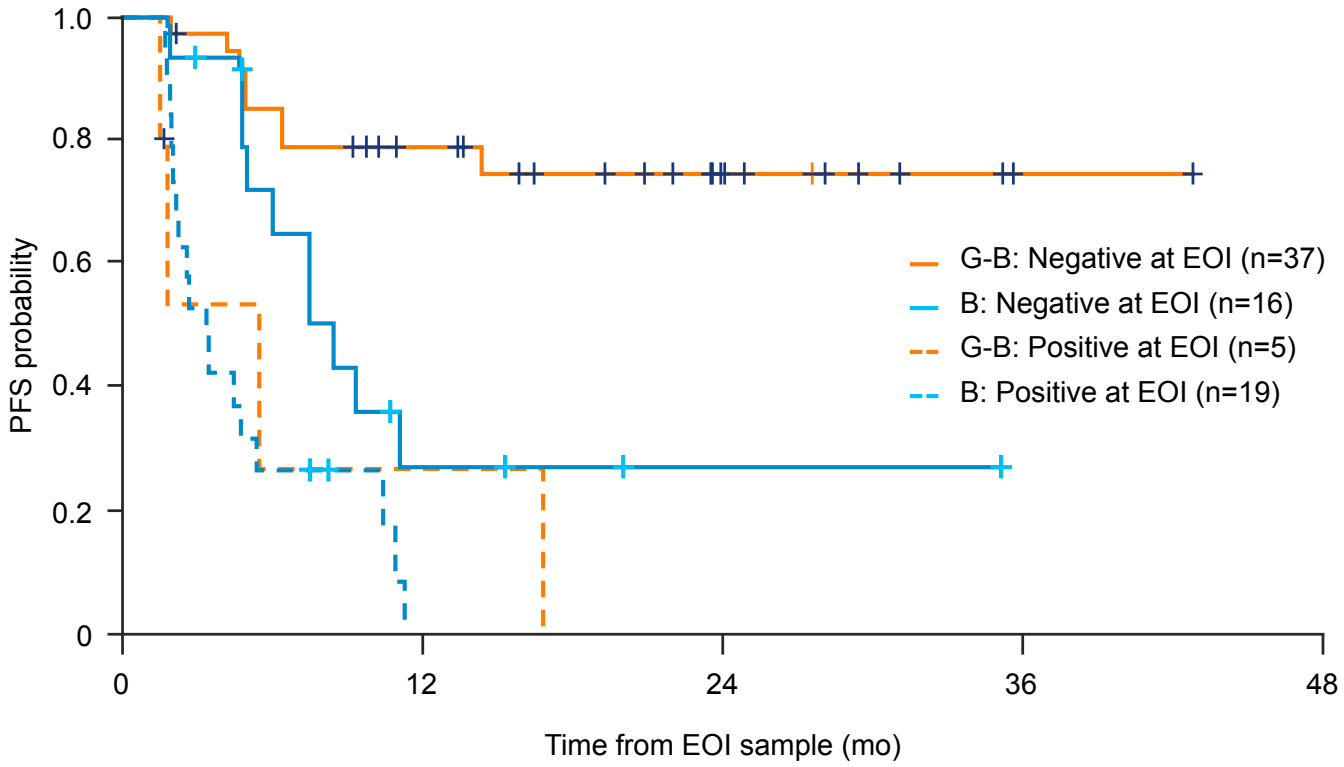


*MRD was analyzed by t(14;18) and/or Ig variable domain allele-specific RQ-PCR in patients with a clonal marker detectable at screening in PB or BM by consensus PCR and defined as negative if RQ-PCR and subsequent nested PCR produced a negative result; †p<0.0029 vs B arm; ‡p=0.0001 vs B arm

1. Pott C, et al. Blood 2015;126:3978

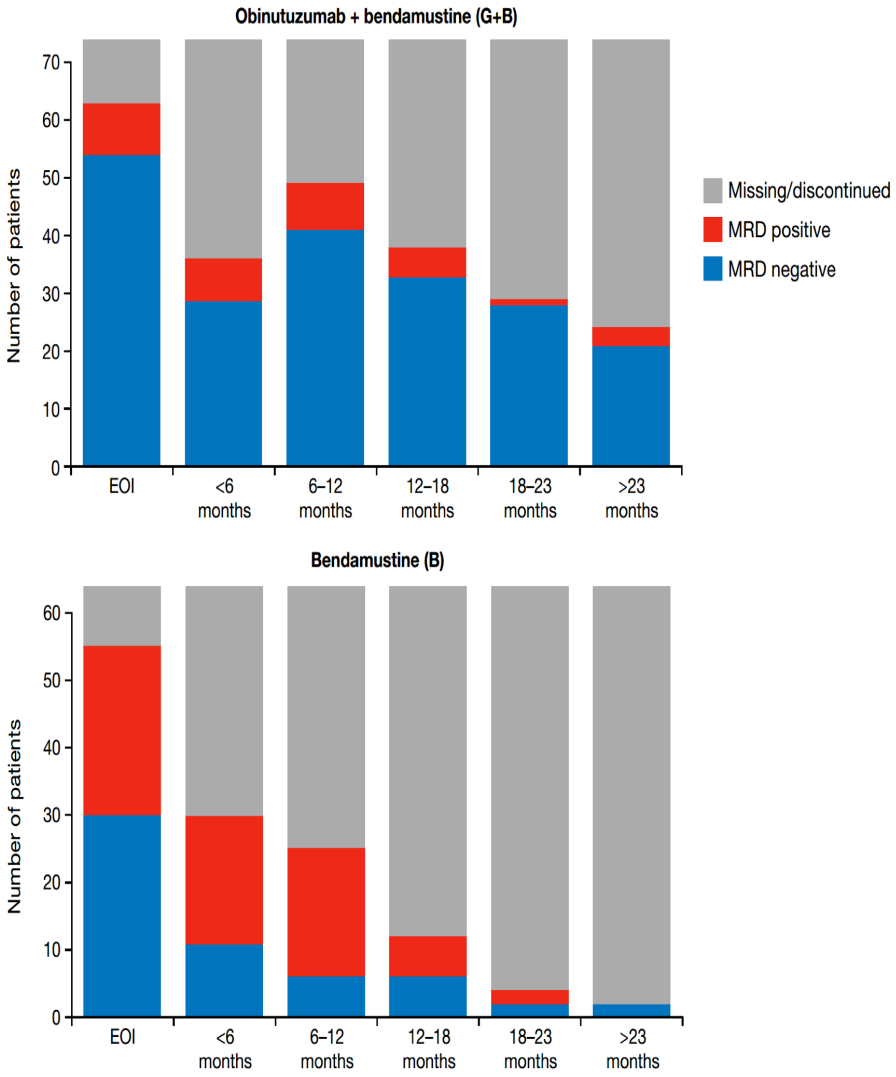
MRD status at EOI and association with PFS in the FL population[1]

Kaplan-Meier plot of PFS by MRD status at EOI and by treatment arm in the FL population



1. Pott C, et al. Blood 2015;126:3978

MRD Status During Induction and Maintenance



MRD status presented for 74 patients in the G+B arm and 64 patients in the B arm who provided ≥1 MRD sample at EOI and/or any of the post-induction timepoints.

Pott et al, Submitted for publication

US Intergroup Study Strategy

- Randomized phase II
  - Lack of a phase III question
  - Lack of a standard comparator
- Focus on high risk population
- Single national study
- Novel non-cytotoxic combination vs "standard" – rapidly rotating
- QOL as an endpoint

Maddocks, Barr, Cheson, et al JNCI 109:e-pub, 2017

US Intergroup Study Strategy

- All histologies centrally reviewed
- Better understand biology
- Explore new biomarkers
  - Collect germline DNA and other markers prior to treatment and at relapse
- Validate MRD and PET as response surrogates

S1608: Schema

FL grade 1-3a

Fail to achieve CR or EFS24 after
Bendamustine + anti-CD20 antibody

lenalidomide + obinutuzumab	TGR-1202 + obinutuzumab	CHOP + obinutuzumab
• Obinu 1000 mg/m2 q28 x12 • Len 20mg daily 21/28d x 12	• Obinu 1000 mg/m2 q28 x12 • TGR 800mg daily 28d x 12	• Obinu x 12 • CHOP x 6

- Restaging will be repeated following 6 cycles of therapy, at 1 year, at 30 months with PET. Primary endpoint CR. Secondary is CR30
- Bone marrow biopsy if initially involved with lymphoma upon achieving CR.

Objectives

- Primary
  - Compare **CR rate** by PET/CT (integral biomarker) of 2 targeted therapeutic regimens (obinutuzumab + TGR-1202 and obinutuzumab + lenalidomide) with obinutuzumab-CHOP in high-risk R/R FL.
- Secondary
  - Determine the 30 month sustained CR rate with each of the experimental regimens.
  - Evaluate additional survival endpoints, including PFS, DOR, and OS with each of the experimental combinations
  - Evaluate side effects of the experimental combinations

Statistics and Support

- Primary endpoint:compare CR rates of 2 experimental regimens to O-CHOP
- Randomized phase 2 design
  - Comparing each experimental regimen to O-CHOP (assumed complete response rate of 20%)
  - Interest if CR rate is >45%
  - Significance level of 10% (probability of falsely concluding a regimen is better than O-CHOP under the null)
  - Power of 85% (probability of correctly concluding a regimen improves the response rate , assuming the specified difference)
- 150 patients (45 in each arm)
  - Estimated 10% ineligibility

New Targeted Agents

Agent	Target
Obinutuzumab/Ublituximab	CD20
Polatuzumab vedotin Blinatumomab	CD79b CD3/CD19
Ibrutinib	Btk
Acalabrutinib (ACP-196)	Btk
Entospletinib (GS-9973)	Syk
Idelalisib	PI3-K
TGR-1202, Copanlisib	PI3-K
Venetoclax (ABT-199) Tazemetostat	Bcl-2 EZH2
Selinexor	XP01 (Nuclear transport)
Lenalidomide	Multiple
Nivolumab/Pembrolizumab	PD-1
Atezolizumab	PDL-1

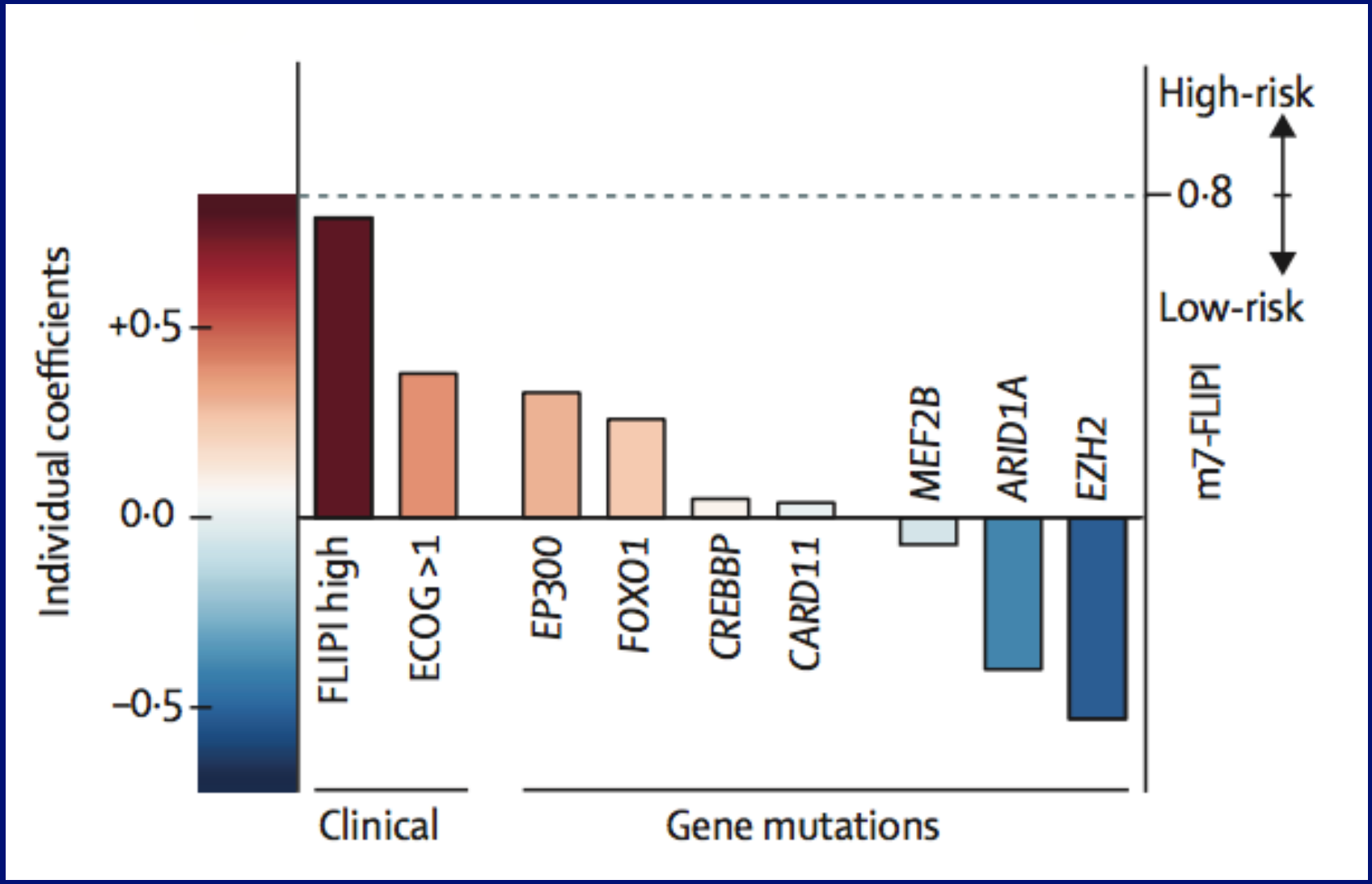
Ongoing “Non-chemo” Combination Trials in FL

Drugs	Sponsor
Obinutuzumab-B/CHOP+Atezolizumab	Genentech
Obinutuzumab+Polatuzumab	Genentech
Obinutuzumab+Atezolizumab+lenalidomide	Genentech
Obinutuzumab+Polatuzumab+lenalidomide	Genentech
Obinutuzumab+Polatuzumab+venetoclax	Genentech
GO29687 (Thiomab)+rituximab	Genentech
Acalabrutinib (ACP-196)+pembrolizumab	Acerta
Acalabrutinib+ACP-319	Acerta
Acalabrutinib+rituximab	Acerta
Ono/GS-4059+idelalisib	Gilead
Ibrutinib+Venetoclax	Georgetown
Ublituximab+ibrutinib	TG Therapeutics
Ublituximab+TGR-1202	TG Therapeutics
Ublituxumab+TGR-1202+ibrutinib	TG Therapeutics
Rituximab +/- copanlisib	Bayer

Surrogates to Predictors

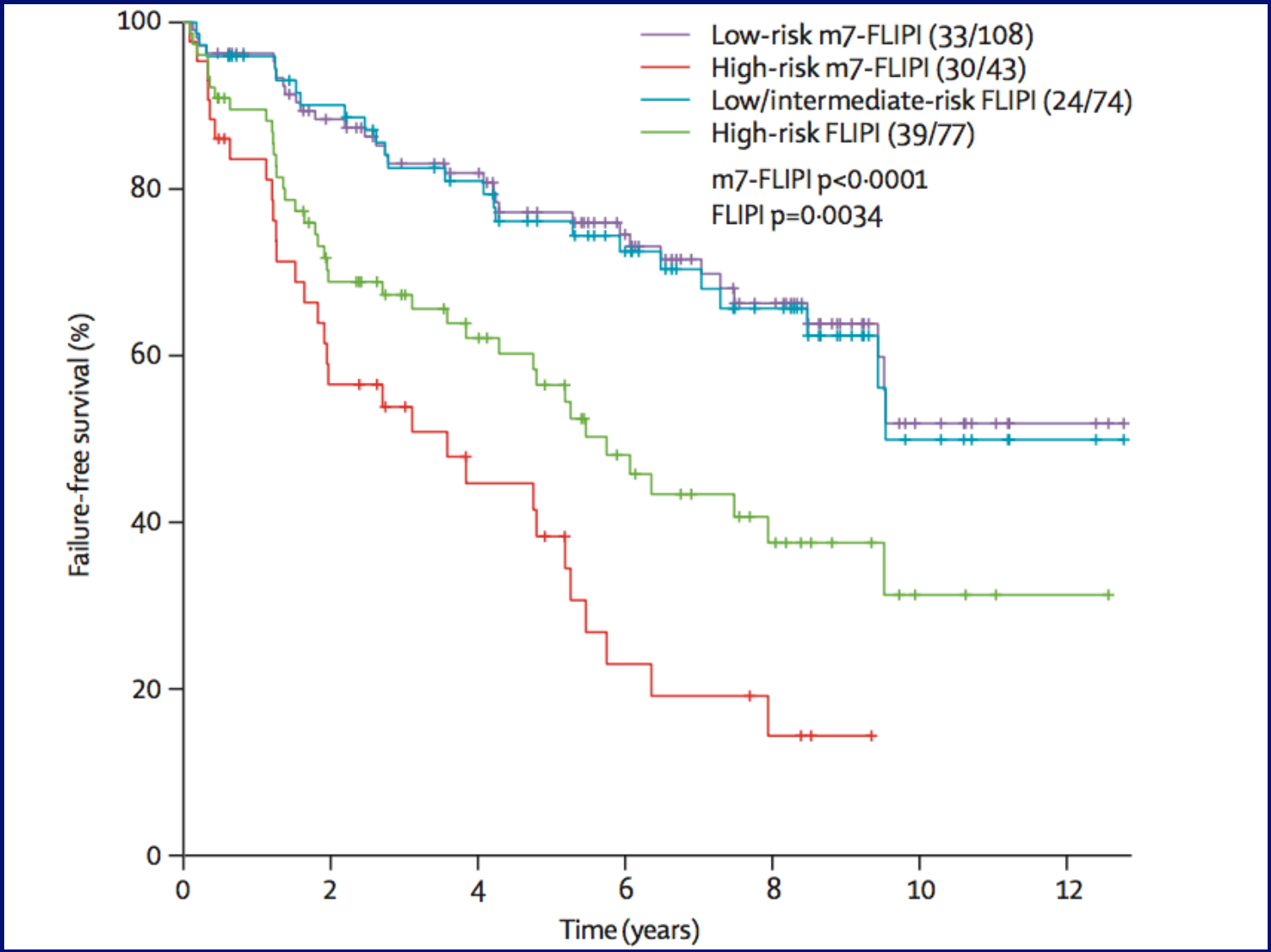
- Maintain CR at 30 months (FLASH)
- Event within 2 years
- Event within 1 year
- PET following induction
- m7-FLIPI
- High TMTV

Calculation of the m7 FLIPI



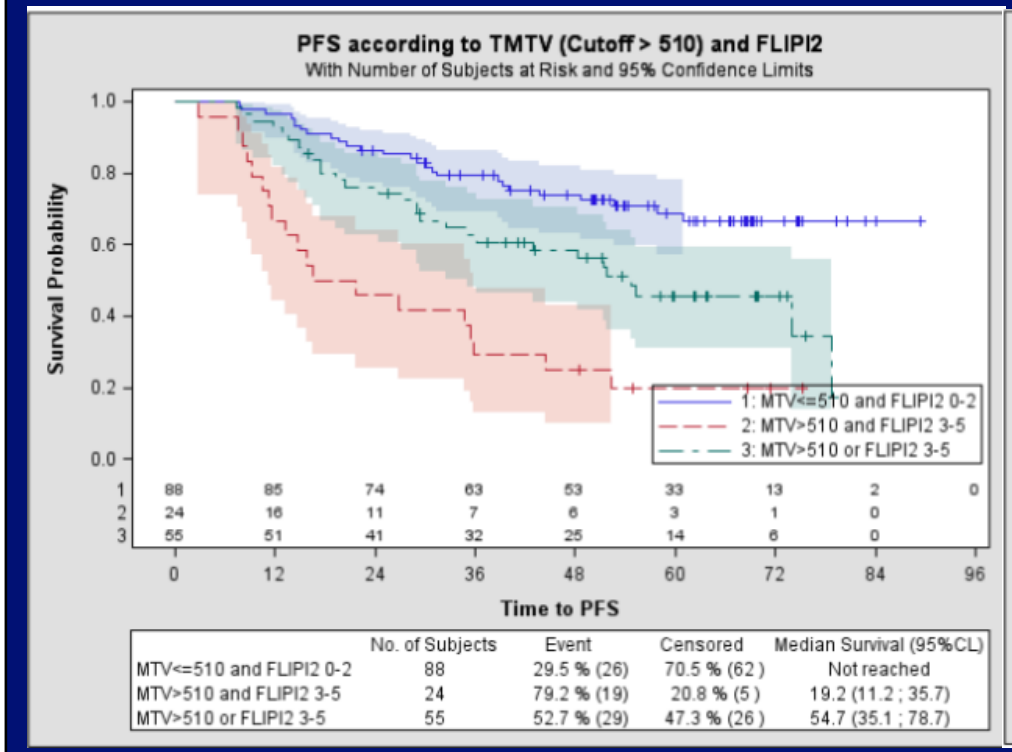
Pastore et al Lancet Oncol 16:1111, 2015

PFS: FLIPI vs m7 FLIPI

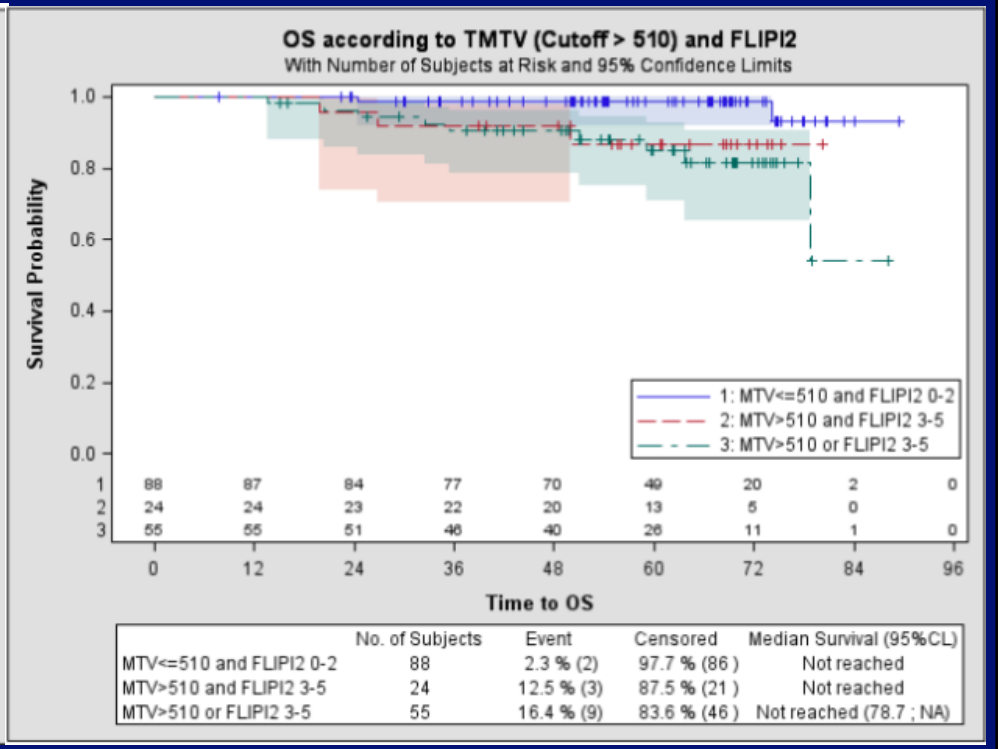


Pastore et al Lancet Oncol 16:1111, 2015

Pre-Treatment TMTV in FL



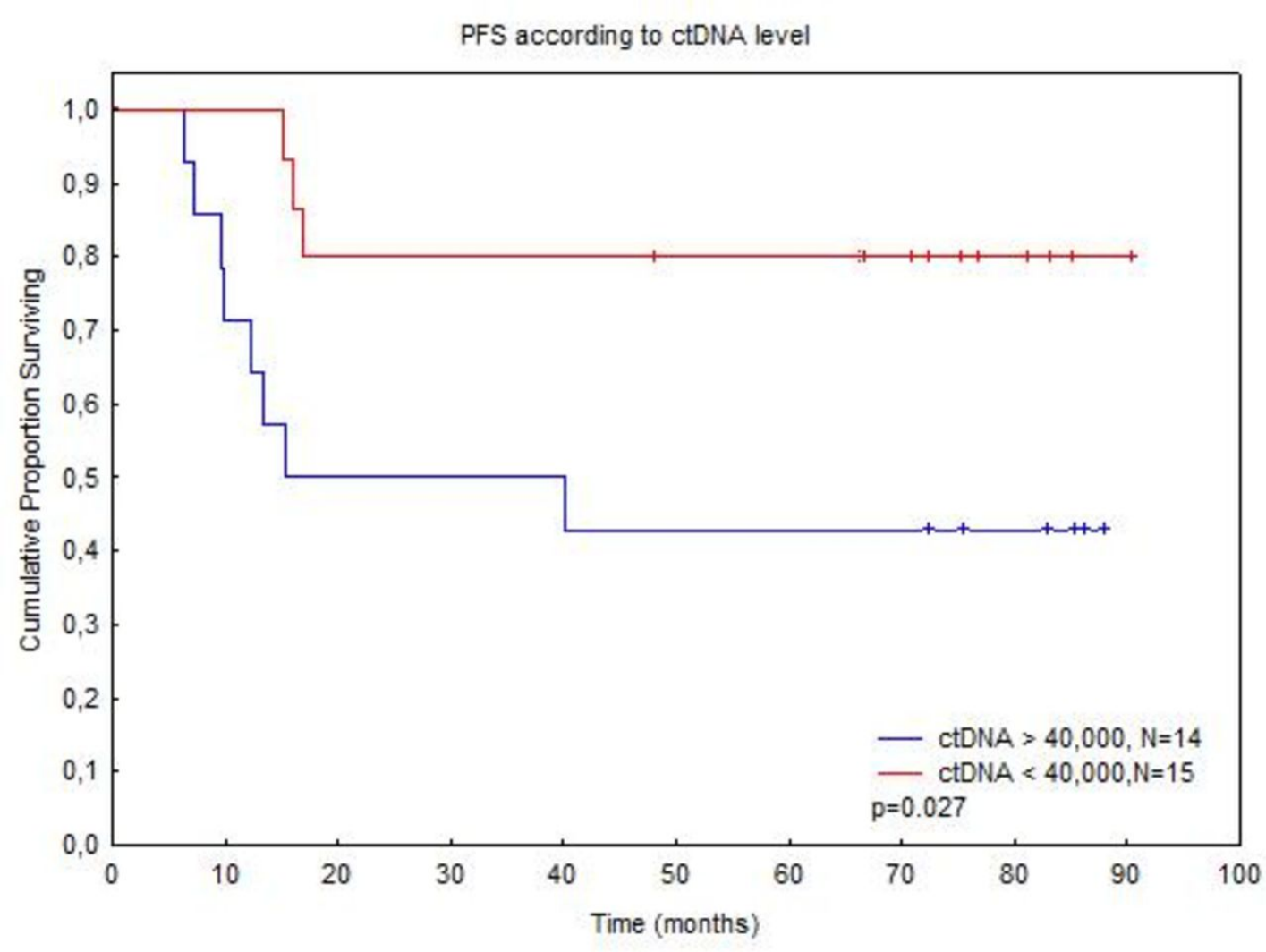
	No. of Subjects	Event	Censored	Median Survival (95%CL)
MTV<=510 and FLIPI2 0-2	88	29.5 % (26)	70.5 % (62)	Not reached
MTV>510 and FLIPI2 3-5	24	79.2 % (19)	20.8 % (5)	19.2 (11.2 ; 35.7)
MTV>510 or FLIPI2 3-5	55	52.7 % (29)	47.3 % (26)	54.7 (35.1 ; 78.7)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
MTV<=510 and FLIPI2 0-2	88	2.3 % (2)	97.7 % (86)	Not reached
MTV>510 and FLIPI2 3-5	24	12.5 % (3)	87.5 % (21)	Not reached
MTV>510 or FLIPI2 3-5	55	16.4 % (9)	83.6 % (46)	Not reached (78.7 ; NA)

Meignan et al, JCO, e-pub, 2017

PFS of FL according to the level of pre-tx circulating tumor DNA (Clonoseq)



Clémentine Sarkozy et al. Blood 2015;126:2675

Conclusions

- FLASH 30, POD24/12, PET-CT define a FL population at high risk for poor outcome
- Novel agents/combinations in trials for these patients
- US Intergroup trial in development
- The real challenge is to identify the molecular-genetic markers of these patients pre-tx (M7-FLIPI, TMTV, clonoseq) and conduct risk-adaptive trials
- More appropriate to focus on better induction regimens than trying to clean up failures