Mantle Cell Lymphoma

New scenario and concepts in front-line treatment for young patients

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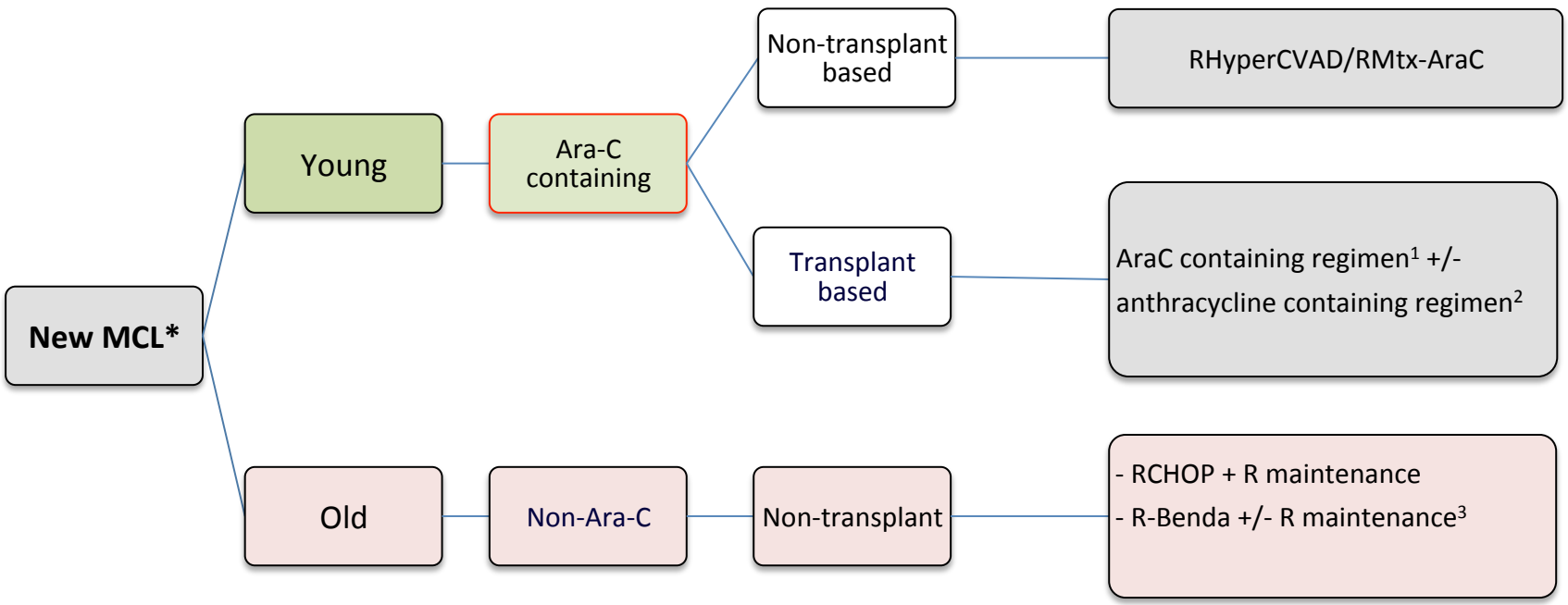
Friday March 16, 2018: 11:15-11:30 am

Treatment Options for Advanced Stage MCL



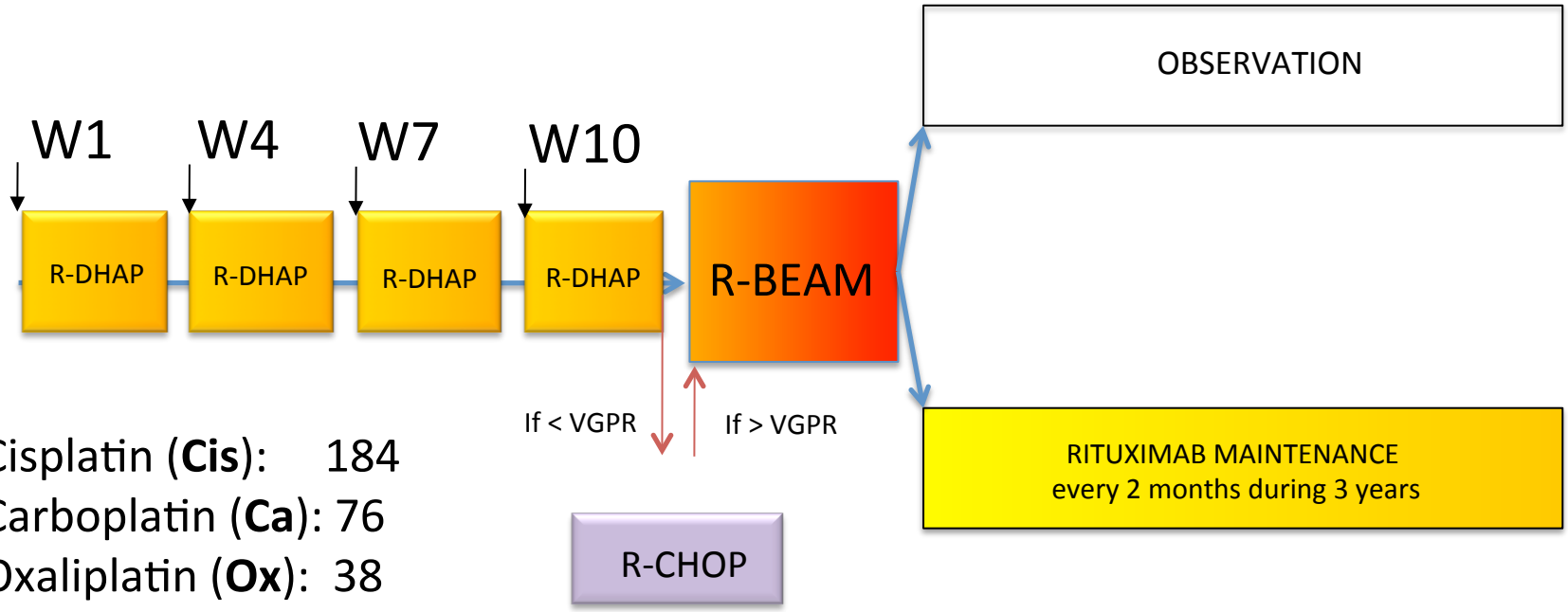
*Some patients may be candidate for initial observation. Patients with localized MCL should be considered for XRT containing therapy

[1] Examples: RDHAP, RDHAx, R-HiAraC

[2]Examples: RCHOP

[3]Although there is randomized data comparing (R)Benda with (R)CHOP, there in no randomized data confirming the benefit of R-maintenance after R-Benda in MCL

LyMA Study in MCL

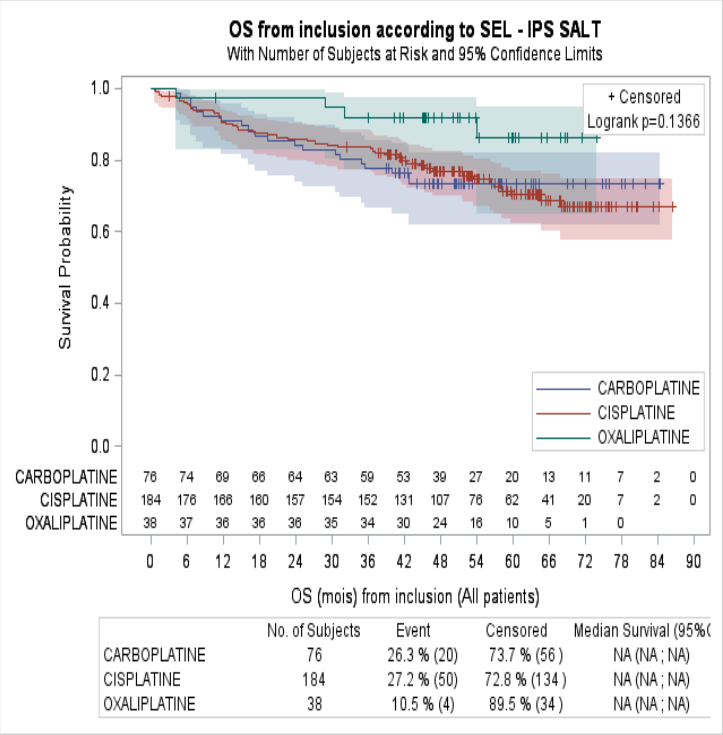


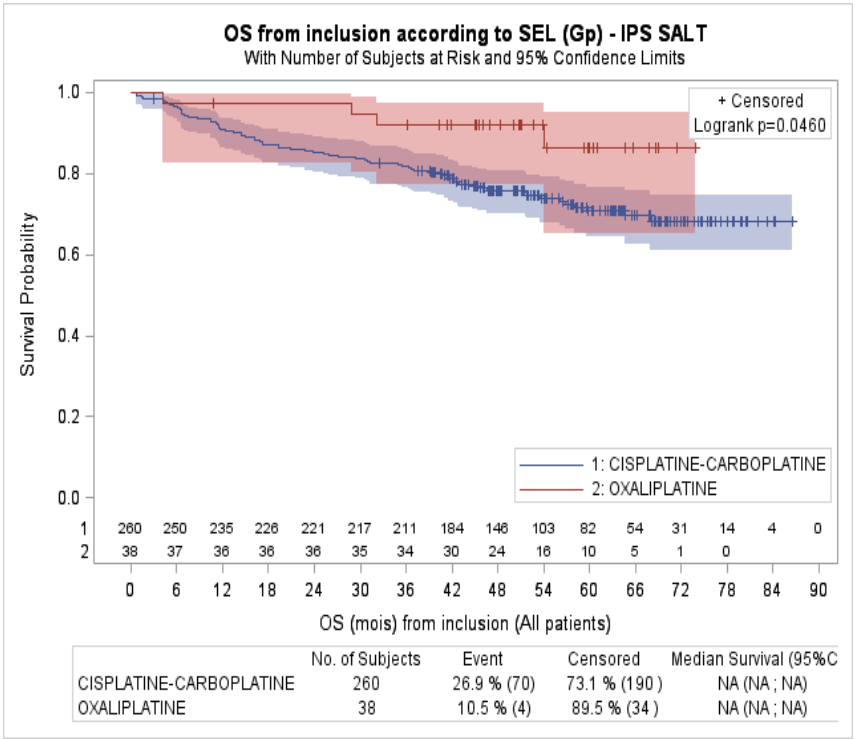
Cisplatin (**Cis**): 184
Carboplatin (**Ca**): 76
Oxaliplatin (**Ox**): 38

Le Gouill et al, ASH 2017
Le Gouill et al., NEJM 2017

LyMa Front Line Study in MCL

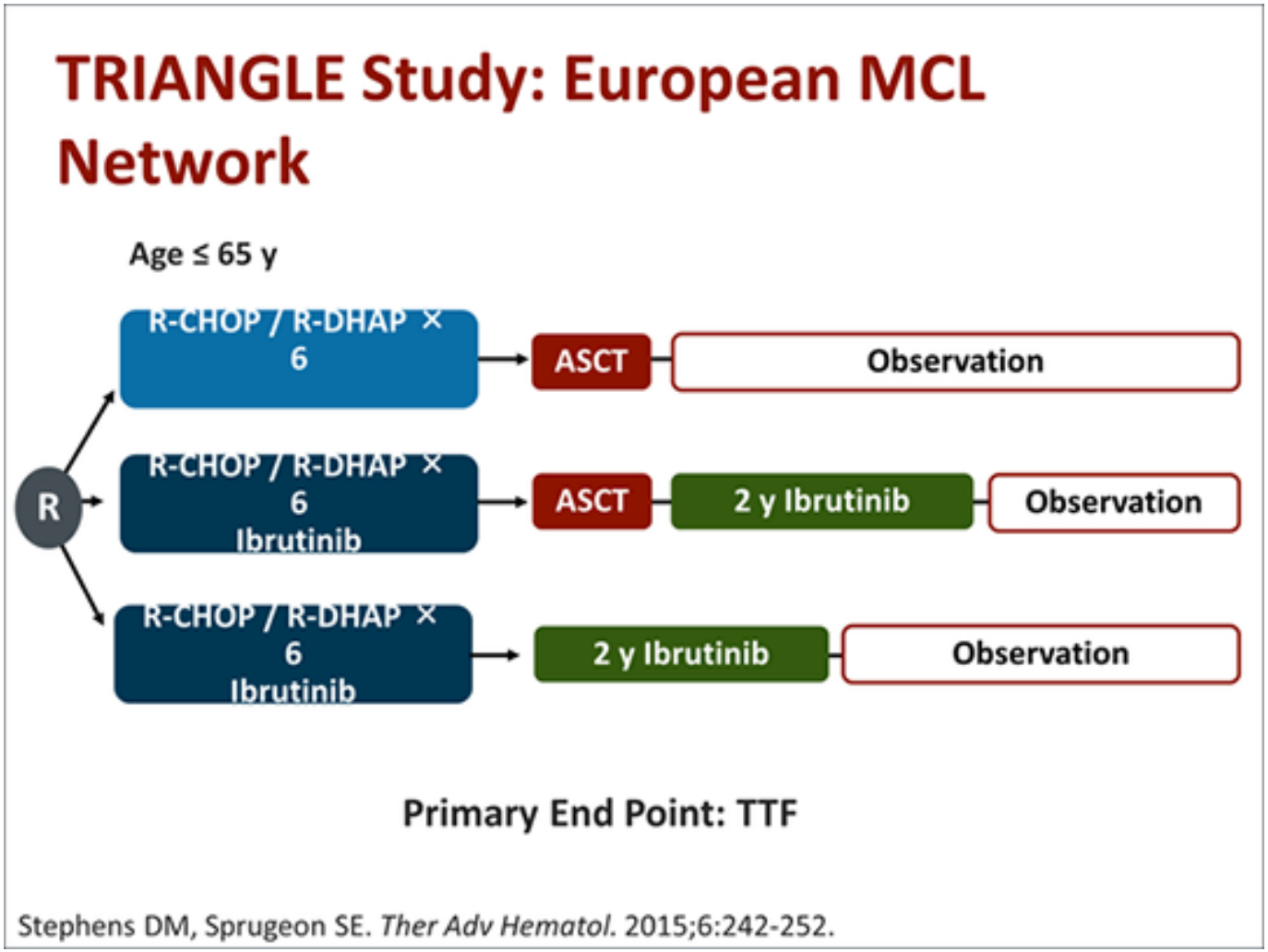
OS by type of platinum compound (ITT)





Le Gouill et al, ASH 2017
Le Gouill et al., NEJM 2017

Is ASCT Needed in 1st Line Regimens

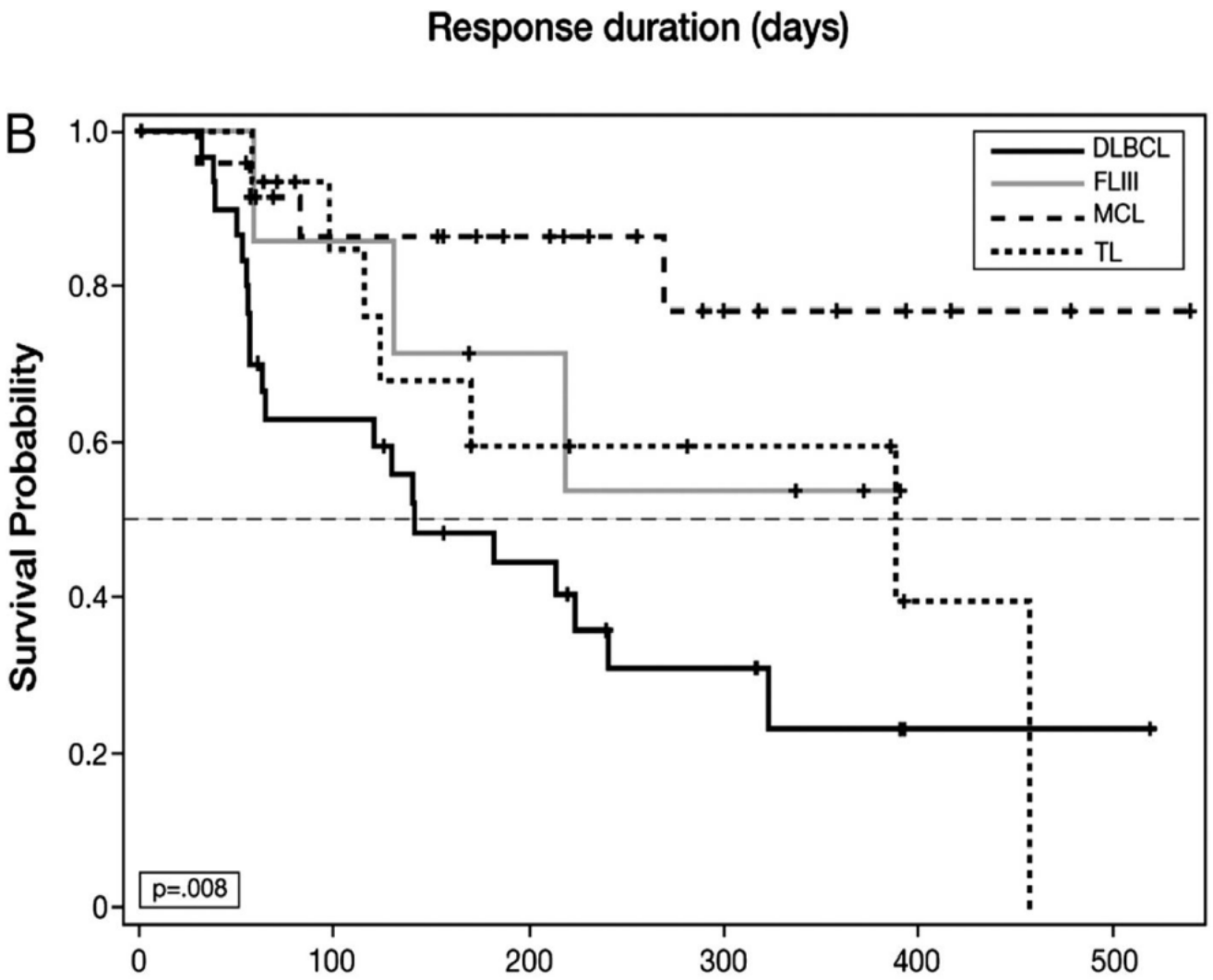


Lenalidomide in Lymphoma

Disease type	*N*	% ORR	CR/Cru *n* (%)	Median PFS (months)	Median response duration (months)
All patients	217	35%	13%	3.7	10.6
DLBCL	108	28%	7%	2.7	4.6
MCL	57	42%	21%	5.7	Not reached
TCL	33	45%	21%	5.4	12.8
FL-III	19	42%	11%	8.9	Not reached

Witzig, Annal Oncol (2011) 22:1622

Lenalidomide in NHL: Outcome



Witzig T E et al. 2011 Ann Oncol

MCL-001: Patient Demographics and Baseline Characteristics

Characteristic (N = 134)	No. of Patients (%)
Median age, years (range)	67 (43-83)
Age ≥ 65 years	85 (63)
Males	108 (81)
Stage III-IV	124 (93)
ECOG PS	
0-1	116 (87)
2	18 (13)
Intermediate to high MIPI score	90 (67)
High tumor burden*	77 (58)
Bulky disease†	44 (33)

*High tumor burden: ie, at least 1 lesion ≥ 5 cm in diameter or at least 3 lesions ≥ 3 cm in diameter

†Bulky disease: at least 1 lesion ≥ 7 cm

} By central radiology review

MCL-001: Prior Treatment History at Baseline

Characteristic (N = 134) Characteristic (N=134)	No. of Patients (%)
≥ 3-year duration of MCL	82 (61)
Median no. of prior treatment regimens (range)	4 (2-10)
No. of prior systemic anti-lymphoma therapies 2 3 ≥ 4	 29 (22) 34 (25) 71 (53)
Refractory to prior bortezomib	81 (60)
Received prior high-dose or dose-intensive therapy*	44 (33)
Refractory to last therapy	74 (55)
Time from last prior systemic anti-lymphoma therapy < 6 months ≥ 6 months	 96 (72) 38 (28)

*Includes stem cell transplant, hyperCVAD, or R-hyperCVAD.

Andre Goy et al. JCO 2013;31:3688-3695

MCL-001: Efficacy of Lenalidomide

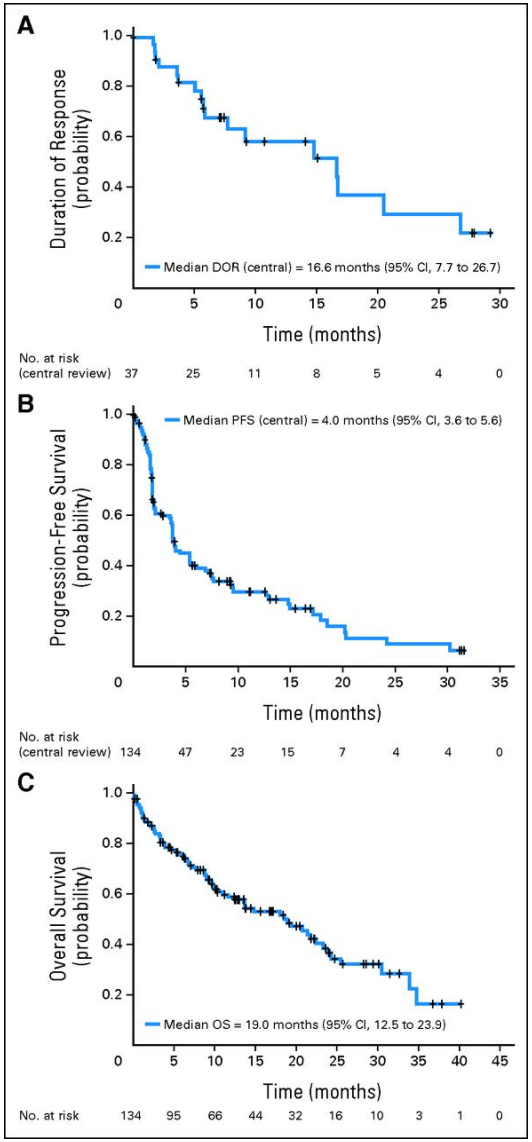
Efficacy Parameter (N = 134)	Central Review n (%)	Site Review n (%)
ORR*	37 (28)	43 (32)
CR/CRu	10 (8)	22 (16)
PR	27 (20)	21 (16)
SD	39 (29)	36 (27)
PD	35 (26)	43 (32)
Median DOR, months (95% CI)	16.6 (7.7-26.7)	18.5 (12.8-26.7)
Median DOR for CR/CRu, months (95% CI)	16.6 (16.6-NR)	26.7 (16.8-NR)

NR, not reached.
*No response assessments were available for 23 patients (central) and 12 patients (investigator).

MCL-001: Efficacy of Lenalidomide

Efficacy Parameter	Central Review (N = 134)	Site Review (N = 134)
Median time to response, months (range)	2.2 (1.7-13.1)	2.0 (1.7-15.9)
Median time to CR/CRu, months (range)	3.7 (1.9-29.5)	5.6 (1.8-24.2)
Median PFS, months (95% CI)	4.0 (3.6-5.6)	3.8 (3.5-6.8)
Median OS, months (95% CI)	19.0 (12.5-23.9) Median follow-up 9.9 months	

Lenalidomide in relapsed/refractory mantle-cell lymphoma



Duration of Response

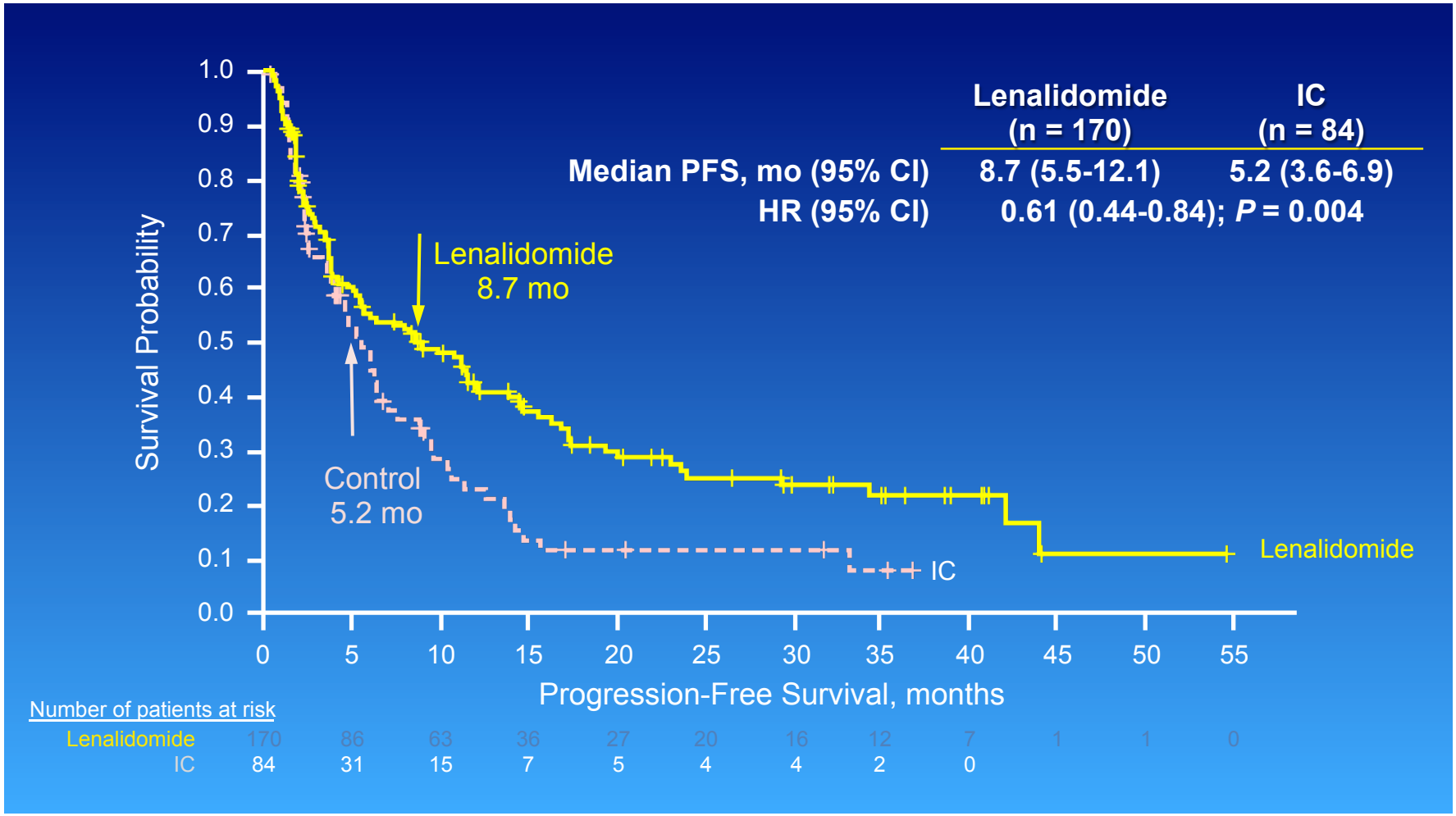
PFS

OS

Andre Goy et al. JCO 2013;31:3688-3695

Rel. Mantle cell lymphoma

Lenalidomide



Trneny, Lancet Oncol 2016

Initial Treatment with Lenalidomide Plus Rituximab for Mantle Cell Lymphoma: 5-year Follow-up and Correlative Analysis from a Multi-center Phase II Study

J Ruan, P Martin, P Christos, L Cerchietti, B Shah, SJ Schuster, W Tam, A Rodriguez, D Hyman, N Calvo-Vidal, L Roman-Gonzalez, S Smith, J Svoboda, RR Furman, M Coleman, JP Leonard

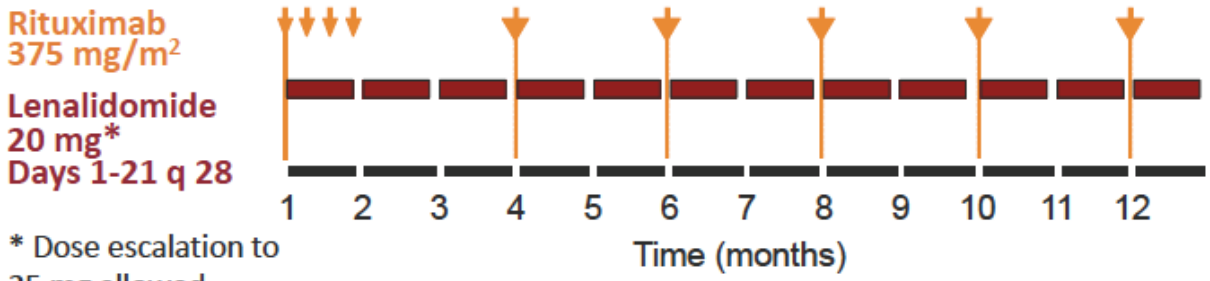
Weill Cornell Medicine; Moffitt Cancer Center; U Penn Abramson Cancer Center; U Chicago Medical Center

Background and Rationale

- Lenalidomide, an immunomodulatory compound with effects on tumor cells and the microenvironment, is active in recurrent MCL
  - Single-agent lenalidomide
    - ORR 28%, CR 8% (*Goy et al, JCO 2013*)
    - ORR 40%, CR 5% *(Trneny et al, Lancet Oncol 2016)*
  - Combination Len +R
    - ORR 57%, CR 36% (*Wang et al, Lancet Oncol 2012)*
- Rituximab maintenance extends survival in frontline settings
  - European Elderly MCL Trial with MR x POD following R-CHOP
    - 4-yr PFS 58%, 4-yr OS 87% *(Kleuin-Nelemans et al NEJM2012)*
    - 5-yr PFS 51%, 5-yr OS 79% *(Hoster et al ASH 2017 Abstract 153)*
  - LYSA study with MR x 3 years following ASCT
    - 4-yr PFS 83%, 4-yr OS 89% *(Le Gouill et al NEJM 2017)*

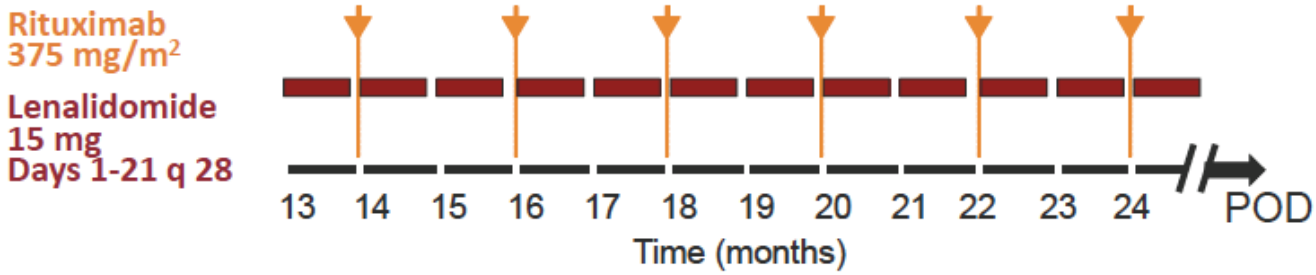
Study Design

Induction (cycles 1-12)



* Dose escalation to 25 mg allowed

Maintenance (cycle 13 - POD)



Response assessment: Cheson 2007; DVT prophylaxis: ASA
Scan frequency: every 3 months Y1-2, every 6 month Y3 & beyond

Ruan et al, ASH 2017

Baseline Patient and Disease Characteristics

Clinical Characteristics		Number	Percentage
Number of patients		38	100%
Median age in year (range)		65 (42-86)	
Gender	Male	27	71%
	Female	11	29%
ECOG	0-1	37	97%
	> 1	1	3%
Stage	III-IV	38	100%
LDH	Elevated	14	37%
Bone marrow involvement		34	89%
MIPI score			
Low risk (score < 5.7)		13	34%
Intermediate risk (5.7≤score<6.2)		13	34%
High risk (score ≥ 6.2)		12	32%
Ki67			
< 30%		26	68%
≥ 30%		8	21%

Ruan et al, ASH 2017

Efficacy: Objective Best Responses

Response	No. of patients	ITT (n=38)	Evaluable (n=36)
Overall response	33	87%	92%
CR	23	61%	64%
PR	10	26%	28%
SD	1	3%	3%
PD	2	5%	6%
Inevaluable#	2		
Median follow-up	61 months (range 21-74)		
Median time to PR	3 months (range 3-13)		
Median time to CR	11 months (range 3-22)		

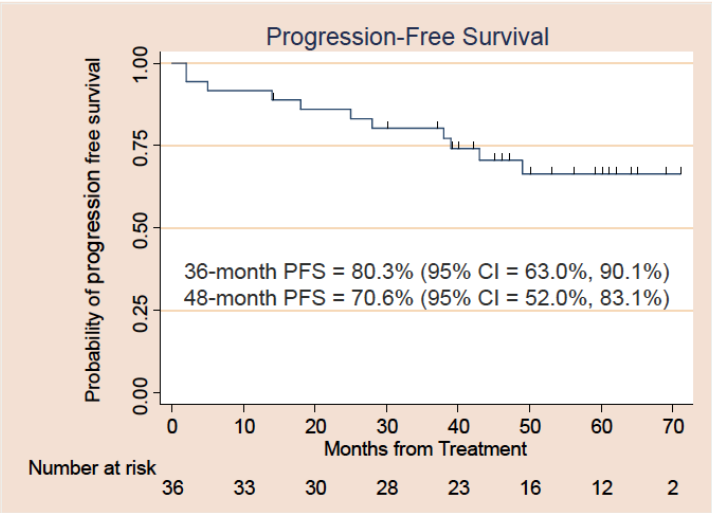
ITT: Intent-to-treat

#: Treatment was discontinued in 2 patients due to tumor flare without progression before tumor response evaluation.

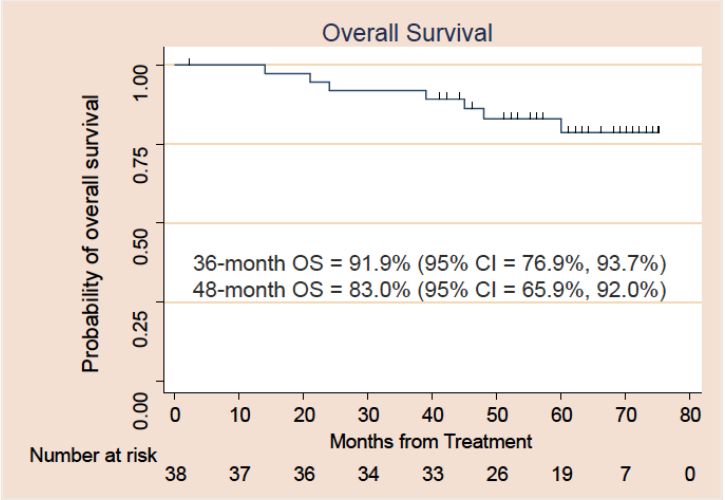
Ruan et al, ASH 2017

Rituximab + Lenalidomide For Newly Diagnosed MCL

Efficacy: Progression-Free Survival



Efficacy: Overall Survival



Ruan et al, ASH 2017

R2CHOP for Non-GCB Type DLBCL

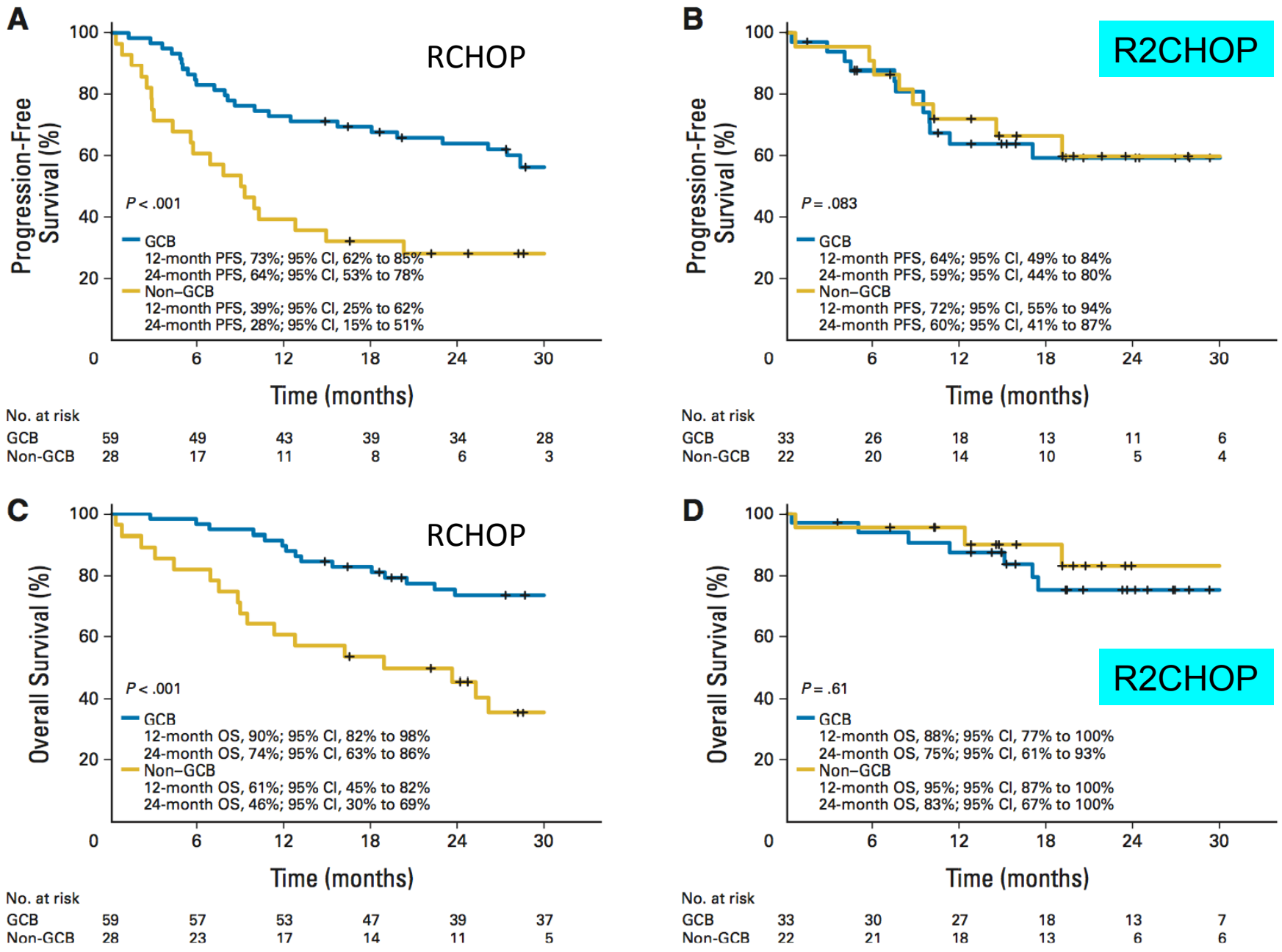
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Lenalidomide Combined With R-CHOP Overcomes Negative Prognostic Impact of Non–Germinal Center B-Cell Phenotype in Newly Diagnosed Diffuse Large B-Cell Lymphoma: A Phase II Study

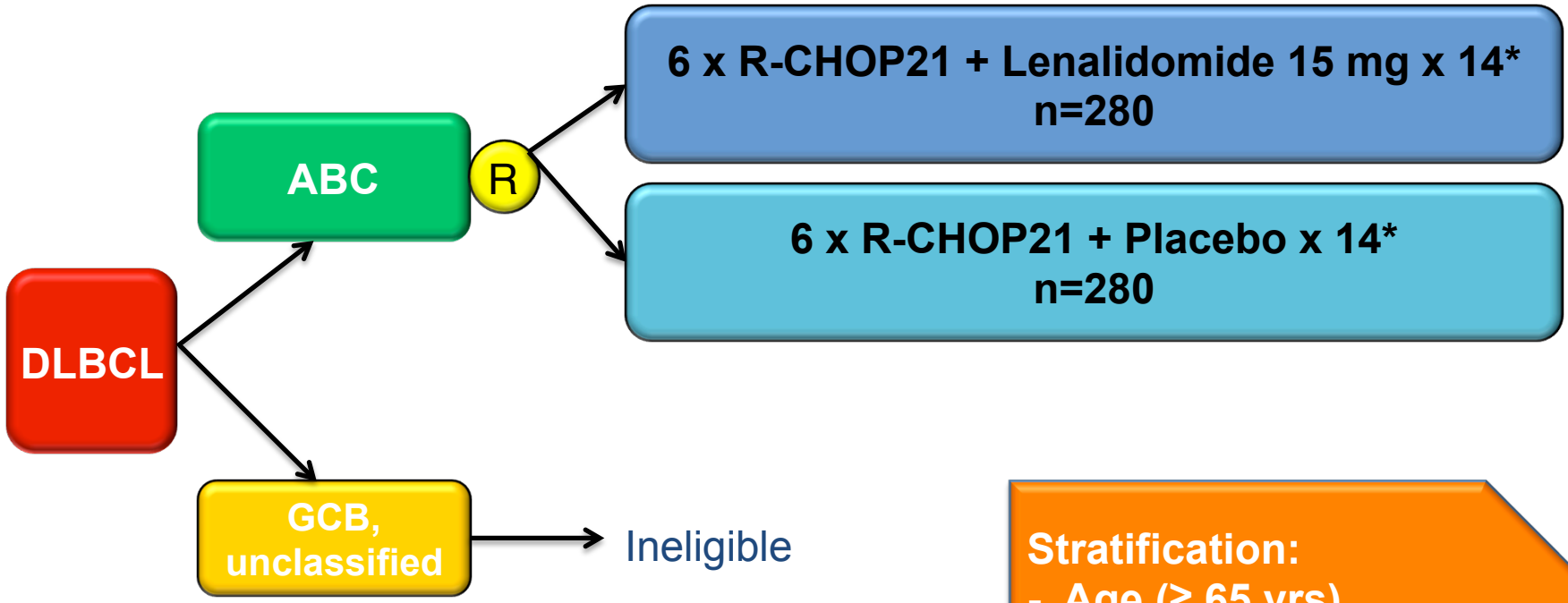
Grzegorz S. Nowakowski, Betsy LaPlant, William R. Macon, Craig B. Reeder, James M. Foran, Garth D. Nelson, Carrie A. Thompson, Candido E. Rivera, David J. Inwards, Ivana N. Micallef, Patrick B. Johnston, Luis F. Porrata, Stephen M. Ansell, Thomas M. Habermann, and Thomas E. Witzig

Nowakowski G et al J Clin Oncol. 2014. Epub 2014/08/20



Nowakowski G et al J Clin Oncol. 2014. Epub 2014/08/20

ROBUST: Clinical Study Schema



- Newly diagnosed DLBCL of ABC type
- IPI ≥ 2; ECOG PS ≤ 2; Age 18–80
- Primary Endpoint = PFS
- N = 560

Stratification:
- **Age (≥ 65 yrs)**
- **Bulky disease (≥7 cm)**
- **IPI (2 versus 3)**

MSKCC Front line study for MCL (15-196)

PI: Anita Kumar

Induction
Len (15mg D1-14)-RCHOP
x 4 cycles

- **KEY ELIGIBILITY CRITERIA**
  - **Clinical stage 2 - 4**
  - **Ages ≥18, KPS ≥ 70%**
  - **ANC≥1500 and Plt ≥100K**
  - **Adequate organ function**

PET/CT
ctDNA

Consolidation
R-HIDAC x 2 cycles

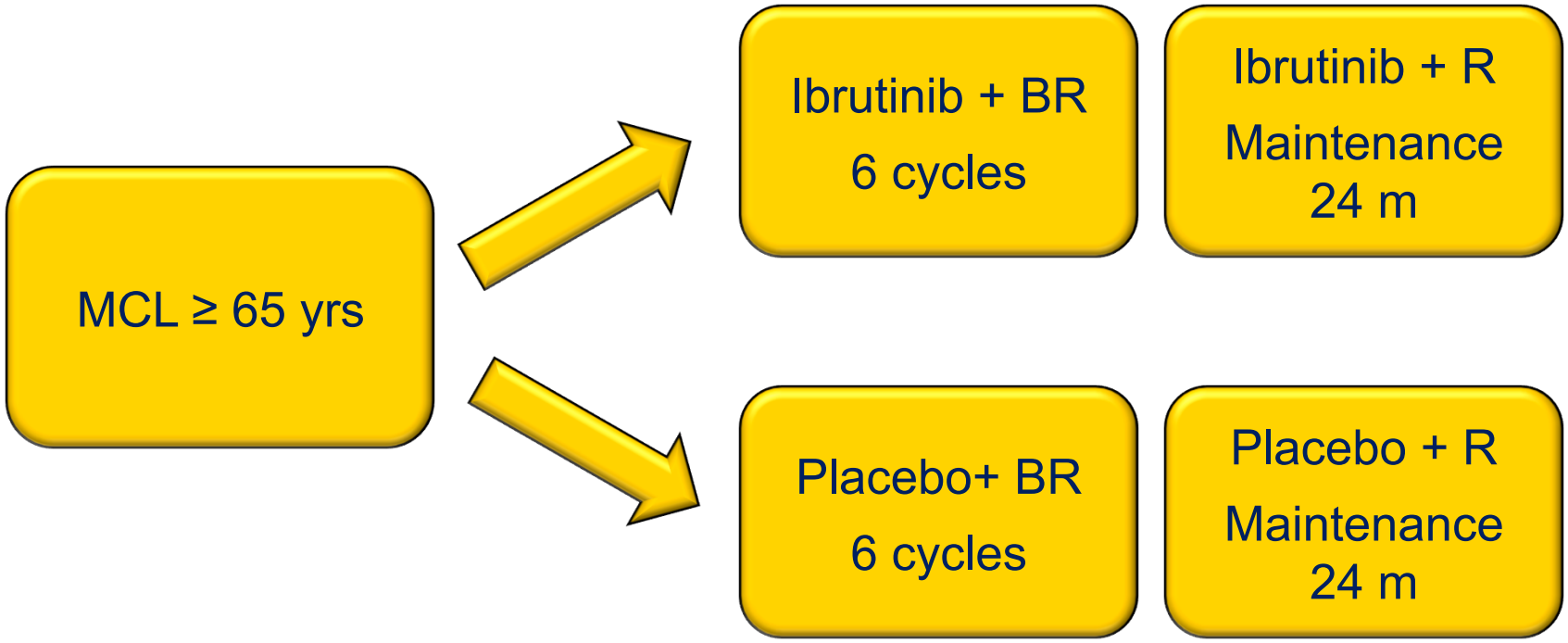
HIDAC :
< 65 years: 3g/m2
65 –70 years: 2g/m2
> 70 years: 1g/m2

PET/CT
ctDNA

Maintenance
Lenalidomide-Rituximab
x 6 months

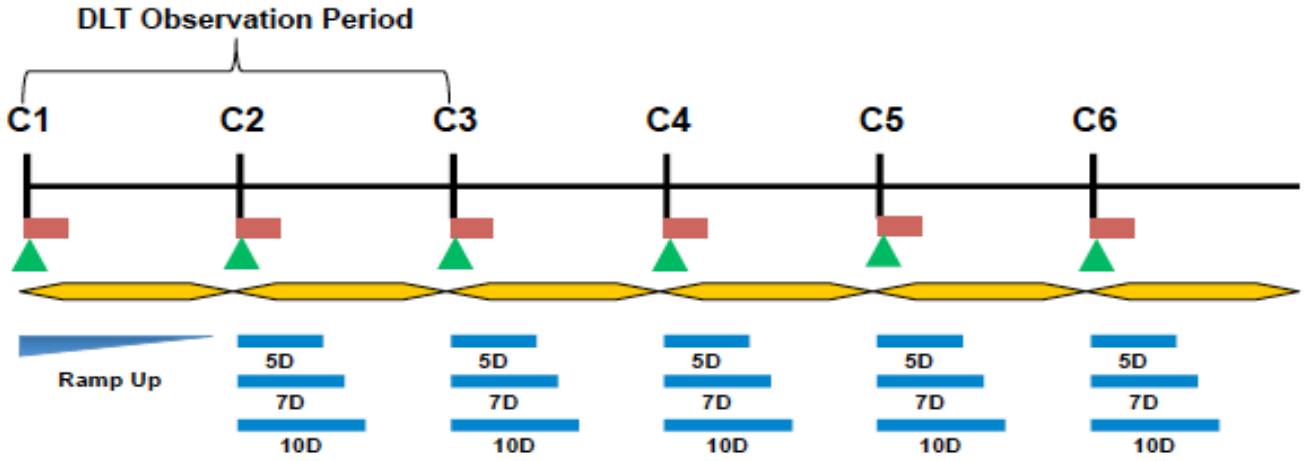
PET/CT
ctDNA

SHINE: Elderly MCL Phase III RCT



MSKCC Phase I Study of Bendamustine, Rituximab, Ibrutinib, and Venetoclax in Relapsed, Refractory Mantle Cell Lymphoma

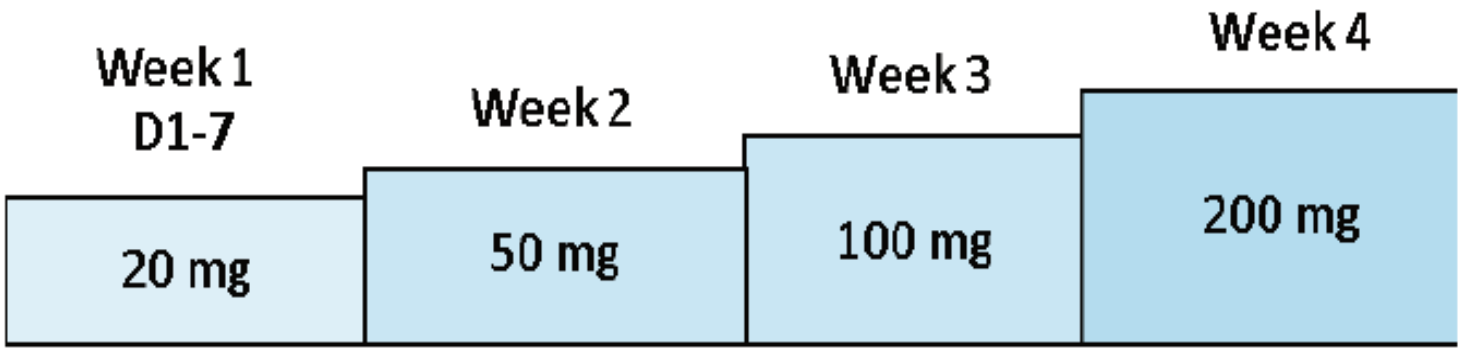
PI: Anita Kumar



Venetoclax Dose Finding Cohorts		
Cohort	Dose	Duration
-1	400 mg	3 days
1	400 mg	5 days
2	400 mg	7 days
3	400 mg	10 days

Traditional 3+3 phase 1 design on sequential dosing cohorts in order to determine the MTD of VEN when given with BR-I.

Cycle 1 - Ramp Up



Low and Medium Risk Groups:

•20 mg daily 1 week, 50 mg daily for week 2, 100 mg daily for week 3, and 200 mg daily for week 4

High Risk Group:

•VEN at 20 mg will be received for 7 days and then the ramp-up will proceed with 50mg x 5 days, 100mg x 7 days, 200mg x 7 days.

•Hospitalized prior and 24hrs after to receive their initial doses of 20 mg, 50mg, 100mg, and 200mg.

•For initial dosing at 20mg, BR-I will be given on day 1-2 as outpatient and VEN at 20 mg in the inpatient setting on day 3.

Study Cohorts

- The first cohort of patients will be treated in cohort 1 at a venetoclax dose of 400 mg daily for a duration of 5 days.
- Dose Finding Cohorts:

Venetoclax Dose Finding Cohorts		
Cohort	Dose	Duration
-1	400 mg	3 days
1	400 mg	5 days
2	400 mg	7 days
3	400 mg	10 days

Conclusions

Frontline therapy of MCL in young patients

- R-DHAoX + BEAM + R maintenance is the current standard of care
- The role of of ASCT in 1st line regimens needs to be examined
- The Triangle study will address the role of ASCT, but the trial has no R maintenance
- Ibrutinib + Venetoclax backbone is highly active in relapsed MCL, and is currently being investigated in 1st line regimens