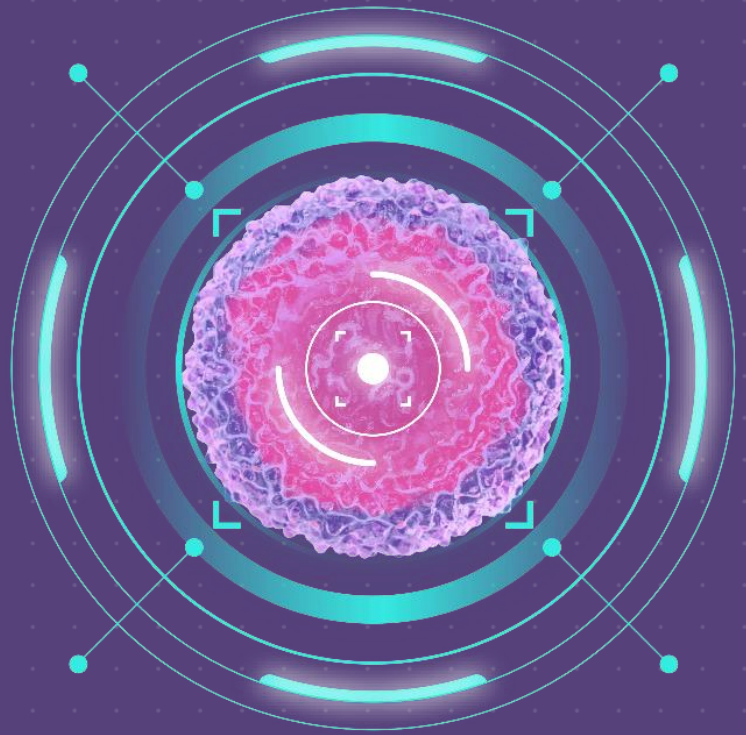
LymphomaHub

LYMPHOID MALIGNANCIES:

CAN WE *SWITCH* TO **CHEMO-FREE?**



Scientific Education Support

Lymphoma Hub is delivered by Scientific Education Support (SES)

MCL – chemotherapy-free regimens: pros and cons

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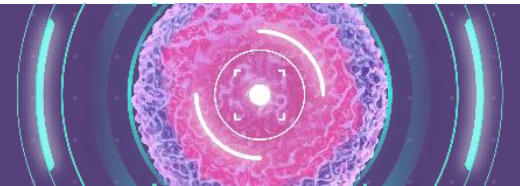
Derriford Hospital Plymouth Hospitals NHS Trust Plymouth, UK

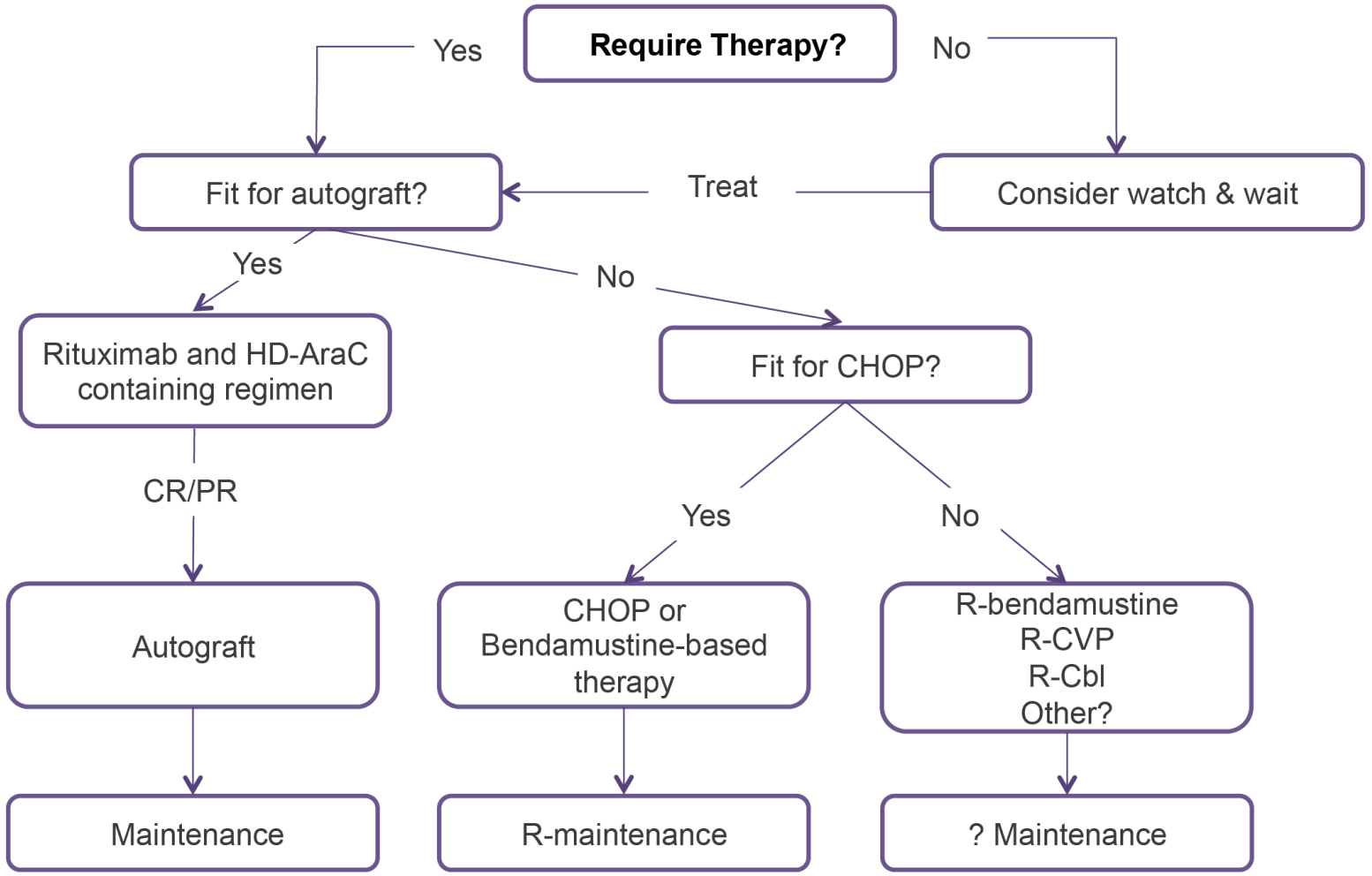
LymphomaHub

Disclosures – Simon Rule

Research support/P.I.	Janssen
Speakers Bureau	Janssen
Honoraria	AbbVie, Janssen, Celgene, Roche, Napp, Pharmacyclics, Gilead, Sunesis, Celtrion, AstraZeneca, Beigene, TG Therapeutics
Scientific Advisory Board	AbbVie, Janssen, Celgene, Roche, Napp, Pharmacyclics, Gilead, AstraZeneca, Celtrion

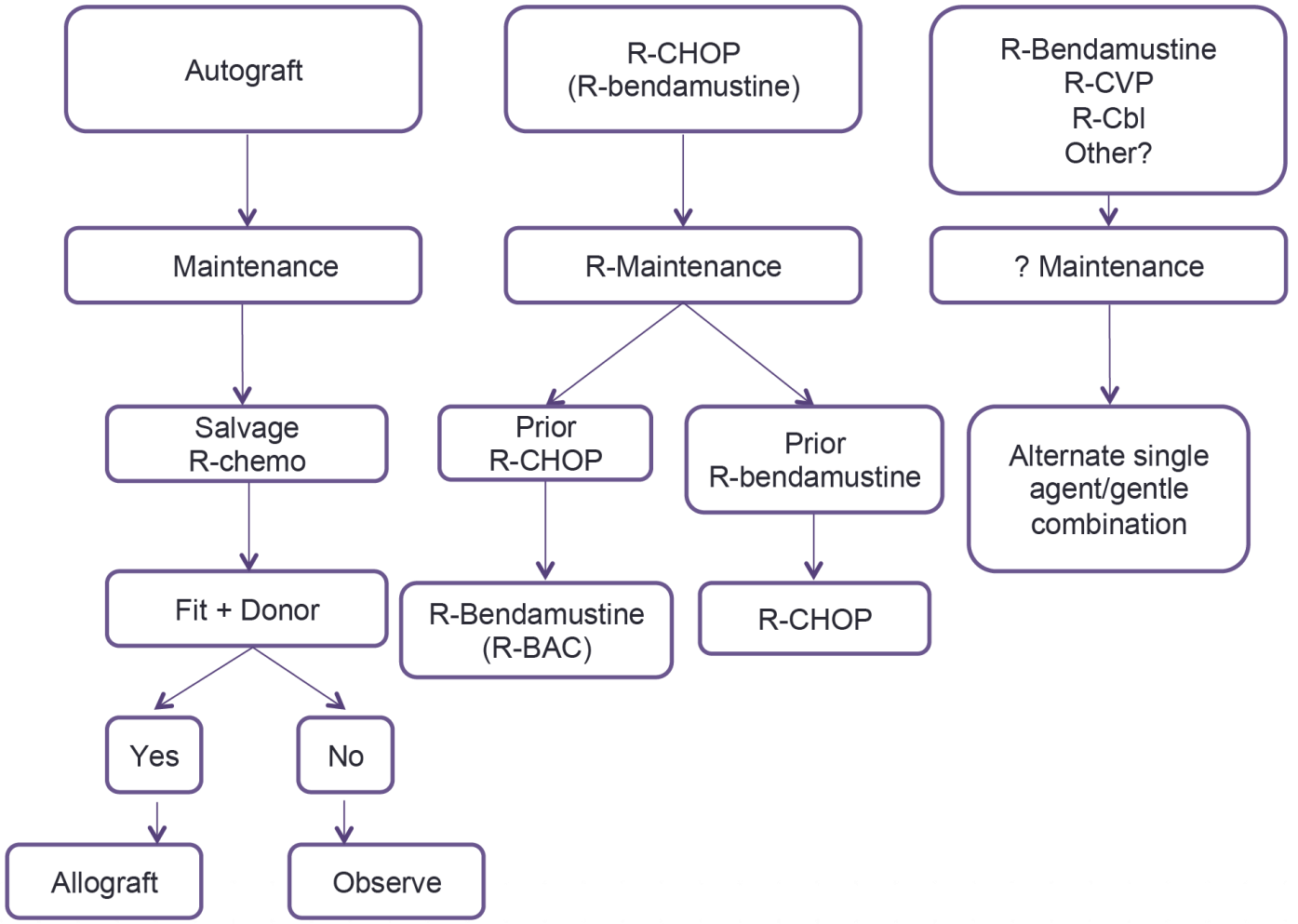


MCL treatment algorithm



Cbl, chlorambucil; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR, complete response; CVP, cyclophosphamide, vincristine, and prednisolone; HD-AraC, high-dose cytarabine; PR, partial response; R, rituximab;
Figure adapted from Campo E, and Rule S. *Blood.* 2015;125:48–55

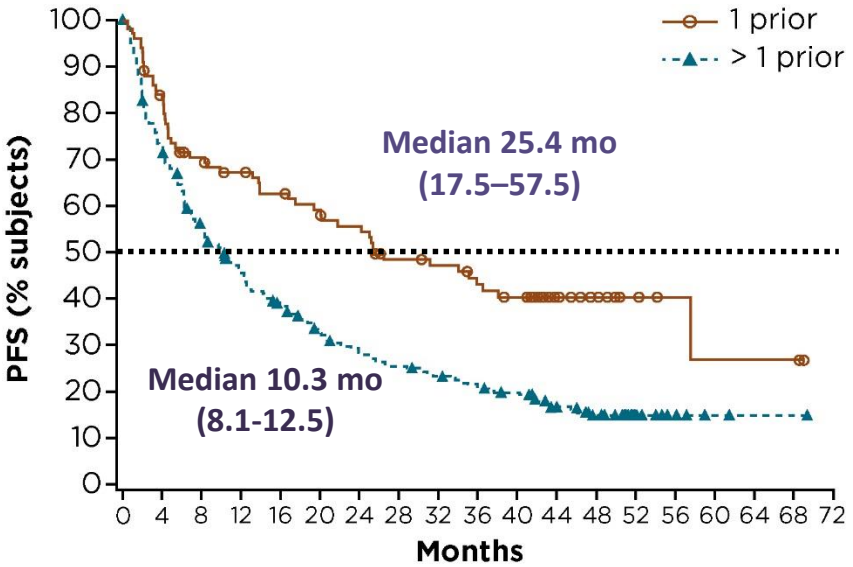
Historic approach to R/R MCL prior to novel agents



Cbl, chlorambucil; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CVP, cyclophosphamide, vincristine, and prednisolone; R, rituximab; R-BAC, rituximab, bendamustine and cytarabine

Ibrutinib: PFS and OS by prior line of therapy: Data from a pooled clinical trial cohort in R/R MCL

Progression-free survival

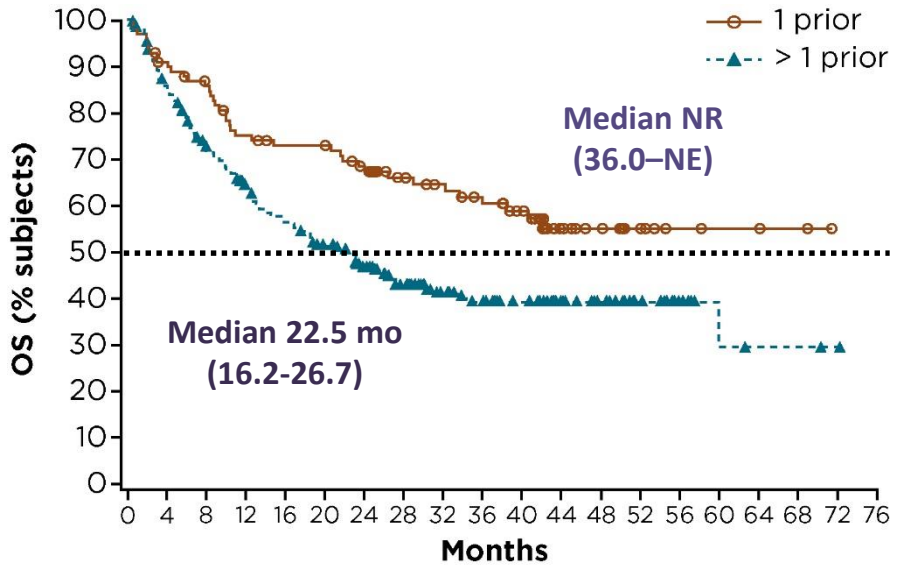


Patients at risk

1 prior	99	81	66	61	55	51	47	38	36	31	27	16	12	5	3	2	2	2	0
> 1 prior	271	193	147	117	97	79	67	60	54	47	43	30	22	12	5	2	1	1	0

Median PFS overall (95% CI): 12.5 (9.8–16.6) months

Overall survival



Patients at risk

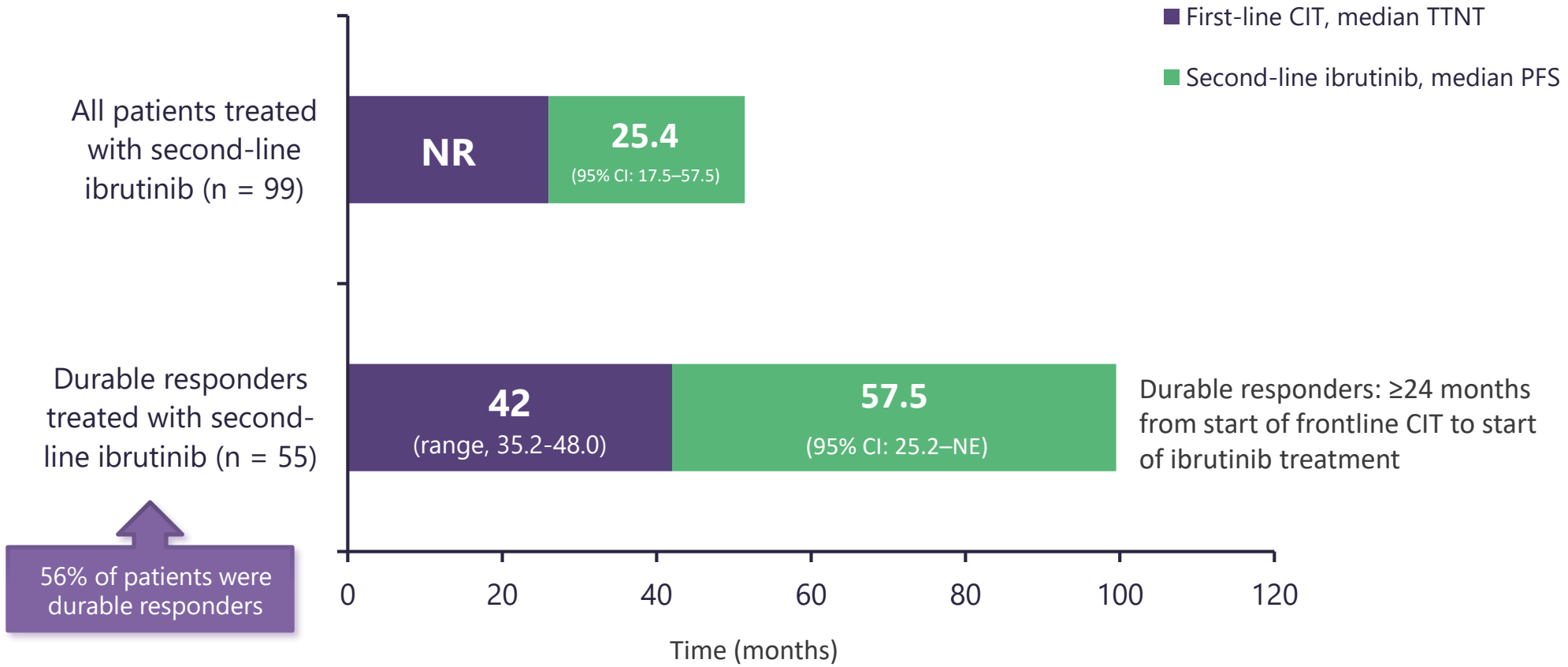
1 prior	99	88	81	70	66	66	59	50	46	41	36	20	15	8	4	3	3	2	0	0
> 1 prior	271	227	186	158	139	122	103	83	68	59	50	37	29	16	8	3	2	2	1	0

Median OS overall (95% CI): 26.7 (22.5–38.4) months

Median PFS was just over 2 years in patients with 1 prior line of therapy

Patients censored from OS analysis upon study discontinuation
CI, confidence interval; NE, not estimable; NR, not reached; mo, months; OS, overall survival; PFS, progression-free survival
Rule S, *el al. Haematologica*. 2019;104:e211–4

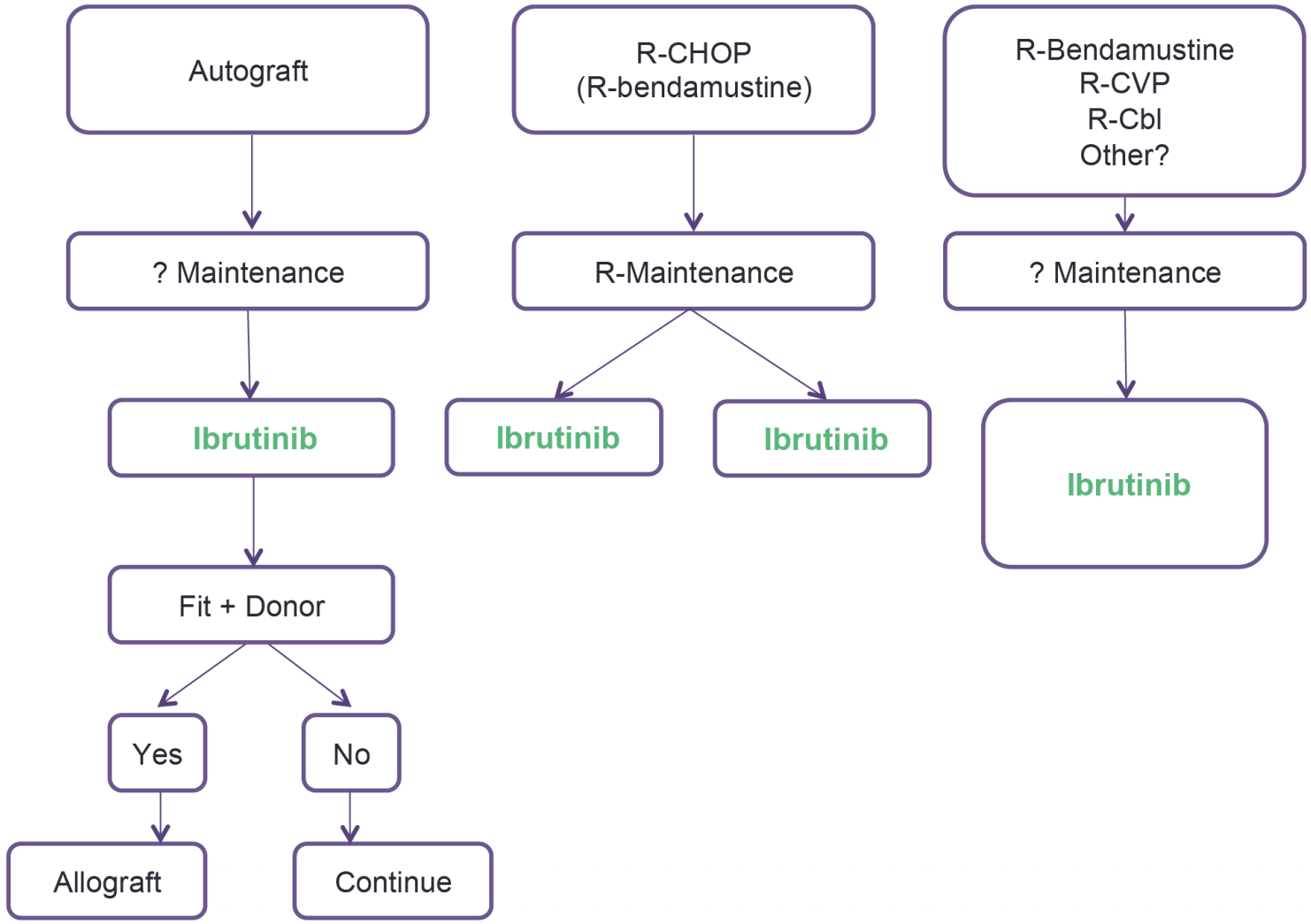
Median PFS with second-line ibrutinib: Data from a pooled clinical trial cohort in R/R MCL



CI, confidence interval; CIT, chemoimmunotherapy; PFS, progression-free survival; NR, not reported; TTNT, time to next treatment, defined as time from start of frontline CIT to start of ibrutinib 2nd line therapy.

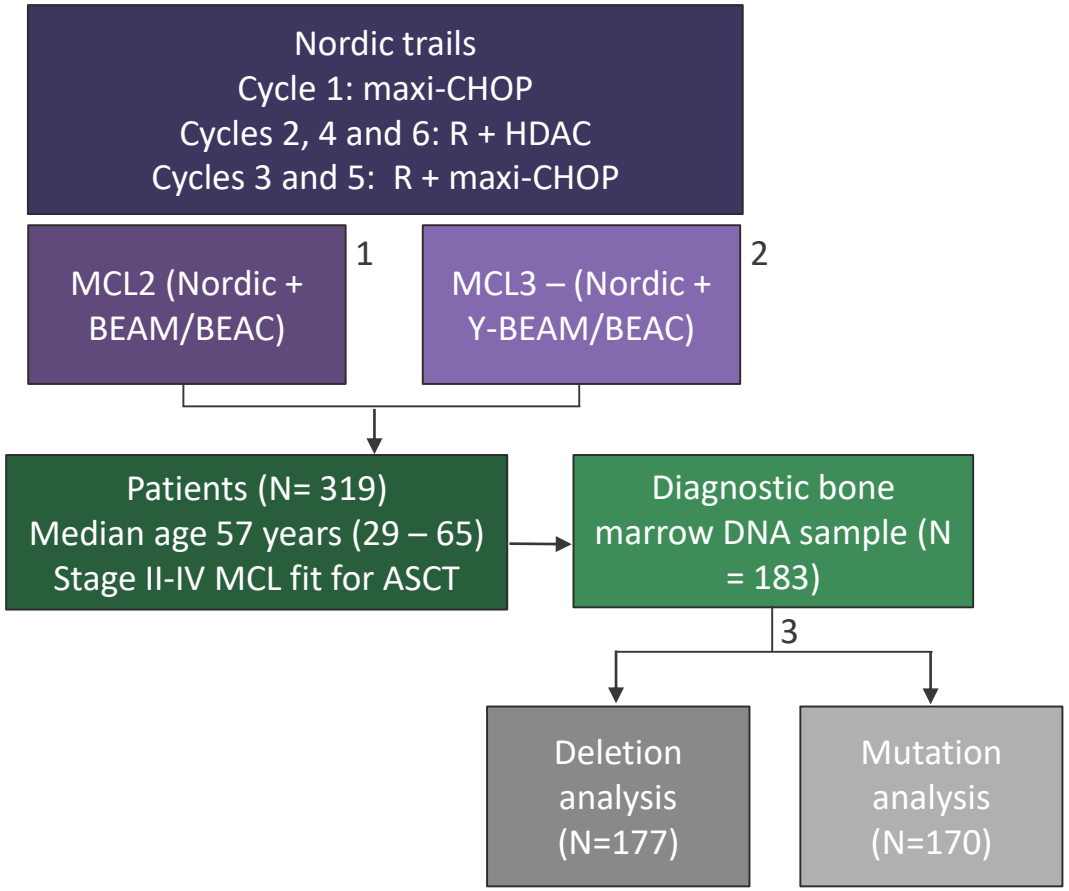
Rule S, *el al. Haematologica*. 2019;104:e211–4

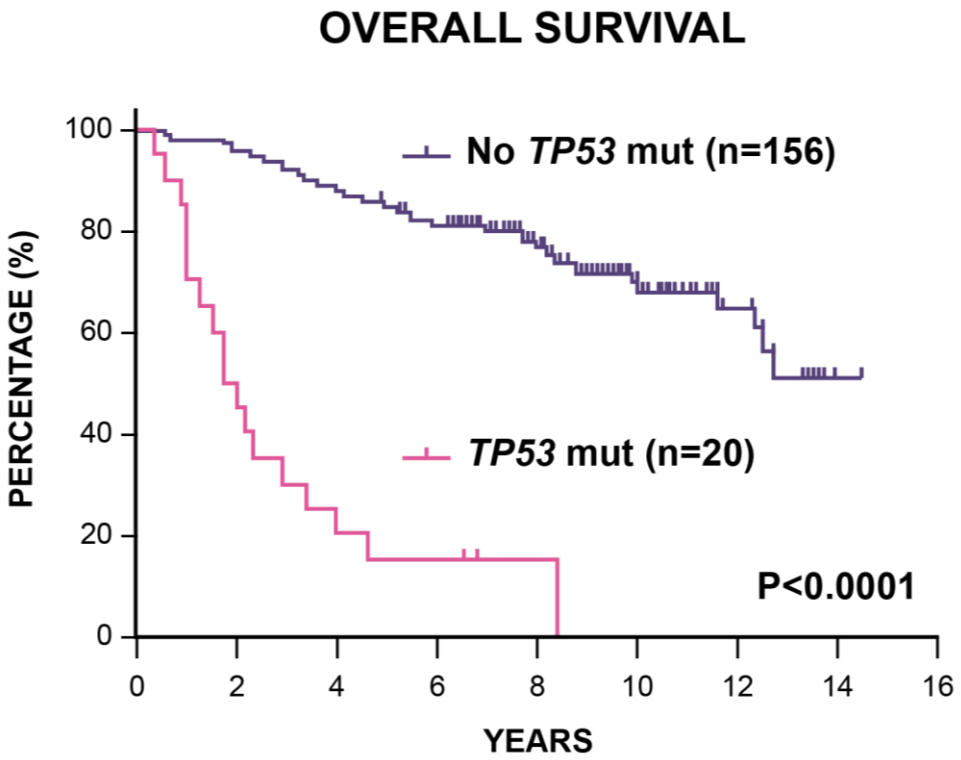
My view



Cbl, chlorambucil; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CVP, cyclophosphamide, vincristine, and prednisolone; R, rituximab

Impact of *TP53* in Nordic trials





ASCT, autologous stem cell transplantation; BEAM, bis-chloroethylnitrosourea, etoposide, cytarabine, and melphalan; BEAC, bis-chloroethylnitrosourea, etoposide, cytarabine, and cyclophosphamide, ; maxi -HOP, dose-intensified cyclophosphamide, vincristine, doxorubicin, prednisone ; HDAC, high-dose cytarabine; R, rituximab; Y, 90Y-ibritumomab-tiuxetan;

1. Geisler CH et al. Blood. 2008; 112:2687-269; 2. Kolstad *et al*. Blood. 2014; 123:2953-2959; 3. Eskelund CW, *et al. Blood.* 2017;17:1903–10

Ibrutinib outcomes by *TP53* mutational status

Patients with mutated *versus* Wild-Type *TP53*

	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Best Response		
			ORR, %	CR, %	PR, %
Patients with known TP53 mutational status: 144					
Mutated TP53 (n = 20)*	4.0 (2.1-8.3)	10.3 (2.5-12.6)	55.0	0	55.0
Wild-type TP53 (n = 124)	12.0 (7.1-15.6)	33.6 (18.3-NE)	70.2	25.0	45.2

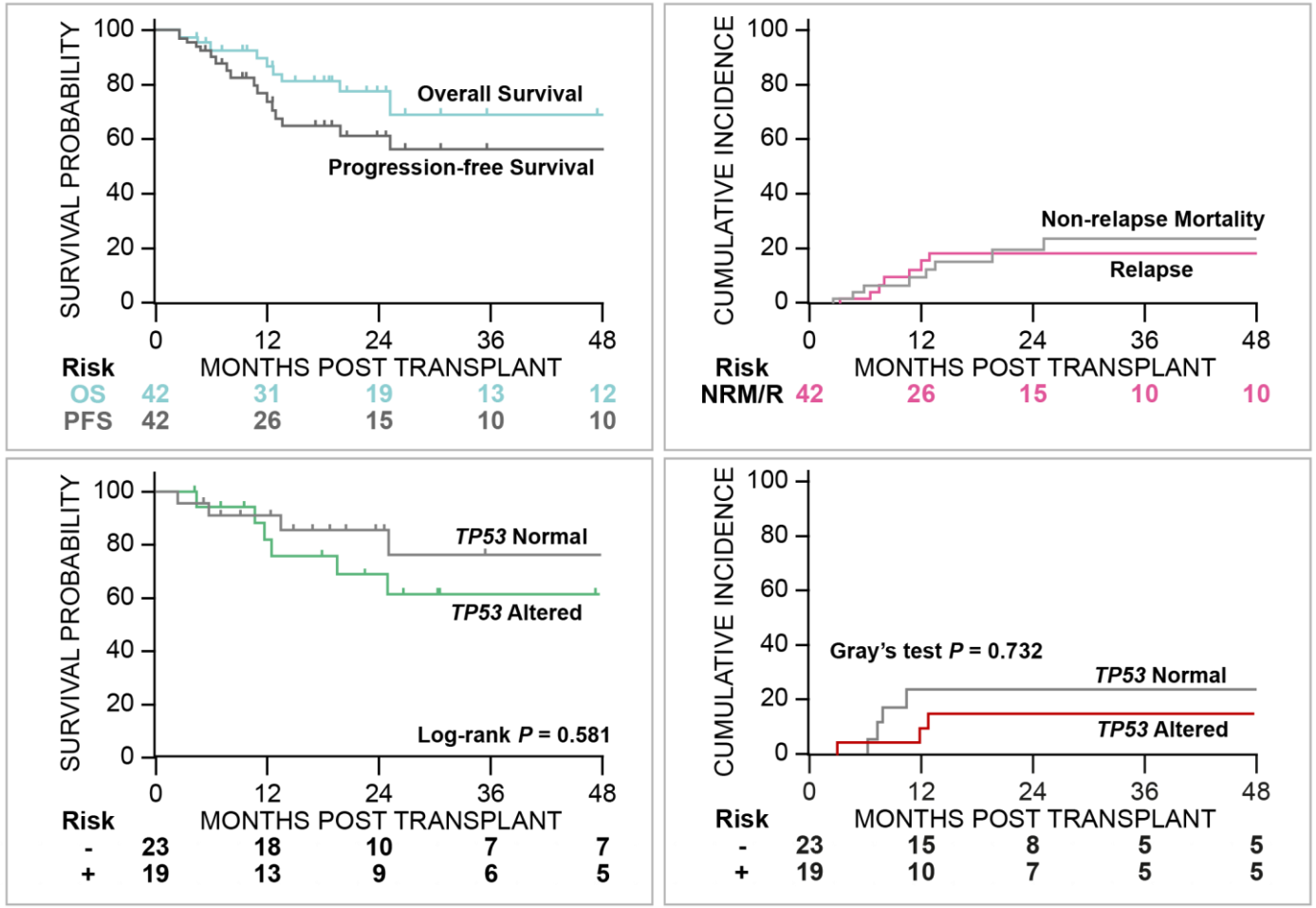
*Response data missing for 3 patients.

Responses to ibrutinib were less favorable in patients with mutated *versus* wild-type *TP53*

CI, confidence interval; CR, complete response; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response

Rule S, *el al. Haematologica*. 2019;104:e211–4

Allogeneic hematopoietic cell transplantation impacts on outcomes of MCL with *TP53* alterations

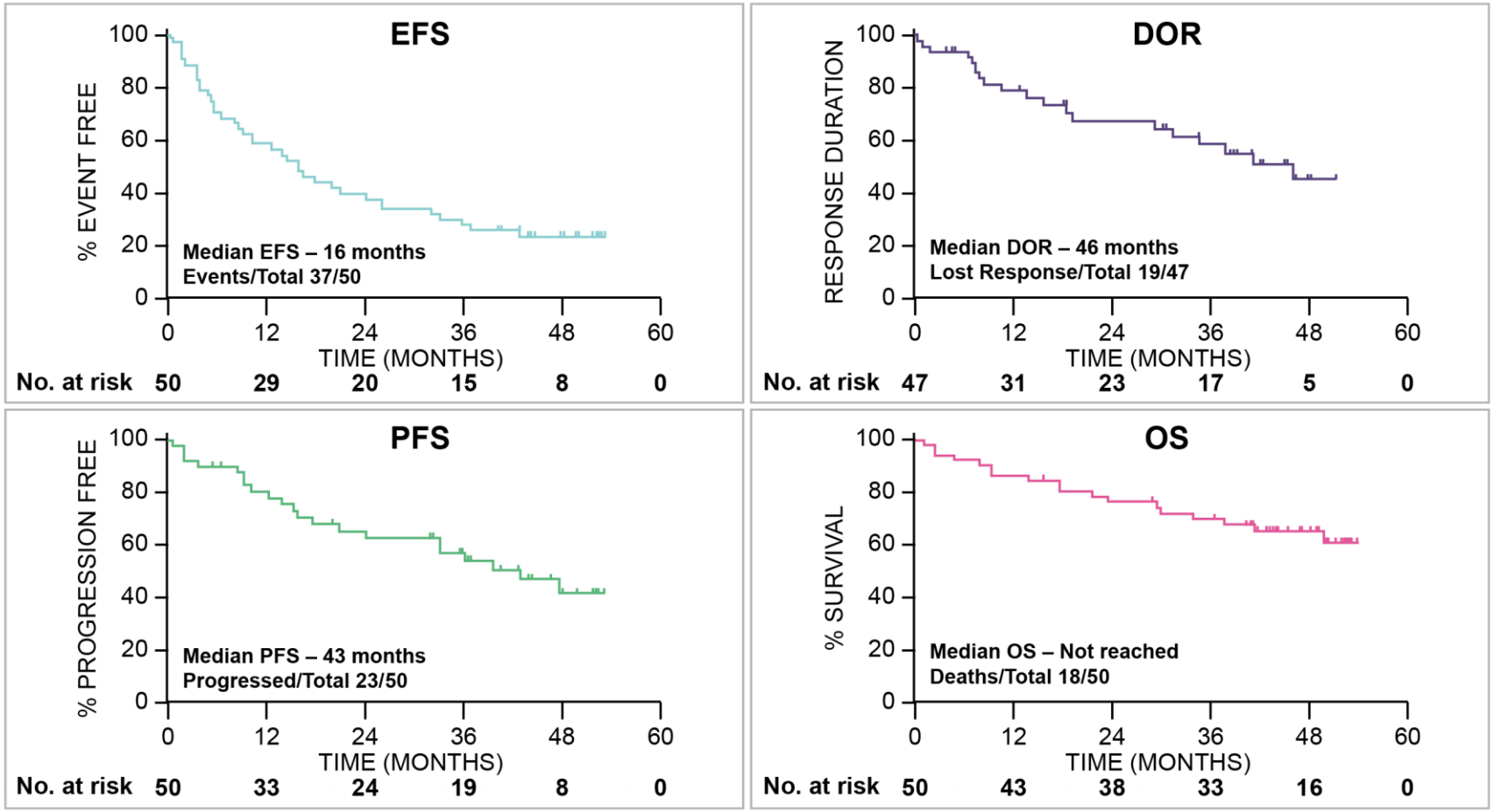


MCL, mantle cell lymphoma

Adapted from Lin RJ, *et al*. Br J Haemoatol. 2019 Mar;184(6):1006-1010

Novel agent ibrutinib in combination (after relapse)

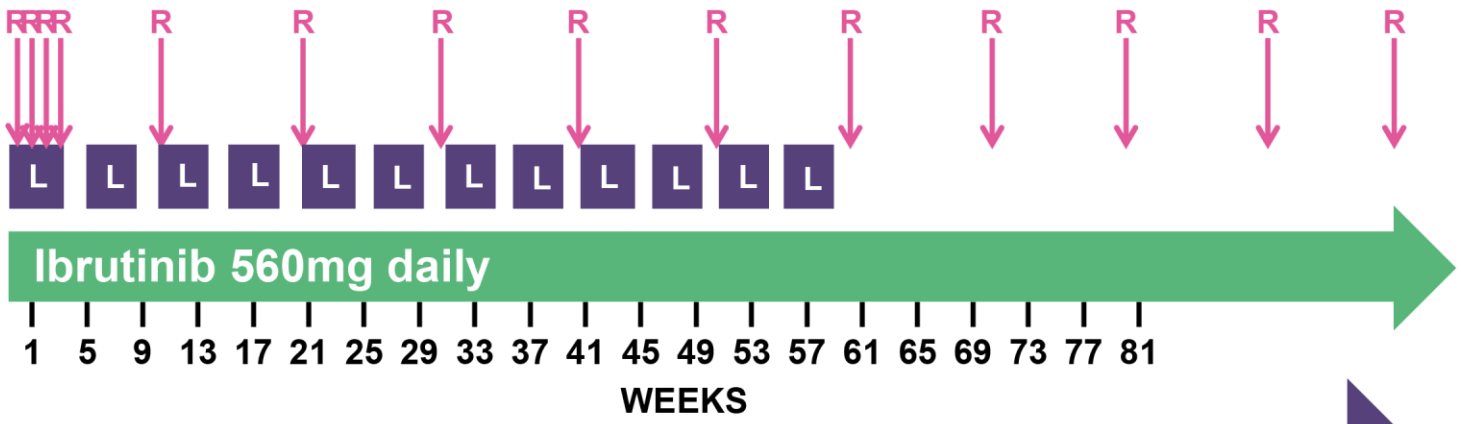
Survival outcomes for patients with MCL treated with ibrutinib-rituximab (IR) after a median follow-up of 47 months*



DOR, duration of response; EFS, event-free survival; OS, overall survival; PFS, progression-free survival

Jain P, *et al. Br J Haematol.* 2018;182:404–11

Ibrutinib-lenalidomide-rituximab: PHILEMON study design



- R2 induction schedule adapted from Ruan *et al, NEJM* 2015
- Len 15 mg d 1–21, 28 days cycle, up to 12 months
- Eligible: R/R MCL, ≥1 rituximab regimen, no age limit
- Primary endpoint: ORR
- Aim: to improve ORR in R/R MCL, compared to single agent ibrutinib

LEN, lenalidomide; MCL, mantle cell lymphoma; ORR, overall response rate; R, rituximab; R2, rituximab plus lenalidomide; R/R, relapsed/refractory;
Jerkemann M, *et al.* ASH 2016. Abstract #148 Jain P, et al. Br J Haematol. 2018;182:404–11

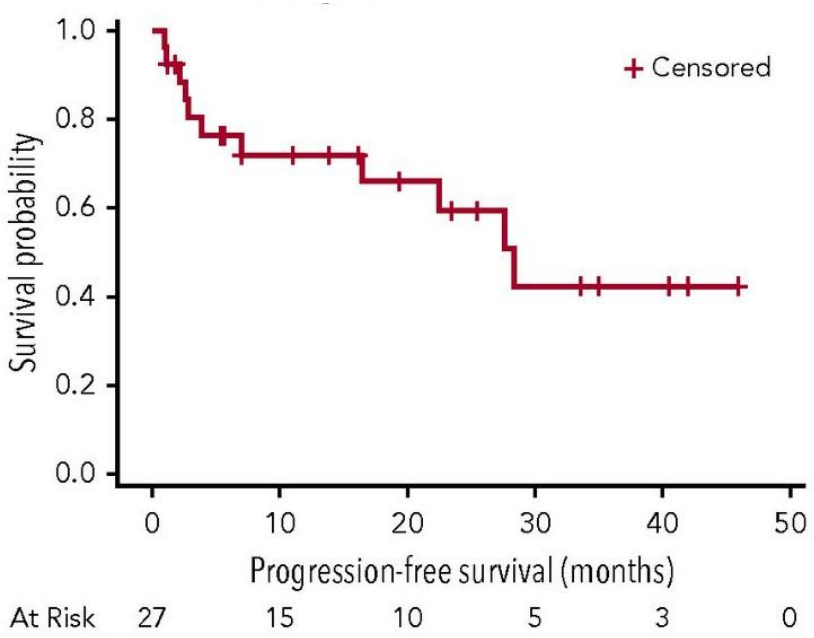
Maximal responses to treatment in all patients and according to presence of *TP53* mutation

	All patients (n=50)	TP53 wild type (n=38)	TP53 mutated (n=11)
Overall response	38 (76%, 63–86)	30 (79%, 64–89)	8 (73%, 43–90)
Complete remission	28 (56%, 42–69)	21 (55%, 40–70)	7 (64%, 35–85)
Partial remission	10 (20%, 11–33)	9 (24%, 13–39)	1 (9%, 2–38)
Stable disease	1 (2%, 0–1)	1 (3%, 0–14)	0 (0%, 0–0)
Progressive disease	5 (10%, 4–21)	3 (8%, 3–21)	2 (18%, 5–48)
Not evaluable	6 (12%, 6–24)	4 (11%, 4–24)	1 (9%, 2–38)

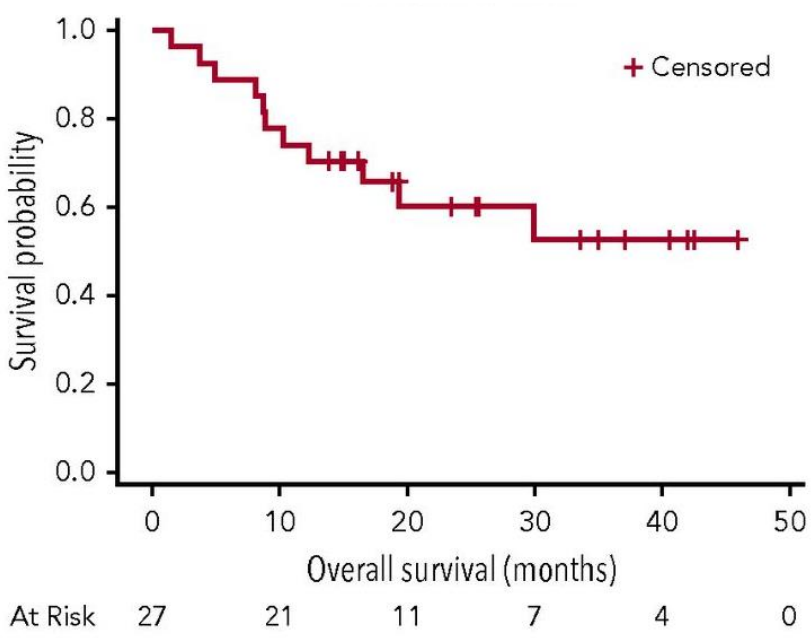
Jerkemann M, *et al.* ASH 2016. Abstract #148

A Phase I trial of ibrutinib plus palbociclib (CDK4/6i) in previously treated MCL

Progression-free survival
(2 yr = 59.4%)



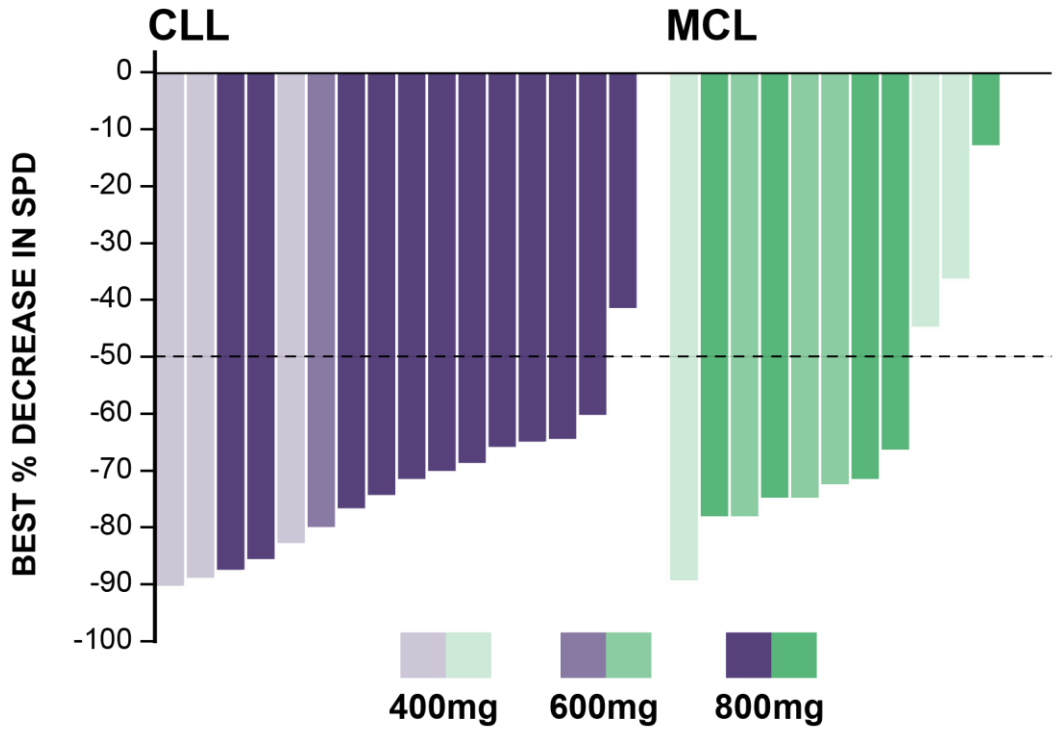
Overall survival
(2 yr = 60.6%)



ORR = 67%
CR = 37%

MCL, mantle cell lymphoma
Martin P, *et al. Blood.*2019;133:1201–4

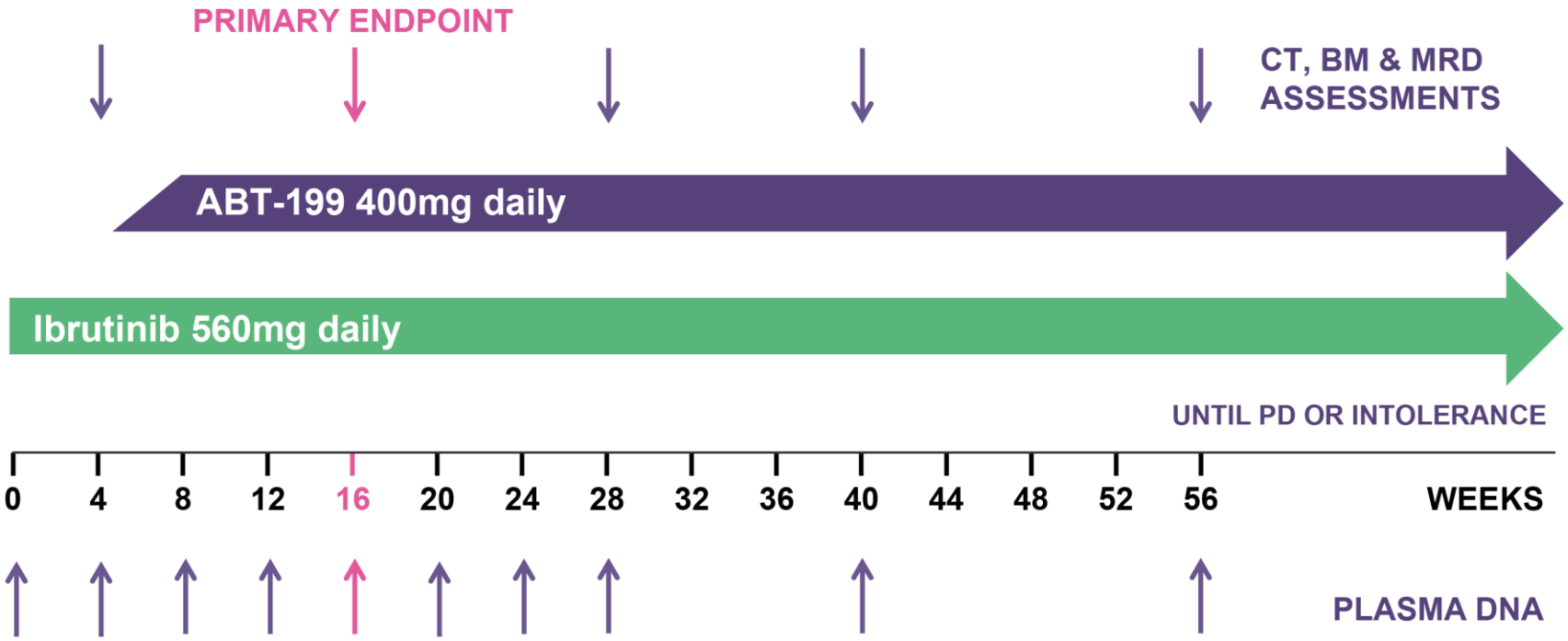
PI3K-delta inhibitor (TGR-1202) + ibrutinib: primary efficacy analysis (MCL, n=11)



- ORR: 8/11 (73%), all PRs
- Clinical benefit observed in 2 additional patients
- 1-year PFS and OS for MCL is 37% and 52%, respectively (n=11)
- 6 MCL patients have died (5 due to PD, 1 due to toxicity from subsequent therapy)

MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response;
Davids MS, *et al.* ASH 2016. Abstract #641

AIM (ABT-199 & Ibrutinib in MCL)
Study schema



Patient characteristics

- R/R MCL (n=23)
- Untreated MCL (n=1)
- Median age 68 years (47–81)
- 88% male
- *TP53* aberration 50%
- NF-κB pathway mutation 25%

BM, bone marrow; CT, computed tomography; MRD, minimal residual disease; PD, progressive disease; R/R, relapsed/refractory
Figure adapted from Tam CS, *et al. N Engl J Med*. 2018;378:1211–23

AIM Study: response rates (PET)

	Week 16, CT only (N=24)	Week 16, PET/CT (N=24)
Complete response (CR)	10 (42%)	15 (62%)
CR, unconfirmed	4 (17%)	-
Partial response (PR)	4 (17%)	2 (8%)
Stable disease (SD)	2 (8%)	1 (4%)
Progressive disease (PD)	3 (12%)	4 (17%)
Not evaluable	1 (4%)*	2 (8%)*†

Patients were restaged at Week 16 using CT, PET, double endoscopy (if baseline involvement) and BMAT with MRD studies

Week 16

OR = 71%

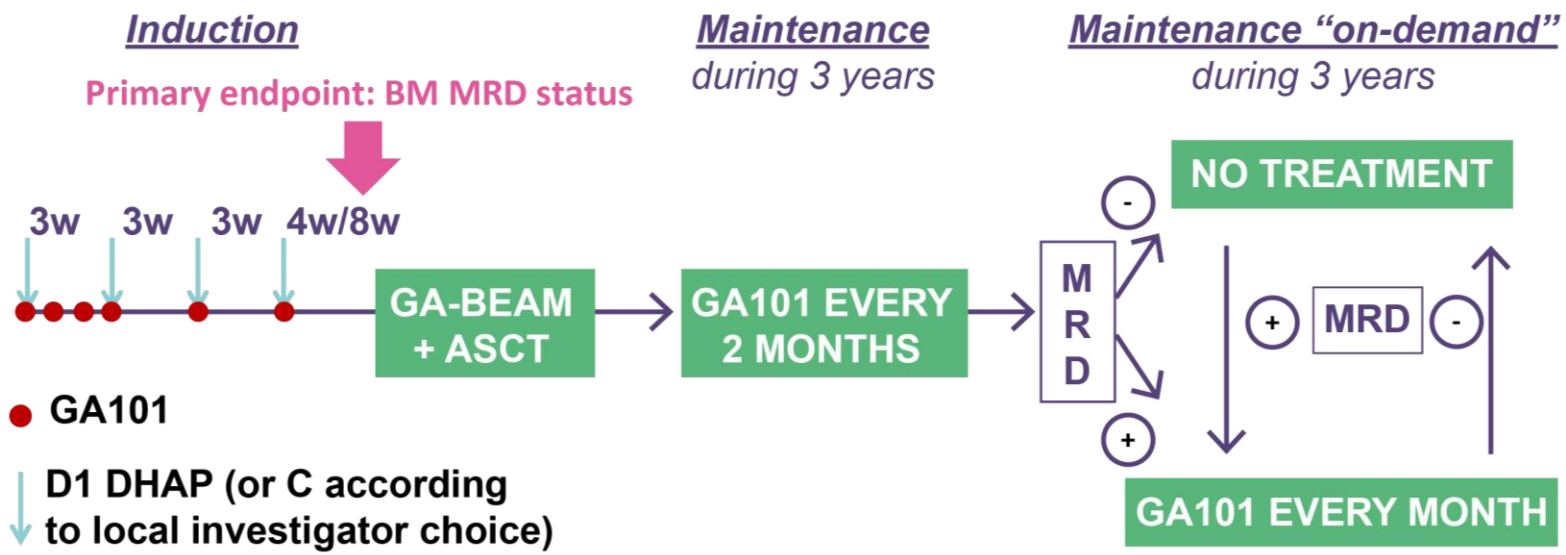
CR = 62%

50% *TP53* aberrations
Half achieved CR

* One patient with stable disease died from infection at Week 6 and so could not be evaluated for CT or PET response at the week 16 time point.
† Disease was not able to be assessed by PET in one patient
BMAT, bone marrow aspirate and trephine; CT, computed tomography; MRD, minimal residual disease; PD, progressive disease; PET, positron-emission tomography
Tam CS, *et al. N Engl J Med.* 2018;378:1211–23

Front-line therapy (newly diagnosed)

Lyma-101 trial: Obinutuzumab + DHAP followed by autologous SCT + obinutuzumab maintenance in untreated MCL[1,2]



Primary end point: MRD (ITT)[2*]

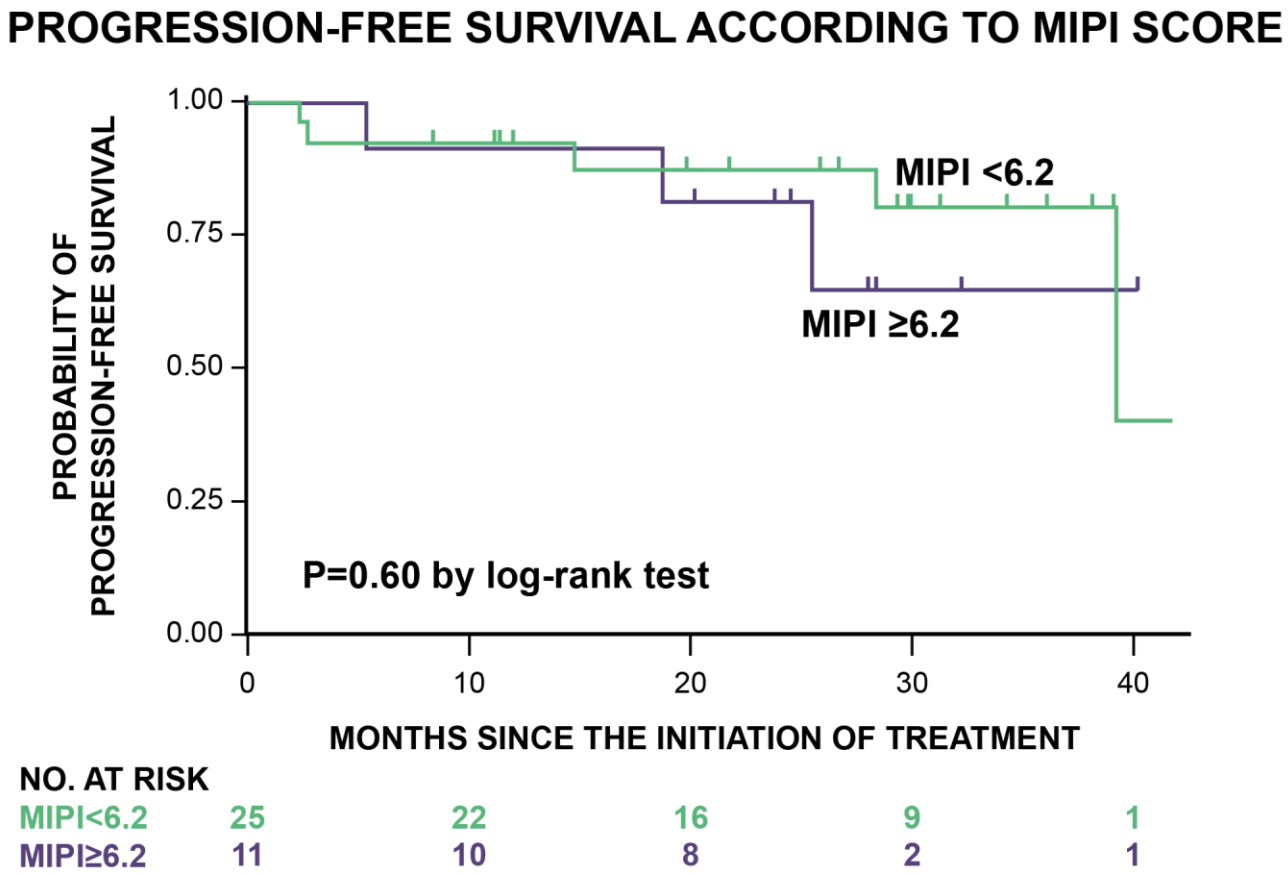
MRD status (end of induction in BM)	qPCR (n=71)	ddPCR (n=73)
MRD neg.	53 (75%)	62 (85%)
MRD pos.	13	6
Not evaluable**	5	5

Patients aged 18–65 years with previously untreated mantle cell lymphoma, eligible for ASCT (N=85 safety set; N=73 efficacy set)

* 2 patients were only analyzed by ddPCR, when both were negative and one patient was only analyzed by ddPCR, but was positive at 1x10E-4 and was considered to be positive also by qPCR; ** premature withdraw before C4
BM, bone marrow; MRD, minimal residual disease
1. Le Gouill, *et al*. EHA 2019; Abstract # S103; 2. Drandi, et al. EHA-2580, lymphoma biology and translational research.

Lenalidomide-rituximab in untreated elderly patients with MCL

Response*	Patients N=38
Overall response, n (%)	33 (87)
CR, n (%)	23 (61)
PR, n (%)	10 (26)
SD, n (%)	1 (3)
PD, n (%)	2 (5)



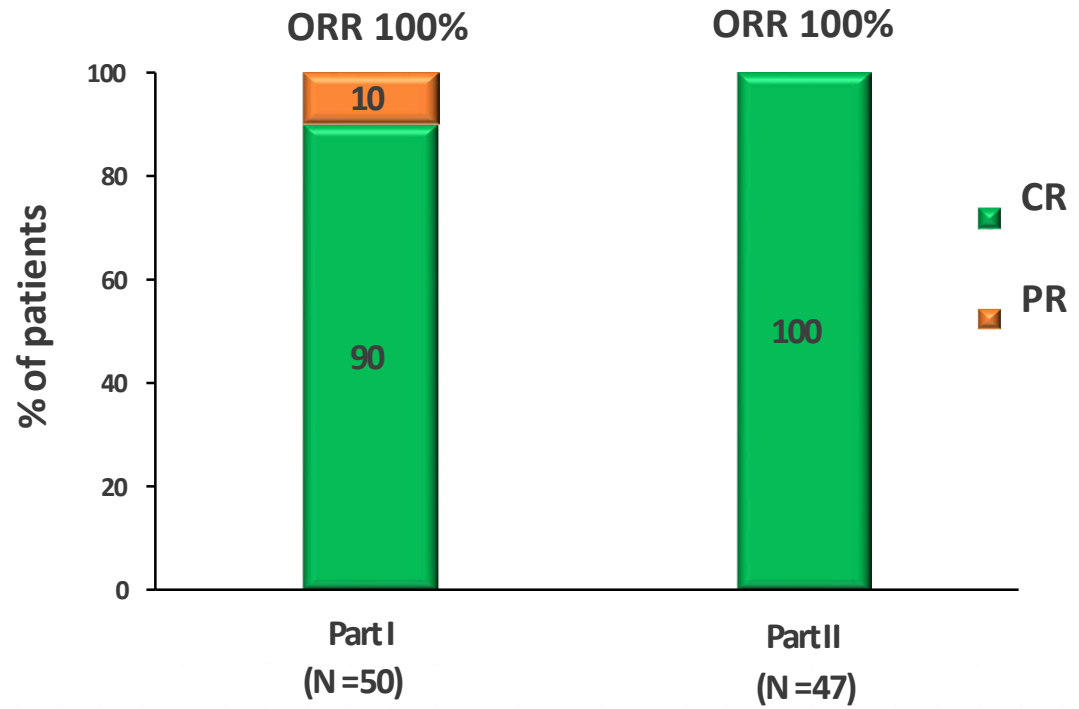
*Median follow-up of 30 months

CR, complete response; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; POD, progression of disease; PR, partial response; SD, stable disease

Ruan J, *et al. N Engl J Med*. 2015;373:1835–44

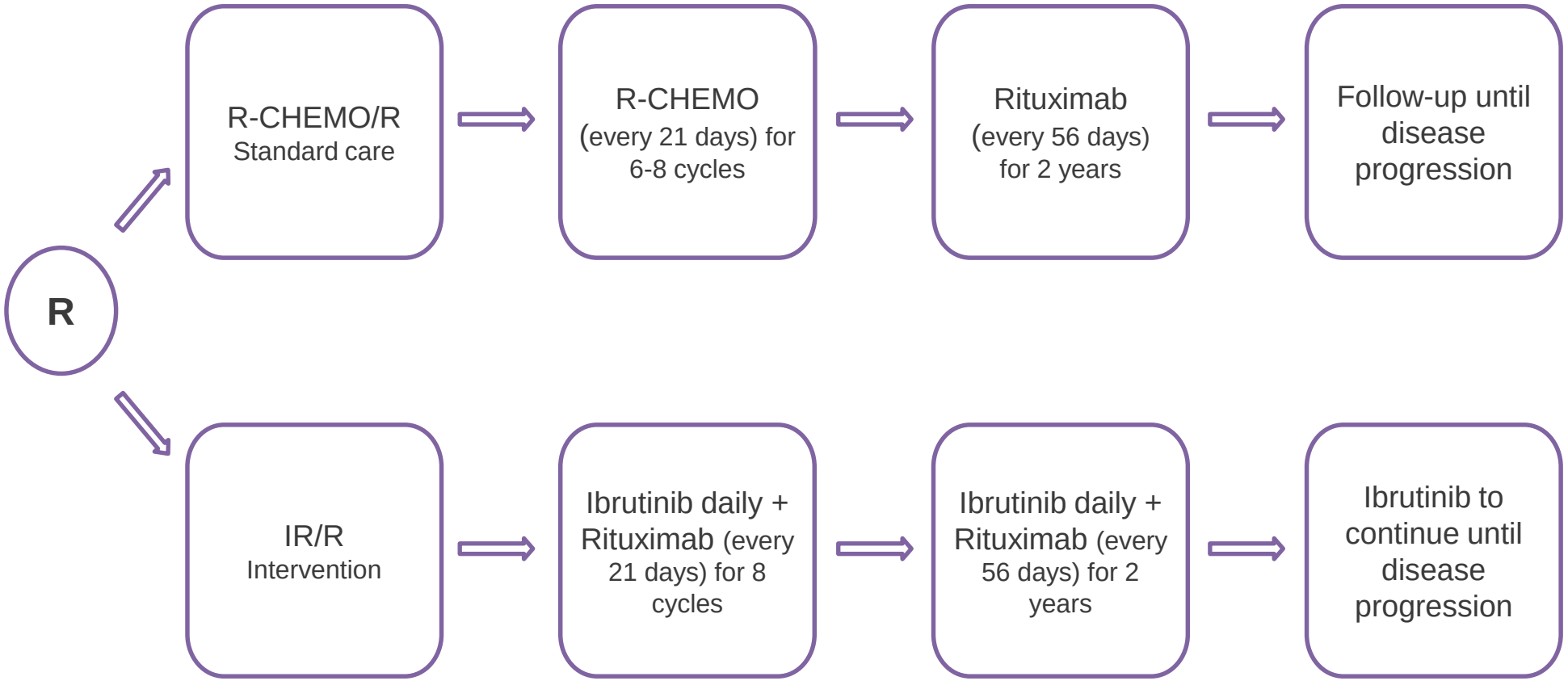
Best response rate in newly-diagnosed patients with MCL (<65 years) Window I/II study

- Single-centre study
- Part 1: chemotherapy-free phase of ibrutinib-rituximab treatment until best response
- Part 2: shortened intense chemo-immunotherapy course



CR, complete response; ORR, overall response rate; PR, partial response,
Wang ML, *et al.* ASH 2017. Abstract #133

ENRICH – NCRI multicentre Randomised open label Phase III trial of rituximab & Ibrutinib *vs* rituximab & CHemotherapy in elderly MCL



I, ibrutinib; MCL, mantle cell lymphoma; R, rituximab
EudraCT Number: 2015-000832-13

OAsIs: A phase I trial of obinutuzumab, venetoclax plus ibrutinib in R/R and untreated MCL patients

PIs: Prof Rule Simon (UK), Prof Le Gouill Steven (France)

Design:

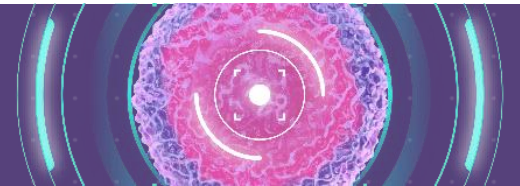
- **Step A**: safety of obinutuzumab + ibrutinib in patients with R/R MCL (n = 9).
- **Step B:** MTD of obinutuzumab + venetoclax + ibrutinib in patients with R/R MCL (n=24)
- **Step C:** safety of obinutuzumab + venetoclax + ibrutinib in patients with untreated MCL (n=12)

Data will be presented at ASH 2019

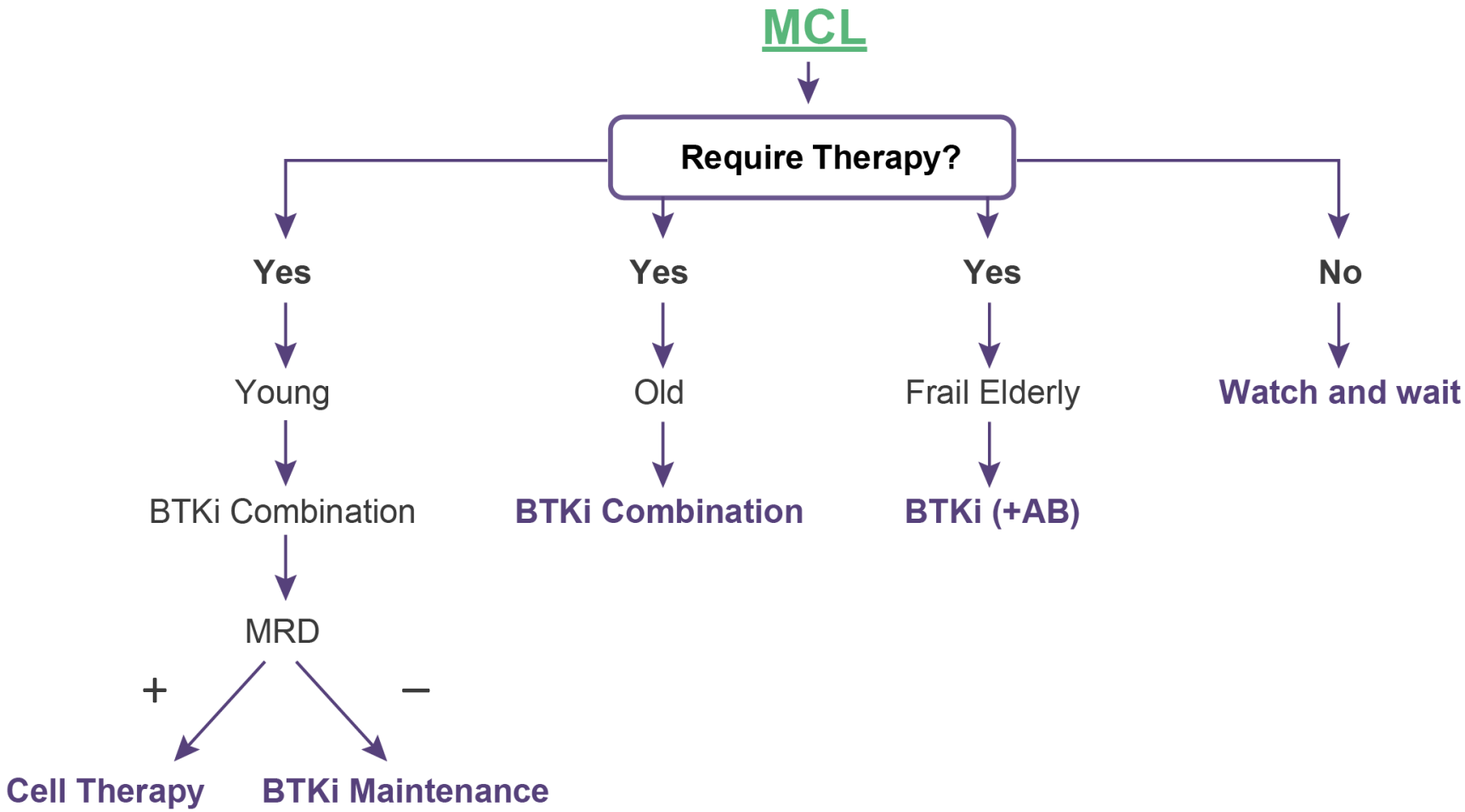
Le Gouill *et al*. ICML 2017; Abstract #213

Summary

- BTKi have made a significant impact on the treatment algorithm in MCL
- Ibrutinib is now the standard of care in relapsed MCL
- Some combination approaches further improve outcomes
    - Rituximab
    - Venetoclax
- Trials are now exploring the front line setting
        - Seems likely to be part of the standard of care soon
- Clinical trials are how we improve outcomes



Possible future?



AB, antibody; BTKi, Bruton's tyrosine kinase inhibitor


Round table
discussion

Thank you