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MANTLE CELL LYMPHOMA MTOR-INHIBITION

Rome, 23. March 2017

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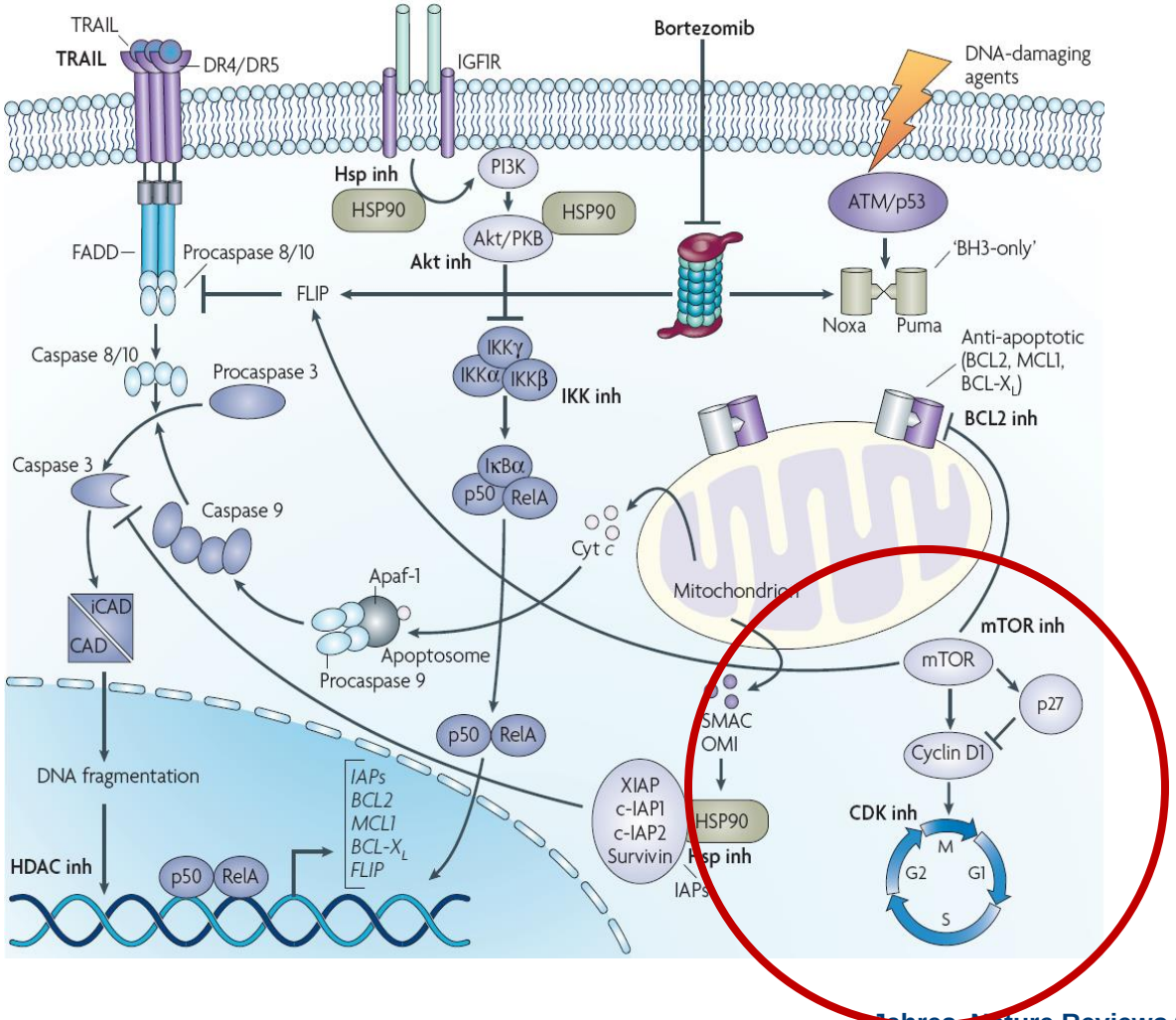
Conflicts of interest

Employment/Leadership	none
Stock	none
Honoraria (consultancy, lecture)	Pfizer, Janssen, Roche, Celgene, CTI, Novartis, Morphosys
Research funding	Pfizer, Roche, CTI, Celgene
Testimony	none
Other	none

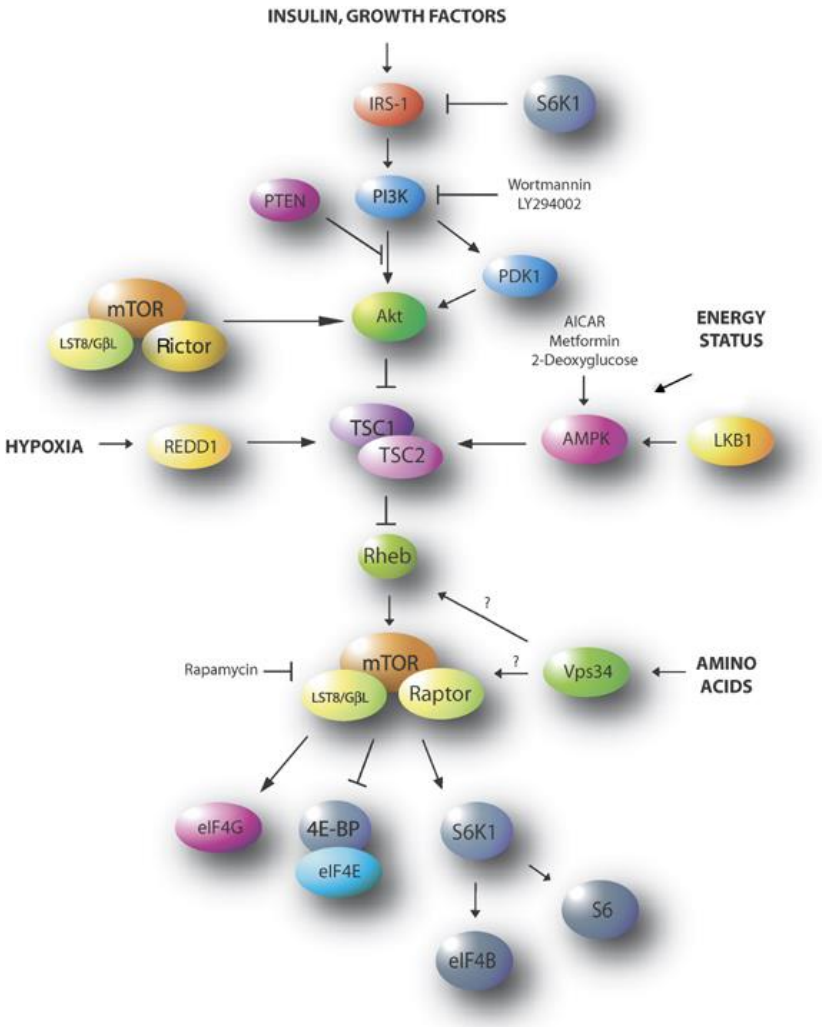
BACKGROUND

Altered pathways in MCL



Jahrsc, Nature Reviews Cancer, 2007

Physiologic functions of mTOR

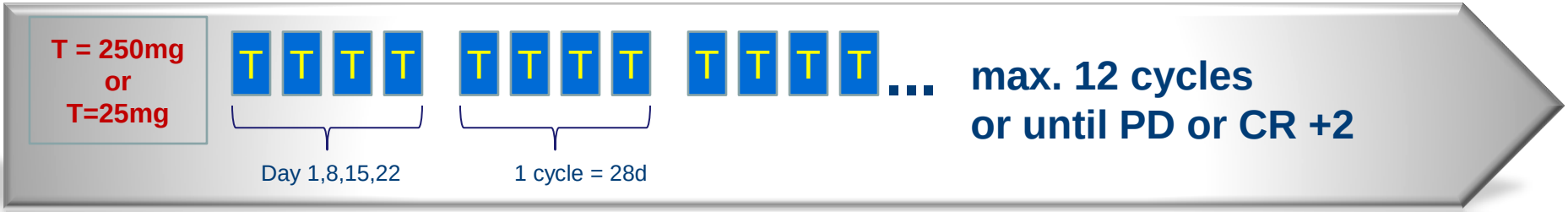


- **General functions**
  - Highly conserved key kinase acting downstream of PI3K
  - Master switch of cellular catabolism and anabolism
  - PI3K/AKT/mTOR: cardinal role in cancer cell metabolism and growth
- **Pleiotropic downstream effects**
  - Regulation of initiation of mRNA transcription and protein translation - nutritient sensitive
  - Organisation of the actin cytoskeleton
  - Membrane trafficking
  - Protein degradation
  - PKC singaling
  - Ribosome biogenesis
- **Two complexes**
  - mTORC1 with Raptor - rapamycin sensitive
  - mTORC2 with RICTOR – rapamycin insensitive
    - Control of actin cytoskeleton and feedback to AKT/PKB

Mamane Y, et al. *Oncogene.* 2006;25:6416-22.

SINGLE AGENT TREATMENT

Phase II results: Temsirolimus monotherapy



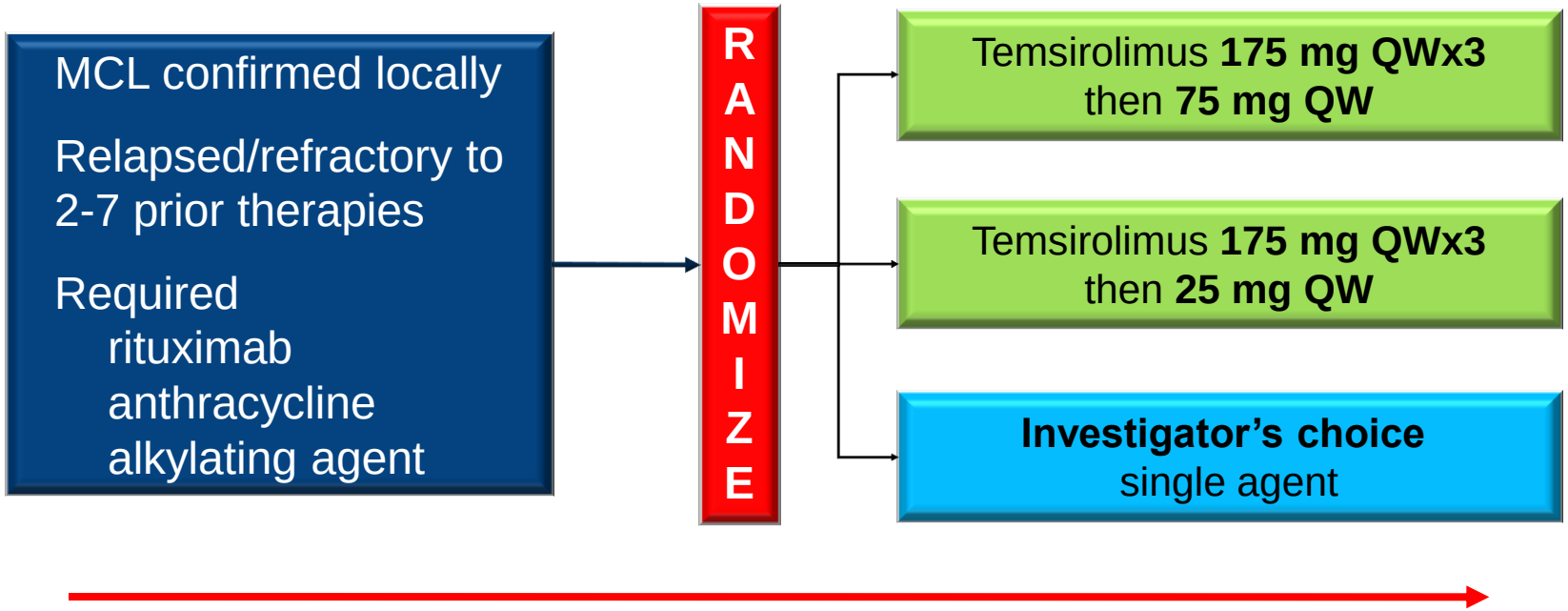
Enrollment	250 mg (n=34)	25 mg (n=27)
ORR	38% 1 CR/12 PR	41% 1 CR/10 PR
Response duration	6.9 months	6.2 months
Median TTP	6.5 months	6 months
Median survival	12 months	Not reported

Witzig T, et al. *J Clin Oncol.* 2005;23:5347-56.
Witzig T, et al. ASCO 2006. Abstract 7532; Ansell S, et al. *Cancer.* 2008;113:508-14.

Temsirolimus in MCL toxicity in phase II trials

	Phase II 250 mg		Phase II 25 mg	
%	All	3° or 4°	All	3° or 4°
Thrombo-penia	**100**	**66**	**82**	**39**
Asthenia	**66**	11	**75**	25
Anemia	66	26		15
Diarrhea	77	11		4
Fever	NR	NR	NR	NR
Anorexia	40	3		4
Mucositis	71	6	39	
Epistaxis	NR	NR	NR	NR
Rash	51	7	36	
Infection	63	**26**	32	**15**

Phase III design: Temsirolimus monotherapy



Temsirolimus treatment to continue until progression, death, or unacceptable toxicity

Hess G, et al. *J Clin Oncol.* 2009;27:3822-9.

Investigator's choice agents used

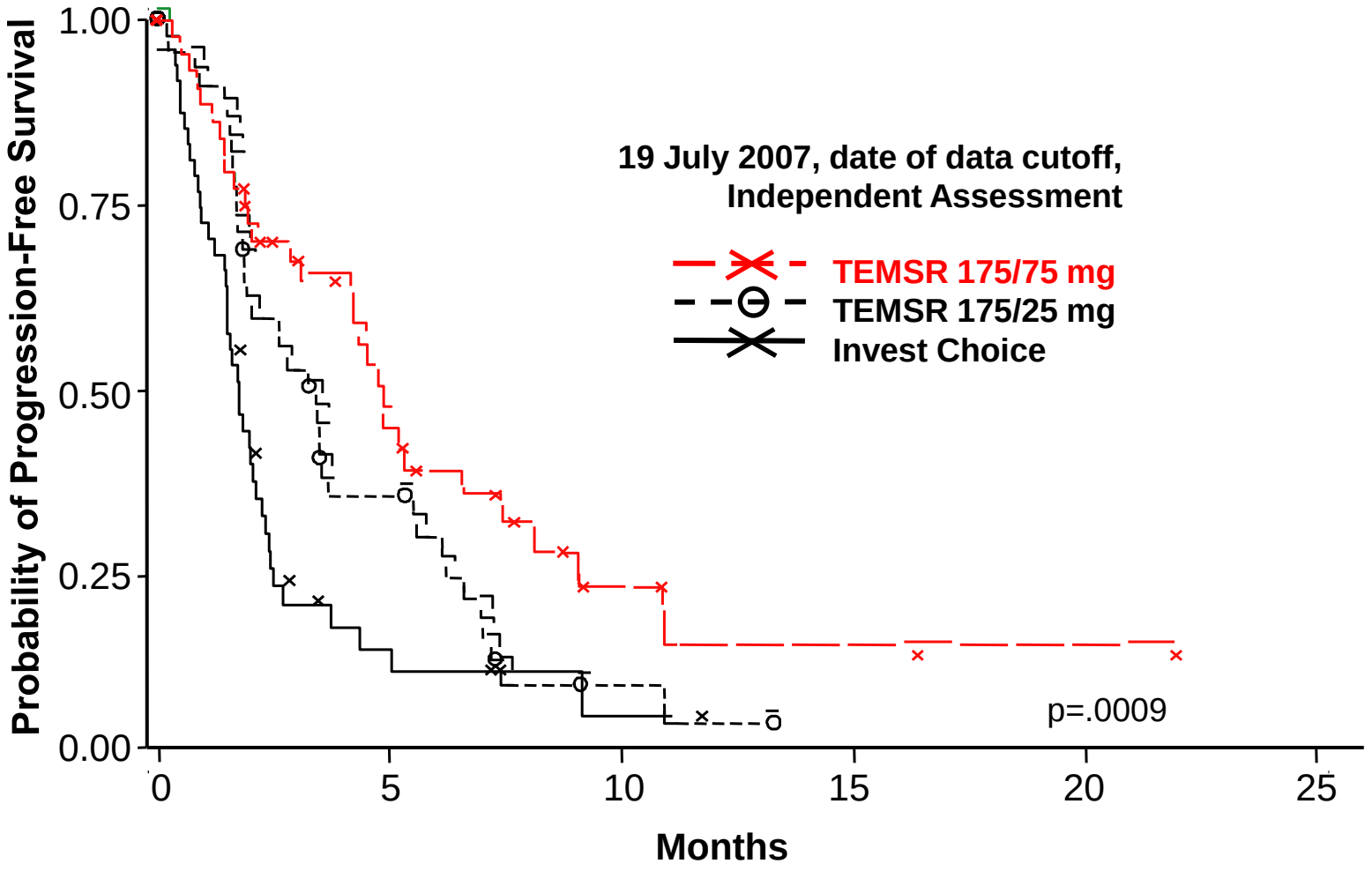
Protocol Specified Drug	n
Gemcitabine IV	22
Fludarabine IV, oral	14
Chlorambucil oral	3
Cladribine IV	3
Etoposide IV	3
Cyclophosphamide oral	2

Approved Additions	n
Thalidomide oral	2
Vinblastine IV	2
Alemtuzumab IV	1
Lenalidomide oral	1

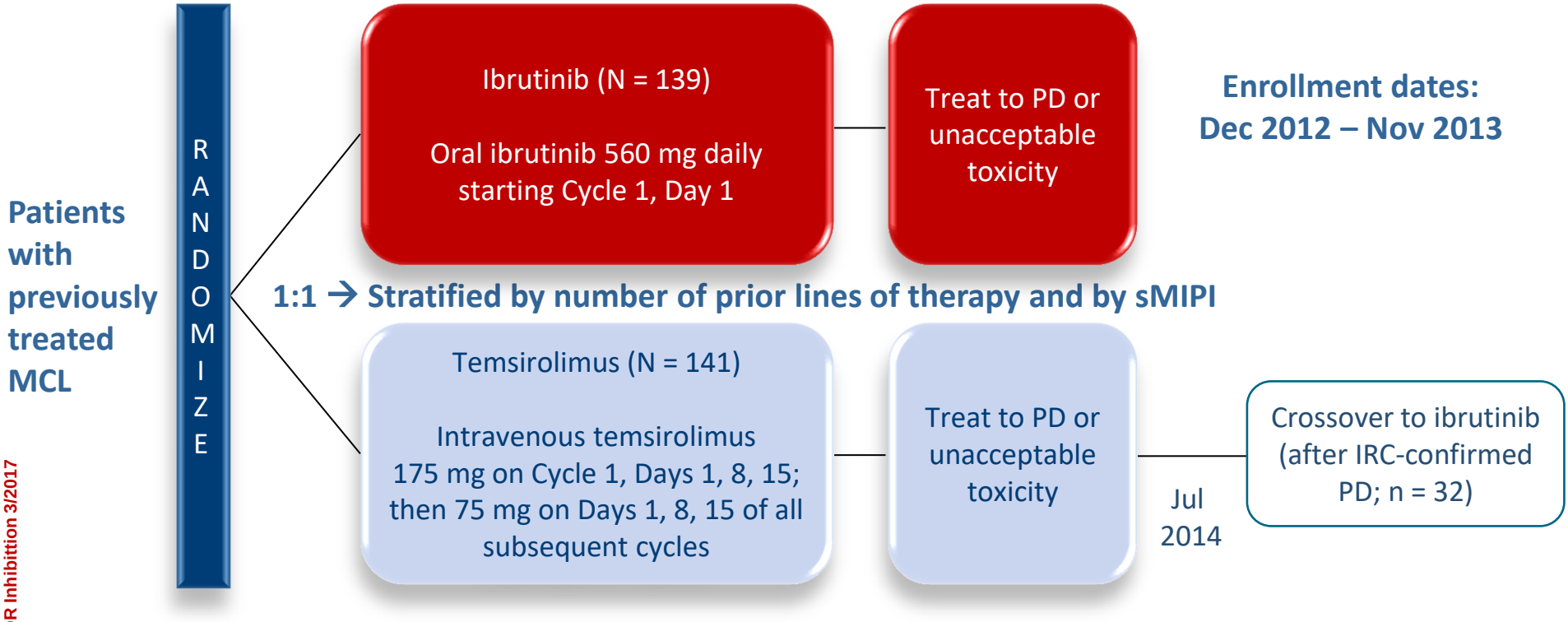
Response rates and duration (ITT)

	TEMSR 175/75 n = 54	TEMSR 175/25 n = 54	Invest. Choice n = 54
Objective response rate	**22%**	**6%**	**2%**
95% CI for response rate	11 - 33	0 - 12	0 - 5
P- value	**.0019**	**.6179**	
Complete response, n	1	0	1
Partial response, n	11	3	0
Duration of response, median (95% CI), mo	7.1 (4.1 - NA)	3.6 (3.2 - 10.6)	NA

Progression-free survival (ITT)

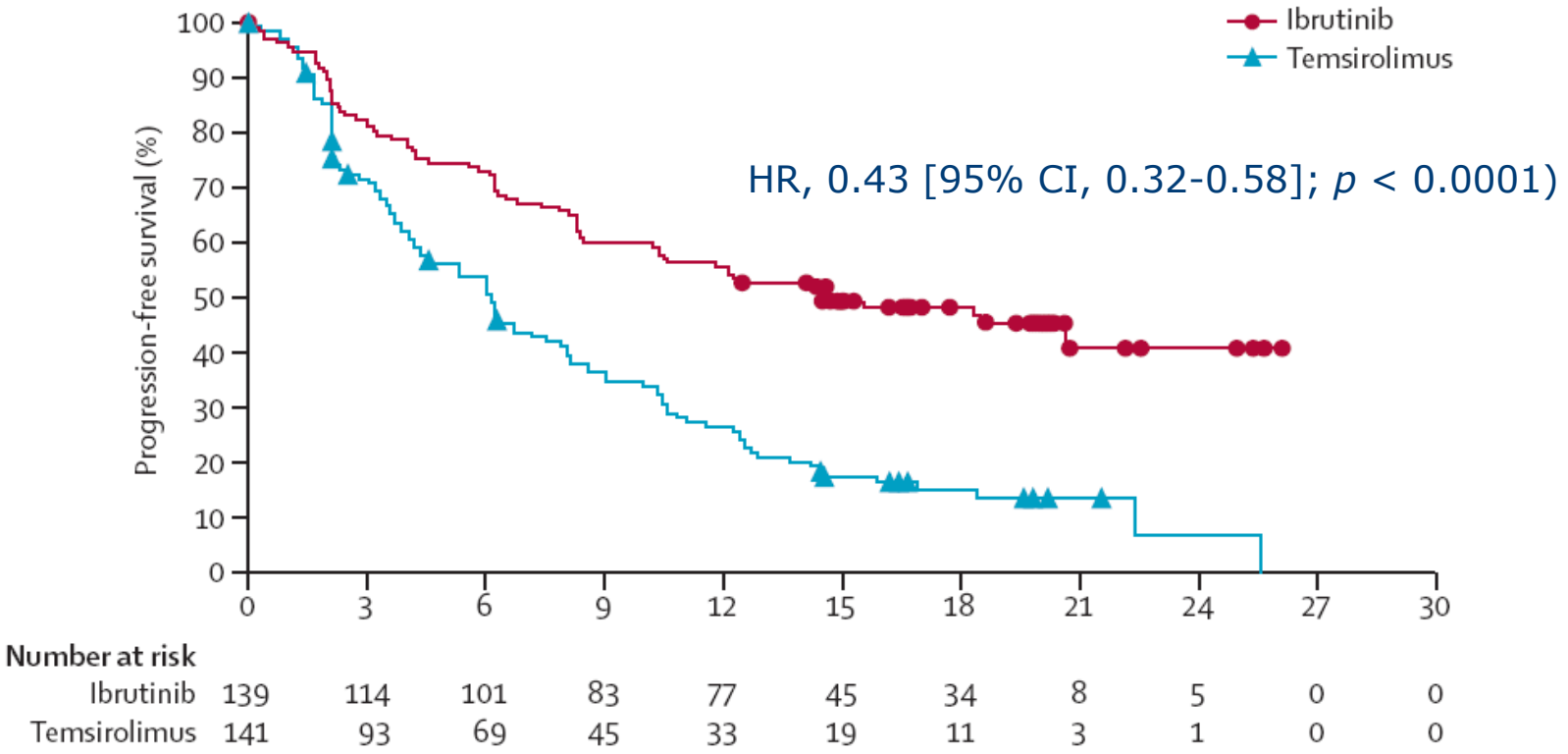


RAY-Trial: Ibrutinib vs. Temsirolimus



Rule et al., ASH 2015, abstract 469

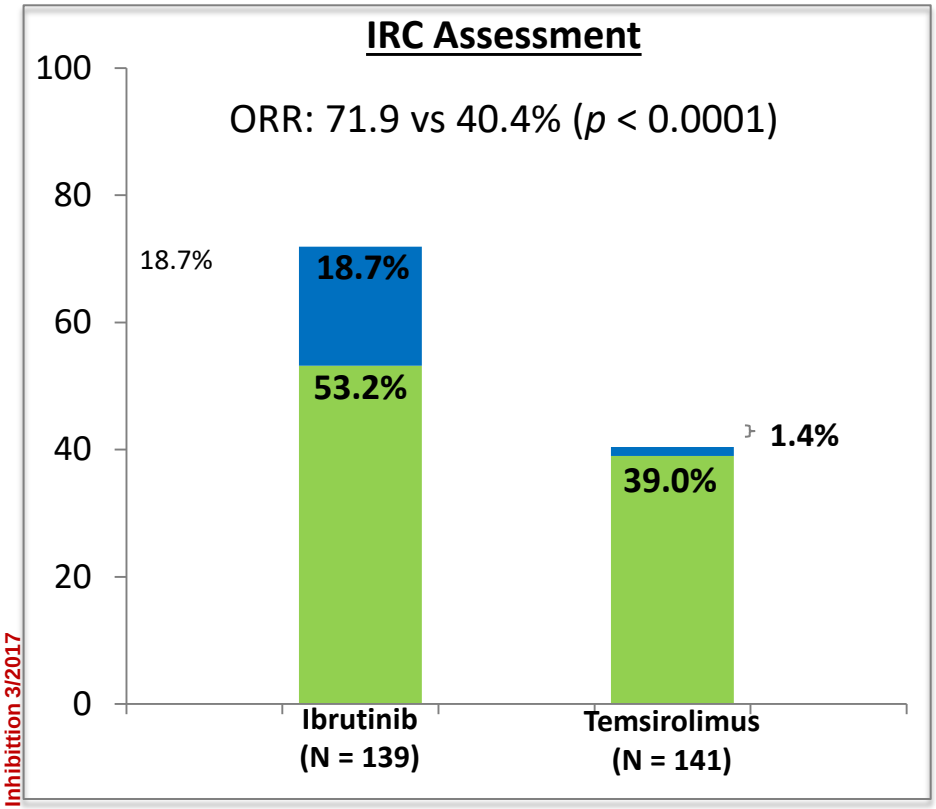
RAY: Ibrutinib vs Temsirolimus in R/R MCL

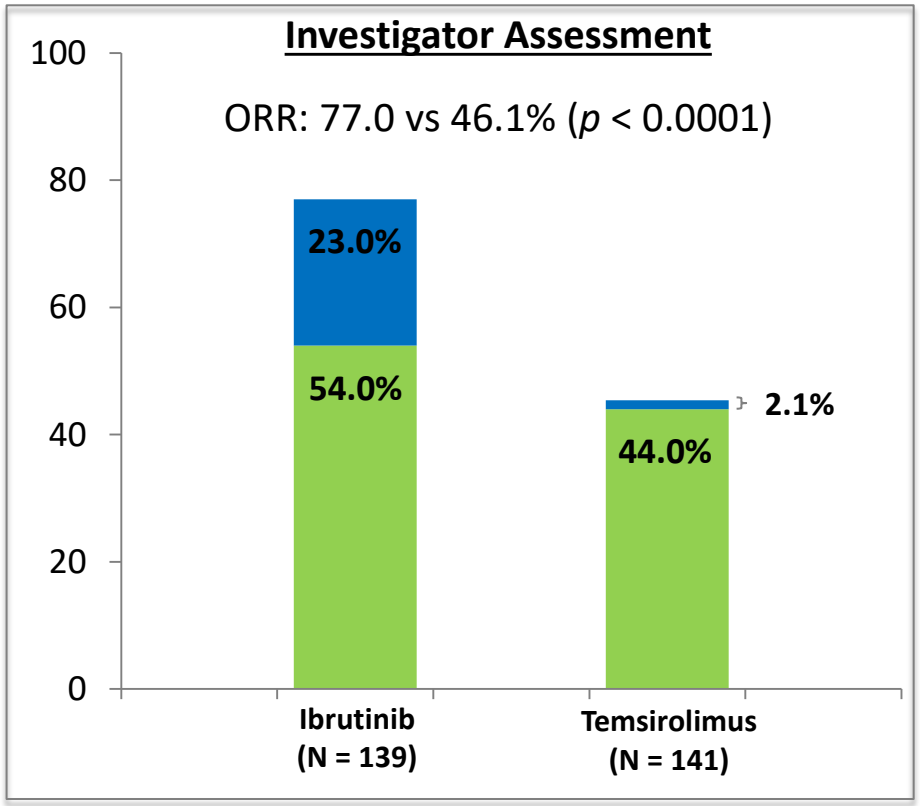


Progression Free Survival
(IRC assessed)

Rule et al., ASH 2015, abstract 469

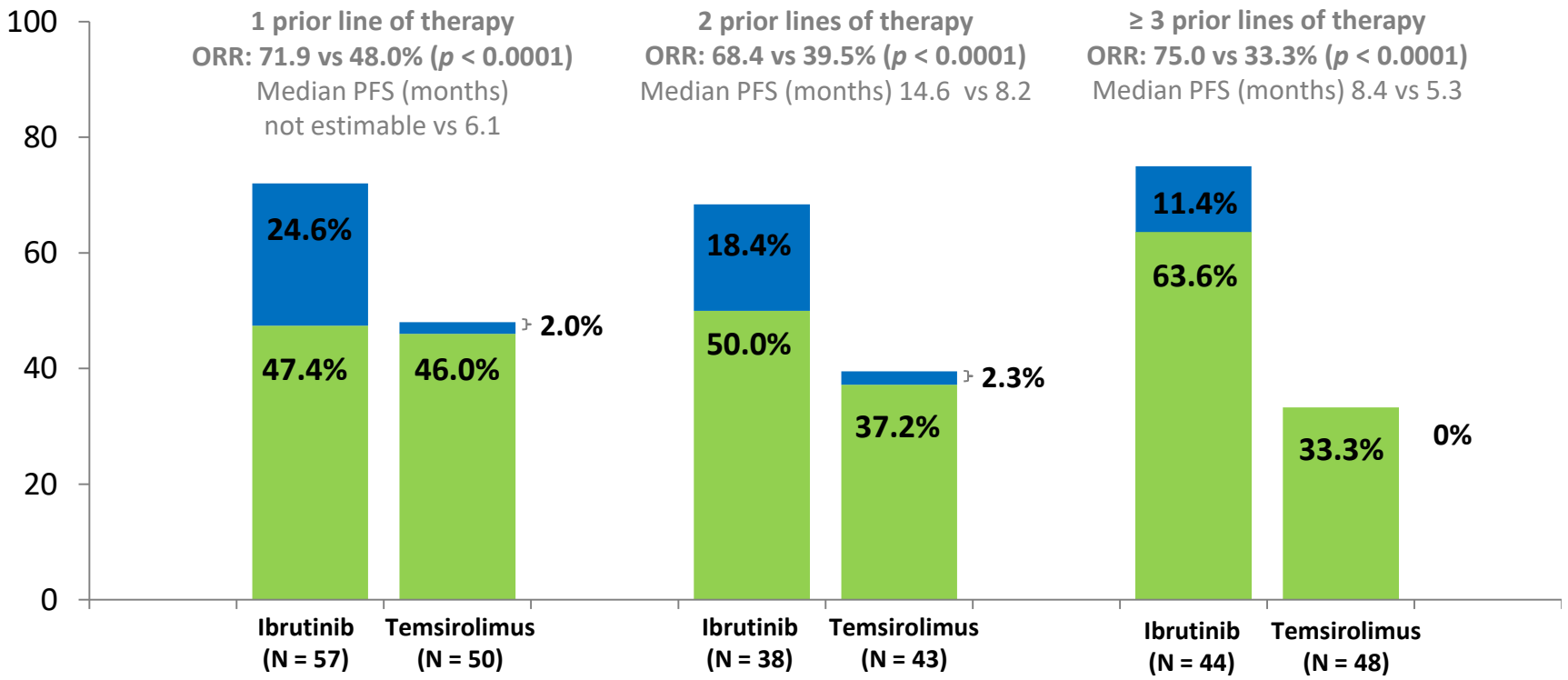
ORR





CR
PR
ORR = CR + PR

PFS and ORR: Outcomes by Number of Lines of Prior Therapy



Real Life observational data - STARTOR

Table 4: Tumor response to Temsirolimus therapy

Best response to Tems (N =51)	N (%)
Complete response (CR)	1 (2.0)
Partial response (PR)	11 (21.6)
Minimal response (MR)	1 (2.0)
Stable disease (SD)	10 (19.6)
Objective response (CR+PR)	12 (23.5)
Clinical benefit (CR+PR+MR+SD)	23 (45.1)
Progressive disease (PD)	16 (31.4)
not assessable	12 (23.5)

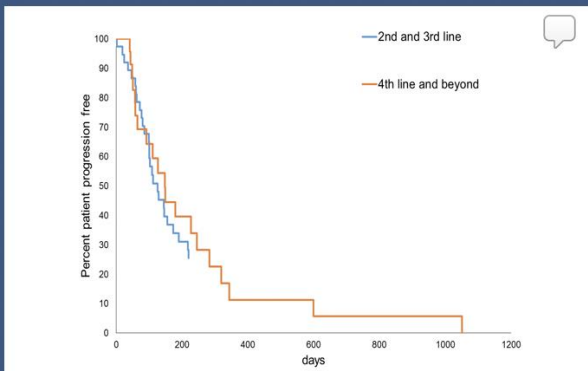
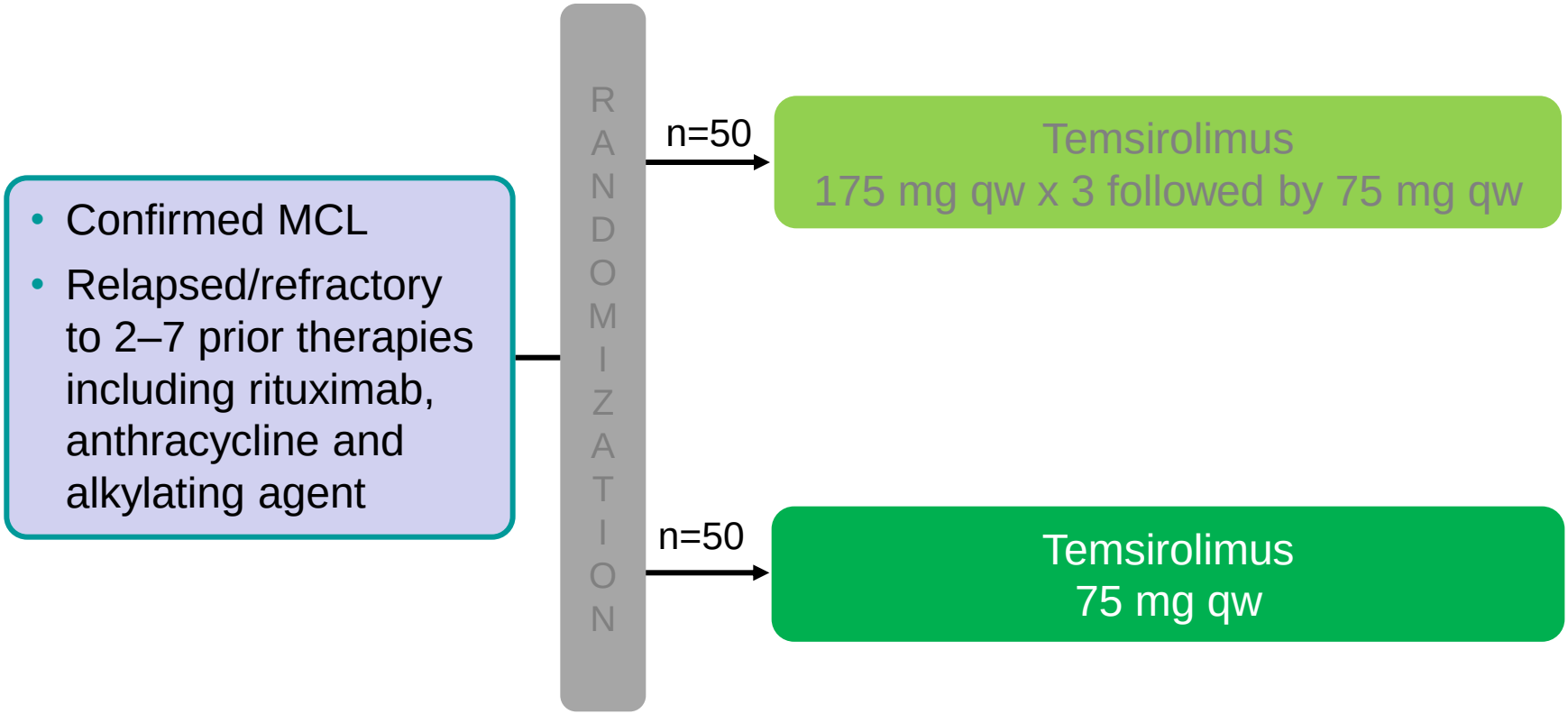


Figure 1: Kaplan-Meier curves for PFS for the subgroups of patients treated with Tems in 2nd to 3rd line (1 – 2 prior therapies) and 4th line and beyond (≥ 3 prior therapies).

Temsirolimus Phase IV Study in MCL: INTORFORM INvestigating TORisel FOR Mantel cell lymphoma



www.clinicaltrials.gov: NCT01180049

The Question of Dosing

Table 2. Best Overall Response

	Independent Assessment			Investigator Assessment		
n (%)*	Temsirolimus 175/75 mg (n=47)	Temsirolimus 75 mg (n=43)	Total (N=90)	Temsirolimus 175/75 mg (n=47)	Temsirolimus 75 mg (n=43)	Total (N=90)
Complete response (CR)	2 (4.3)	1 (2.3)	3 (3.3)	2 (4.3)	0	2 (2.2)
Partial response (PR)	11 (23.4)	8 (18.6)	19 (21.1)	13 (27.7)	8 (18.6)	21 (23.3)
Stable disease	20 (42.6)	22 (51.2)	42 (46.7)	17 (36.2)	25 (58.1)	42 (46.7)
Progressive disease	7 (14.9)	7 (16.3)	14 (15.6)	10 (21.3)	7 (16.3)	17 (18.9)
Non-evaluable	7 (14.9)	5 (11.6)	12 (13.3)	5 (10.6)	3 (7.0)	8 (8.9)
ORR (CR+PR)	13 (27.7)	9 (20.9)	22 (24.4)	15 (31.9)	8 (18.6)	23 (25.6)
80% exact CI	19.1–37.7	13.0–31.0	18.6–31.2	22.9–42.2	11.1–28.5	19.6–32.4
Difference, 175/75 vs 75, % (80% CI)		6.7 (–6.9, 20.3)			13.3 (–0.4, 26.7)	

* Values are n (%) unless otherwise indicated.
CI=confidence interval; ORR=objective response rate

Figure 1. Kaplan–Meier Estimate of Progression-free Survival Based on Independent Assessment: Intent-to-treat Population

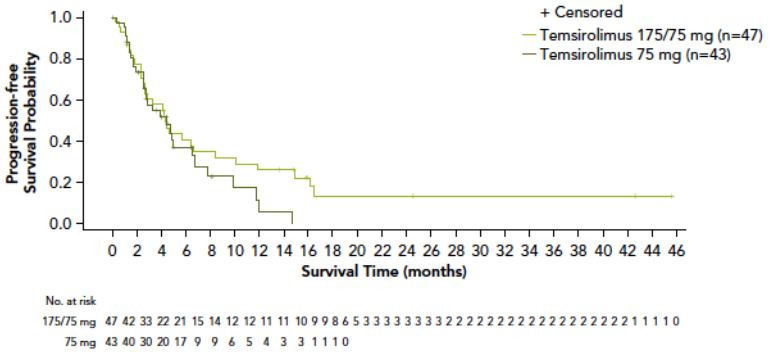
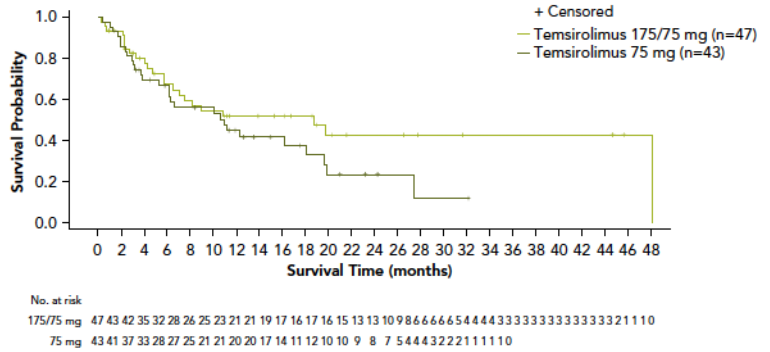


Figure 2. Kaplan–Meier Estimate of Overall Survival: Intent-to-treat Population

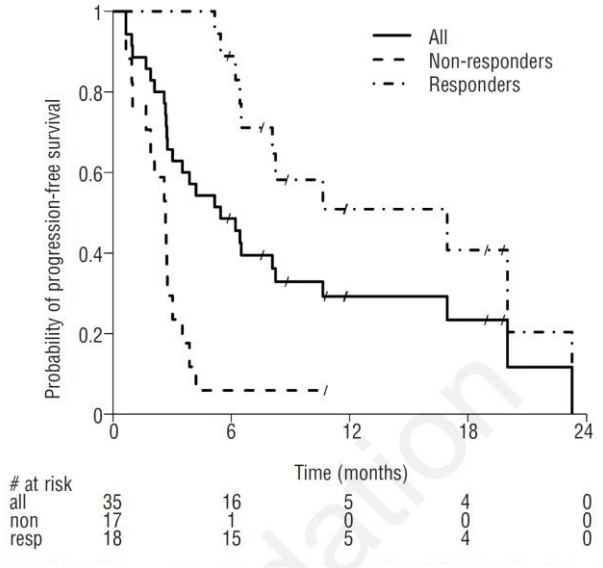


Everolimus I

A multicenter phase II trial (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma

Christoph Renner,[1] Pier Luigi Zinzani,[2] Rémy Gressin,[3] Dirk Klingbiel,[4] Pierre-Yves Dietrich,[5] Felicitas Hitz,[6] Mario Bargetzi,[7] Walter Mingrone,[8] Giovanni Martinelli,[9] Andreas Trojan,[10] Krimo Bouabdallah,[11] Andreas Lohri,[12] Emmanuel Gyan,[13] Christine Biaggi,[4] Sergio Cogliatti,[6] Francesco Bertoni,[14] Michele Ghielmini,[14] Peter Brauchli,[4] and Nicolas Ketterer[15] on behalf of the Swiss SAKK and the French GOELAMS group from the European Mantle Cell Lymphoma Network

Response	Number of patients
CR	2/35 (6%)
PR	5/35 (14%)
SD	17/35 (49%)
PD	10/35 (29%)



Renner et al, Haematologica, 2012

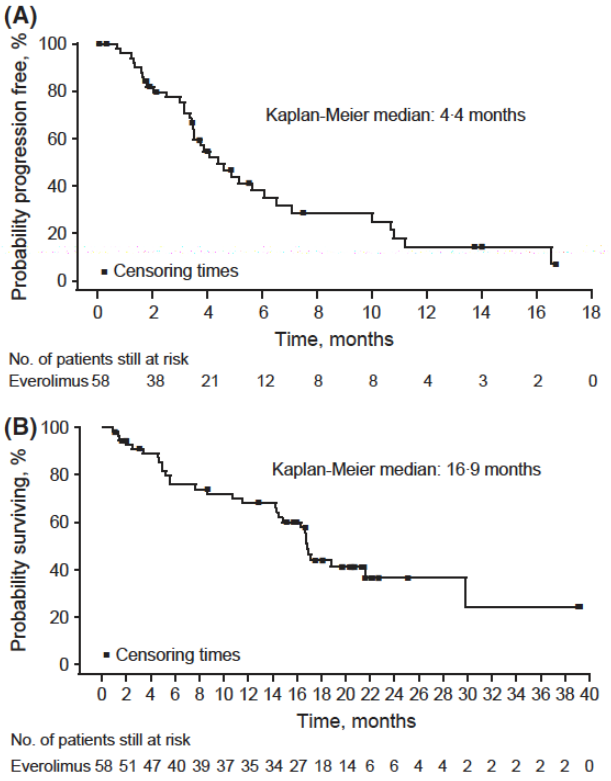
Everolimus II

Everolimus for patients with mantle cell lymphoma refractory to or intolerant of bortezomib: multi … se 2 study

Table III. Best overall response per investigator and central review in the full analysis set.

	Everolimus N = 58	
Best overall response	Investigator review	Central review
Overall response rate, % (90% CI*)	8·6 (3·5–17·3)	10·3 (4·6–19·4)
Complete response	0	0
Partial response	5 (8·6)	6 (10·3)
Stable disease	35 (60·3)	30 (51·7)
Progressive disease	8 (13·8)	9 (15·5)
Unknown	10 (17·2)	13 (22·4)

Data are given as number (%) unless otherwise stated.
*Exact (Clopper Pearson) 90% confidence interval (CI).



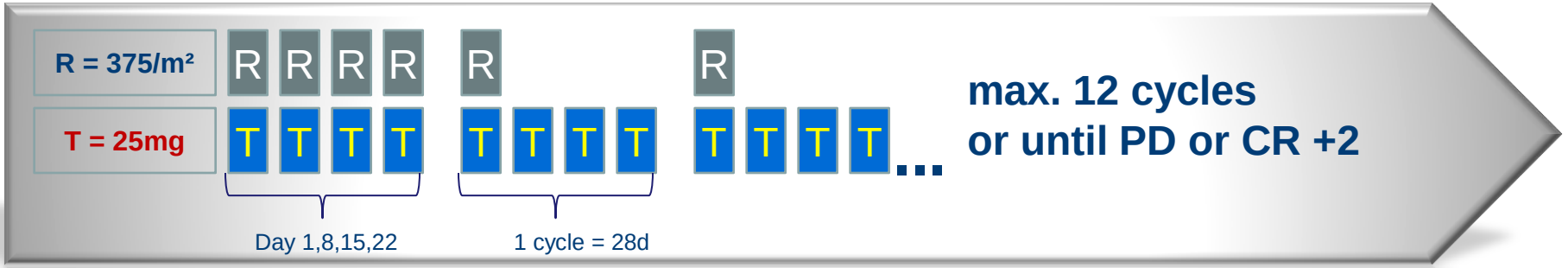
Wang et al, BJH, 2013

Summary Single Agent mTOR inhibitor

- Response rates – line dependent 20-40%
- PFS 4-6 months
- All data gathered in the pre-I-era...

COMBINATION TREATMENT

Phase II results Temsirolimus + Rituximab



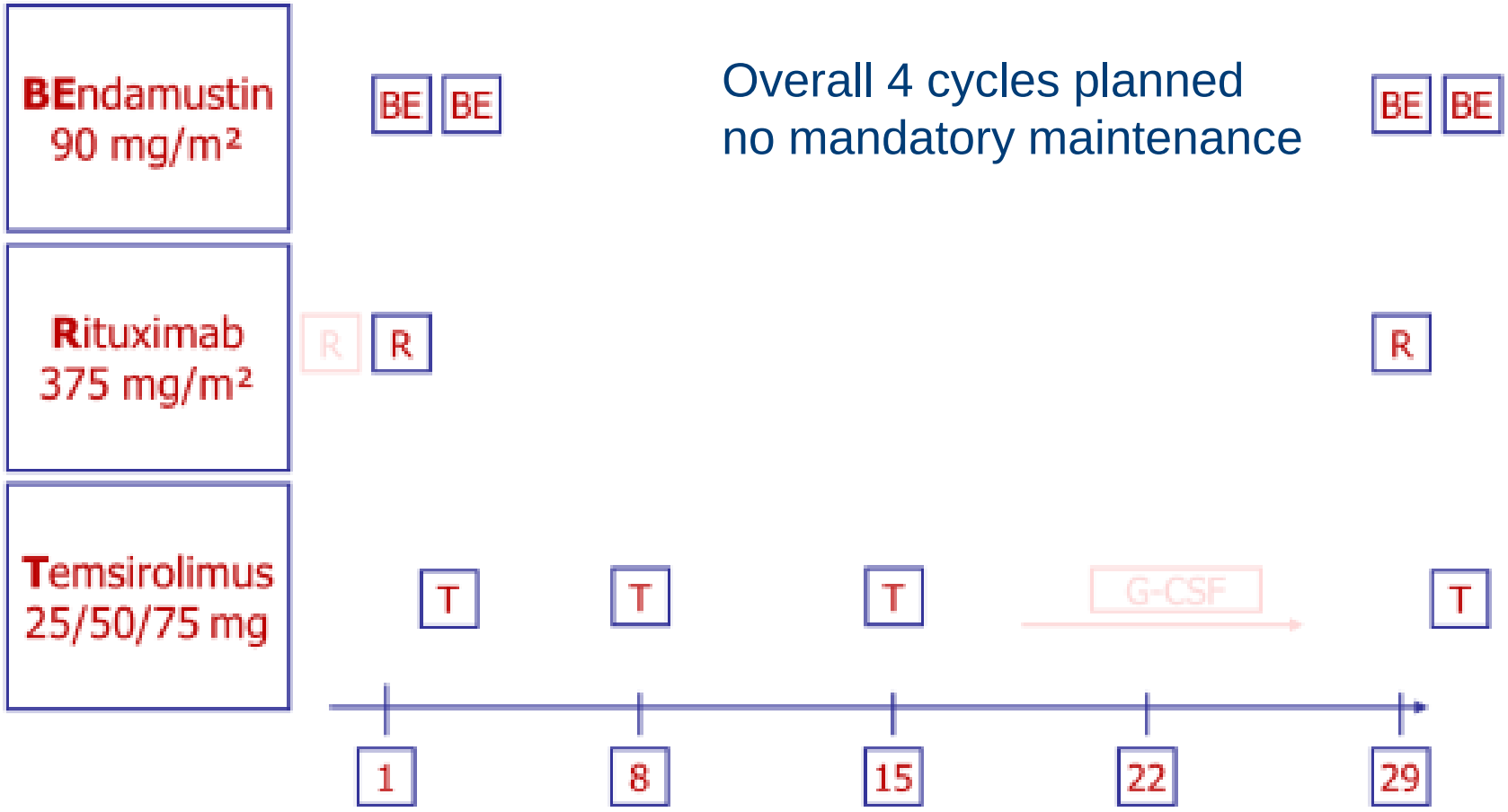
	Rituximab-sensitive patients (n=48)	Rituximab-refractory patients (n=21)	Total (n=69)*
Complete response + partial response	30 (63%; 47–76)	11 (52%; 30–74)	41 (59%)
Complete response	8 (17%; 8–30)	5 (24%; 8–47)	13 (19%)
Partial response	22 (46%; 31–61)	6 (29%; 11–52)	28 (41%)

Data are number (%; 95% CI) or number (%). *95% CIs are not appropriate statistically for the whole group because patients in the two cohorts were analysed separately and with different designs.

Table 2: **Response rates**

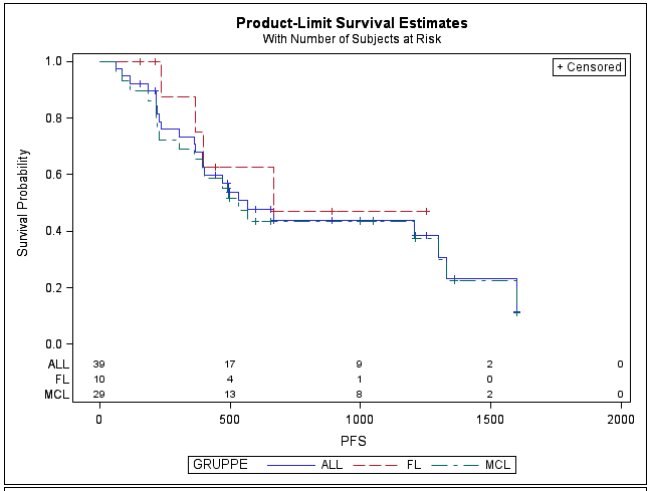
Ansell S, et al. ASH 2009, Abstract 1665; Ansell S, et al. *Lancet Oncol.* 2011;12:361-8.

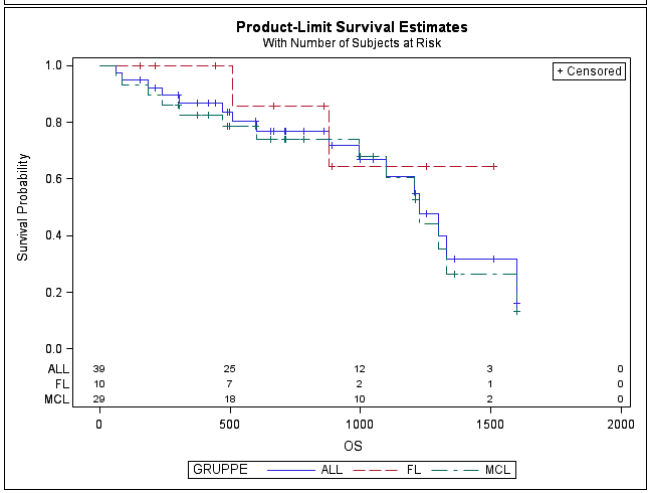
Bendamustin, Rituximab, Temsirolimus



BERT – Best Response, PFS and OS

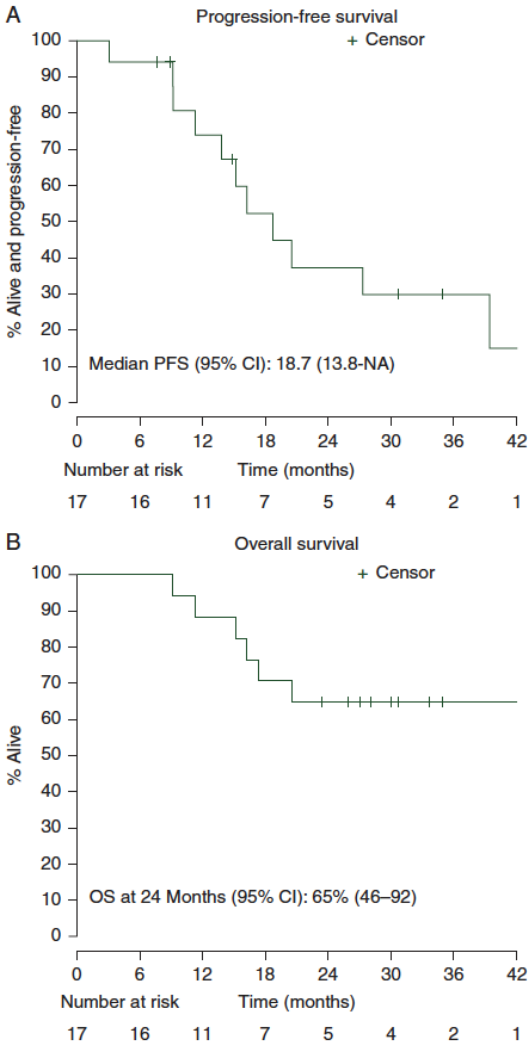
Category-Value	MCL (N= 29)	FL (N= 10)	Total (N= 39)
CR	10 (39%)	2 (20%)	12 (9%)
PR	13 (52%)	7 (70%)	20 (79%)
SD	3 (12%)	1 (10%)	4 (12%)
PD	0 (0%)	0 (0%)	0 (0%)
ORR	23 (88%)	9 (90%)	32 (89%)





Other combinations

- T3
  - T plus R-CHOP, R-DHA, R-FC
  - 15mg dose for R-CHOP, no dose fo
  - Hematologic toxicity - efficacy was g
- STORM (DLBCL)
  - R-DHAP-T – 25mg / hematotoxicity
- R-Clad-Temsirolimus – FL

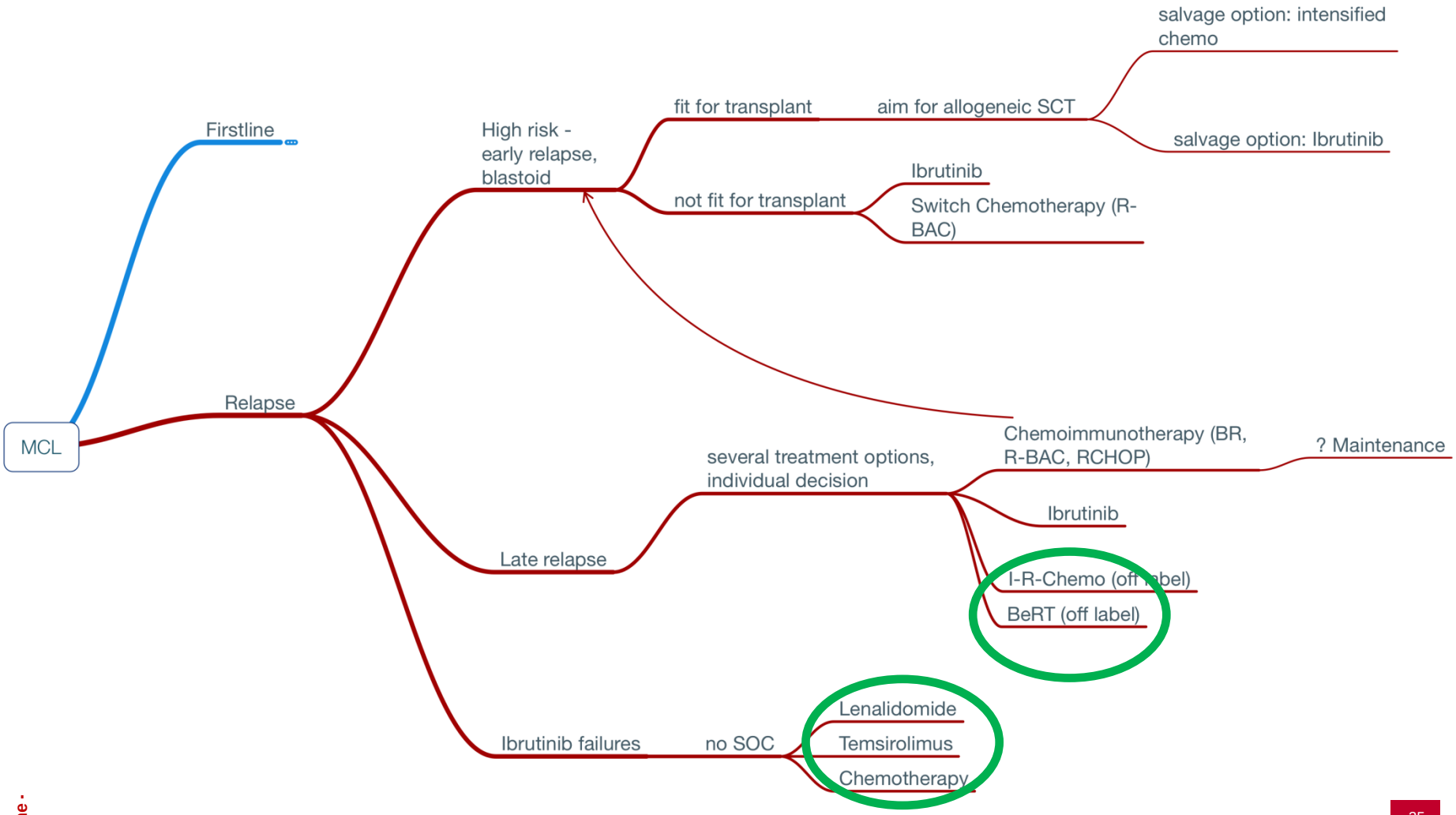


LeGuoill ASH 2016, Witzens-Harig, ASH 2015

Where to place Temsirolimus in the current algorithm?

- Two potential strategies
  - In combination regimen
    - Regimen
      - Rituximab-Temsirolimus
      - BERT
    - Limitations
      - Approval status
  - Single agent
    - Limitations
      - Value in BTK-refractory disease?

Algorithm 2016/17



Register Project of the EMCL

- Indolent MCL & Extranodal MCL
- Molecular mechanisms of relapse - effectivity of salvage treatments