INCONTRO DI AGGIORNAMENTO
SUI **DISORDINI LINFOPROLIFERATIVI**
E SUI PROTOCOLLI
DELLA **FONDAZIONE ITALIANA LINFOMI**

Torino, 14 dicembre 2018

Linfoma a cellule mantellari: Terapia di salvataggio e nuovi farmaci

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Salvage therapy for R/R MCL: outline of discussion

- Autologous stem cell transplatation (ASCT)
- Allogeneic stem cell transplantation (alloSCT)
- New biological drugs

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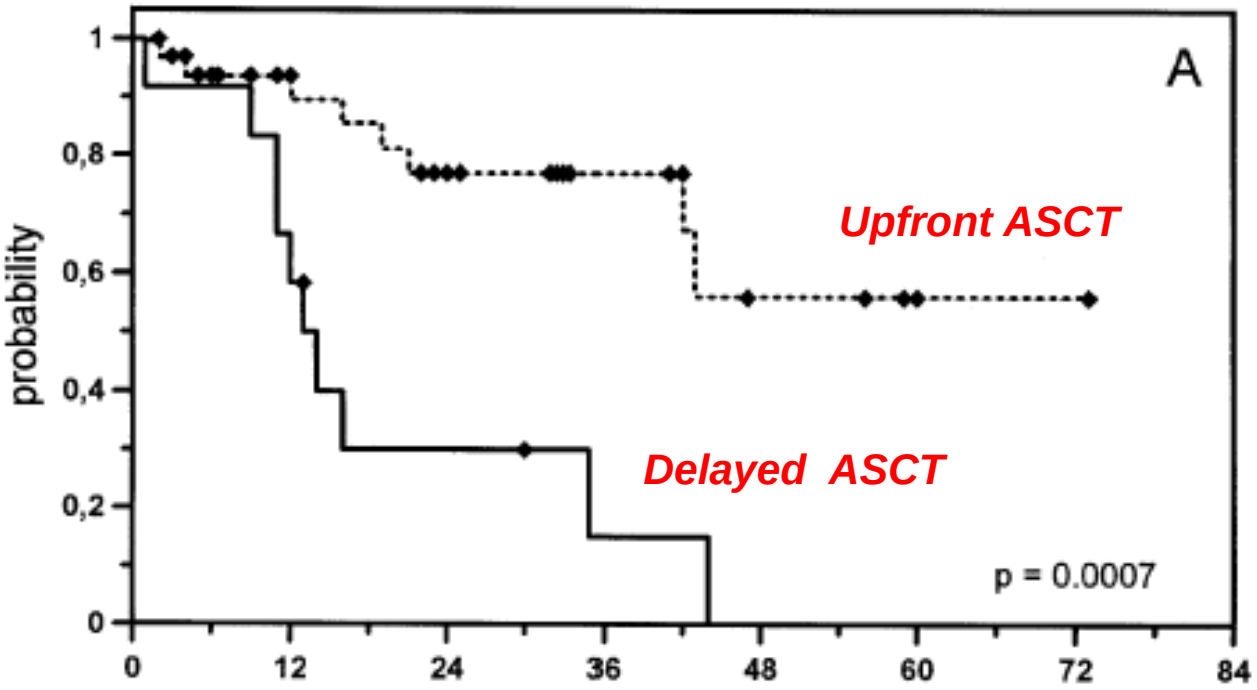
The impact of ASCT on the prognosis of MCL: a joint analysis of two prospective studies

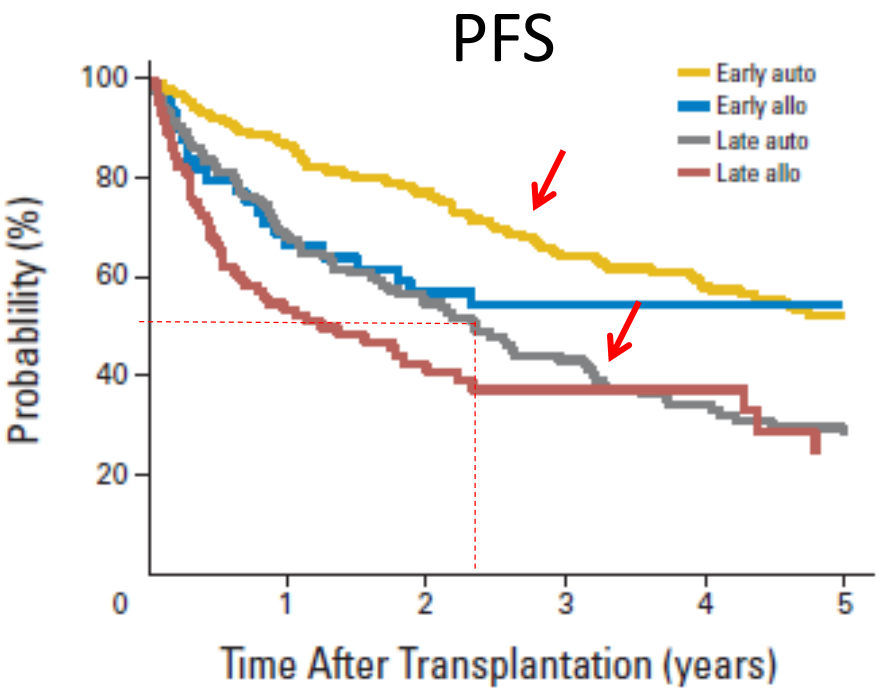
EFS post transplant according to timing of ASCT (46 pts)



Dreger C. et al. The Hematology Journal 1, 87-94, 2000

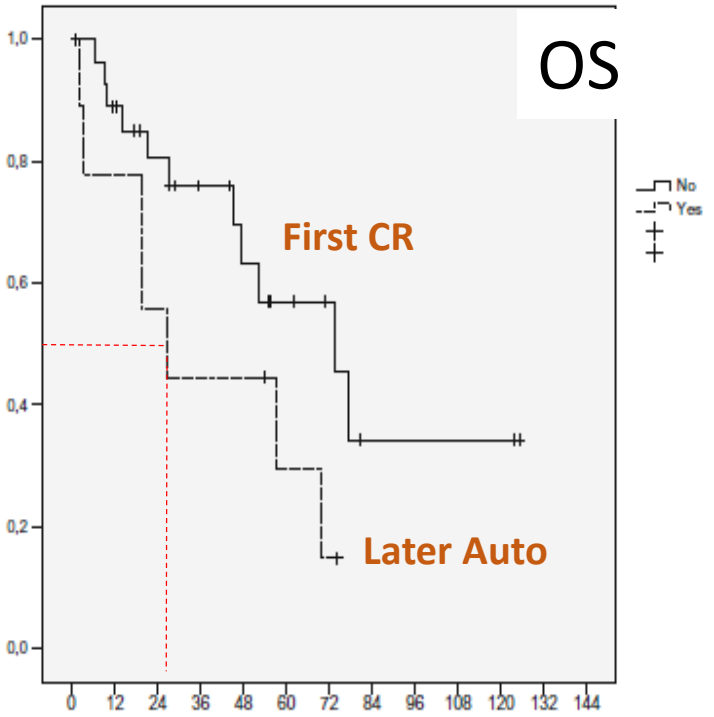
Patients receiving ASCT for Chemosensitive MCL

CIBMTR registry 1996-2007 (n=519)



Fenske CS, JCO 2013

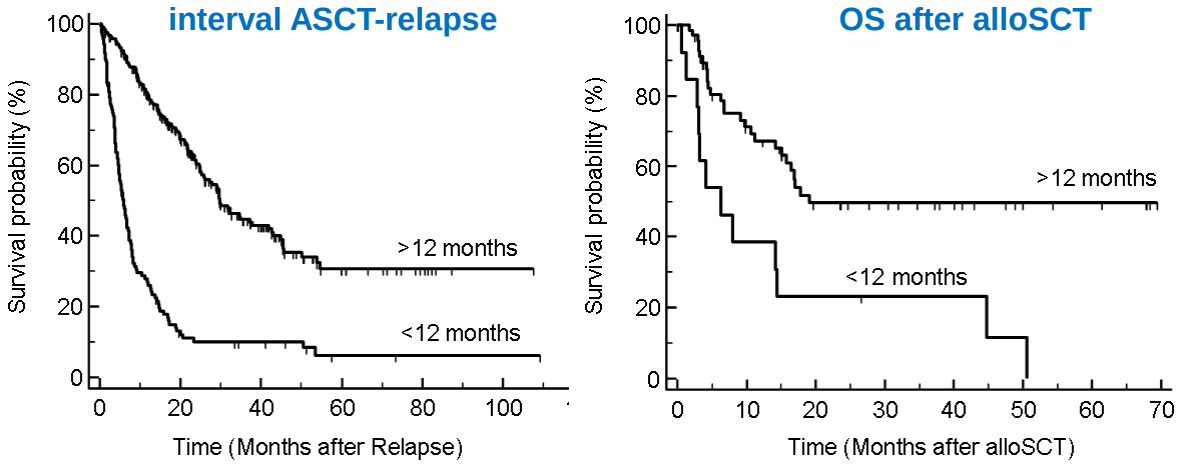
GELTAMO registry 1990-2011 (n=227)



Garcia-Noblejas A, Ann Hematol 2017

Failure after ASCT

- 366 EBMT pts with MCL relapsed after ASCT (1° line 64%; 68% prior rituximab; 49% prior HD-araC; 12% refractory to autoSCT).
- Salvage therapy= alloSCT in 23% and 2nd ASCT in 2%.
- Median f-up= 37 months.

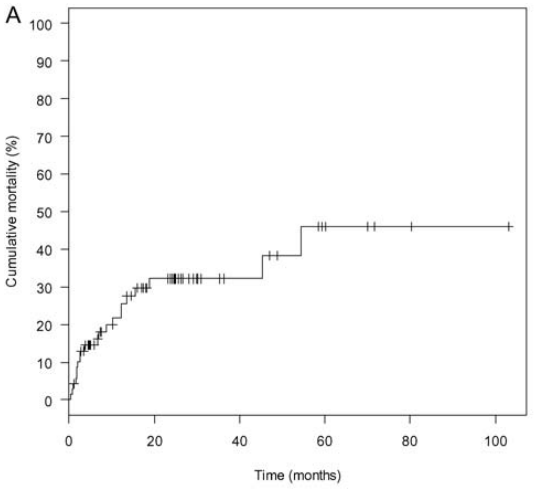


- **OS for pts who received a 2nd ASCT was very poor.**
- **AlloSCT performed for late relapse (>12 mo after ASCT) was associated with superior OS.**
- Donor source, T-cell depletion or conditioning intensity did not affect OS.

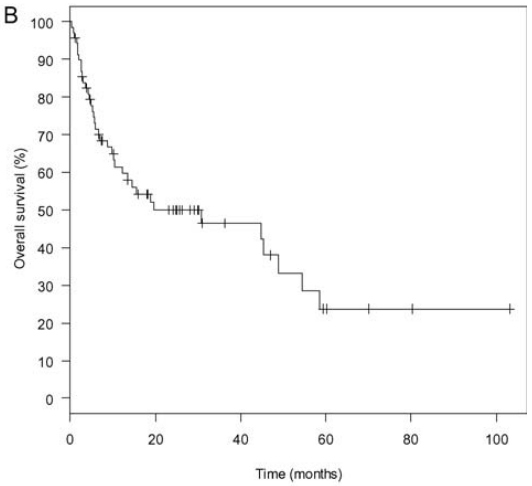
Diethich S, et al. Abstract #474 ASH 2012

RIC alloSCT in relapsed/refractory MCL: a multicenter experience

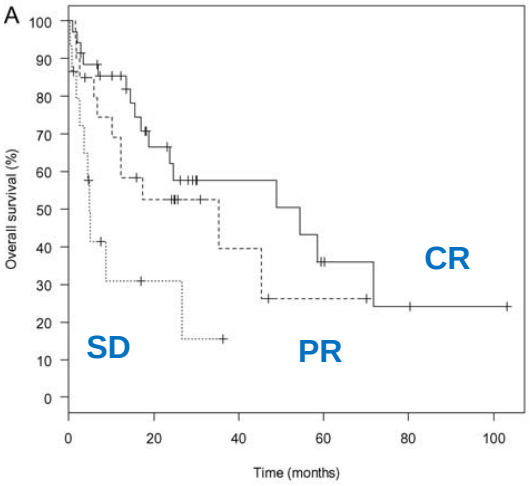
TRM



OS



OS by disease status prior SCT



70 patients
Reduced Intensity conditioning regimens
Median age 56 (33-67)
Previuos therapies: 2 (1-5)
Prior ASCT 44
Prior SCT: CR 55, PR 20, SD 15
2-year EFS, OS, TRM:
50%, 53%, 32%

Le Gouille S et al Ann Oncol 2012

Take home messages

- HDT- ASCT in relapsed refractory MCL leads to a significant shorter survival compared to ASCT in CR1/ PR1

- Allo-SCT should be considered in younger FIT RR/ MCL patients responding to salvage therapy

Salvage therapy for R/R MCL: outline of discussion

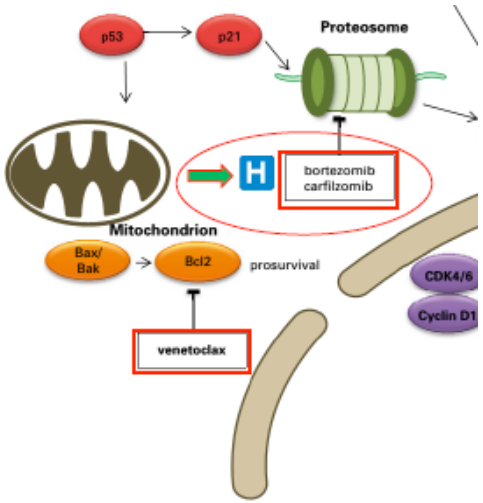
- Autologous stem cell transplatation (ASCT)
- Allogeneic stem cell transplantation (alloSCT)
- New biological drugs

MCL: new options

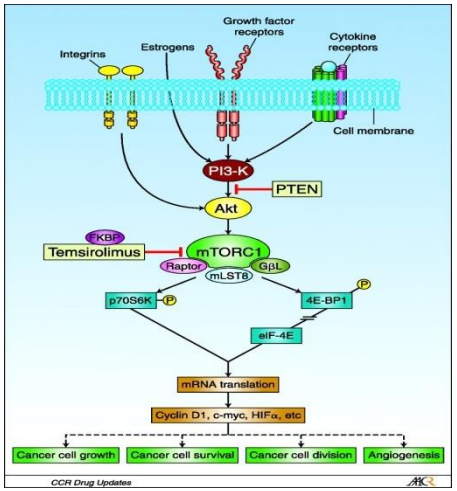
Signaling pathway inhibition

- Immunomodulators: lenalidomide
- Proteasome inhibitors: bortezomib
- mTOR inhibitors: everolimus, temsirolimus
- BCR inhibitors (BTKI: PCI-32765)
- Pro-apoptotic ABT-199 Bcl-2 family;

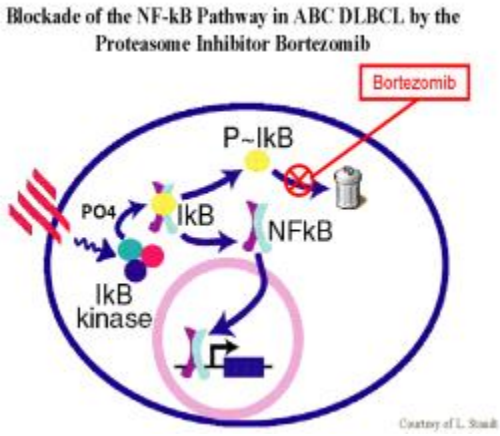
Venetoclax (ABT 199)



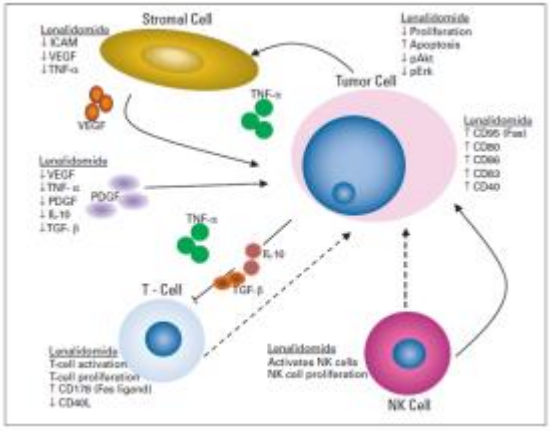
Temsirolimus



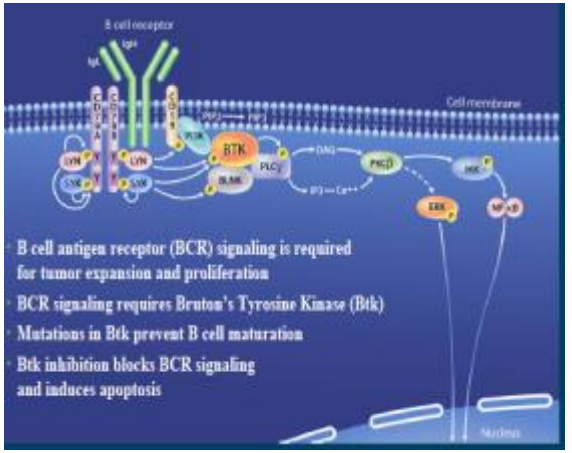
Bortezomib



Lenalidomide



Ibrutinib/Acalabrutinib



Novel approaches to R/R MCL

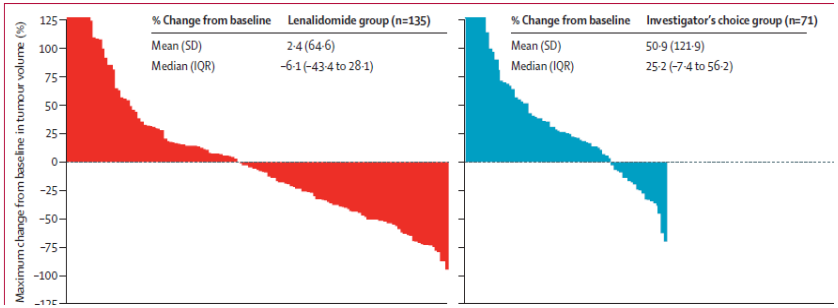
Agent	N	Response rate	m DOR
Bortezomib	155	33%	9.2 months
Temsirolimus	54	22%	7.1 months
Lenalidomide	134	28%	16.6 months
Lenalidomide+Ritux (R2)	52	57%	18.9 months
Idelalisib	40	40%	4 months
Ibrutinib	111	68%	17.5 months
Acalabrutinib	124	81%	72% at 12 months
Venetoclax(ABT-199)	28	75%	?

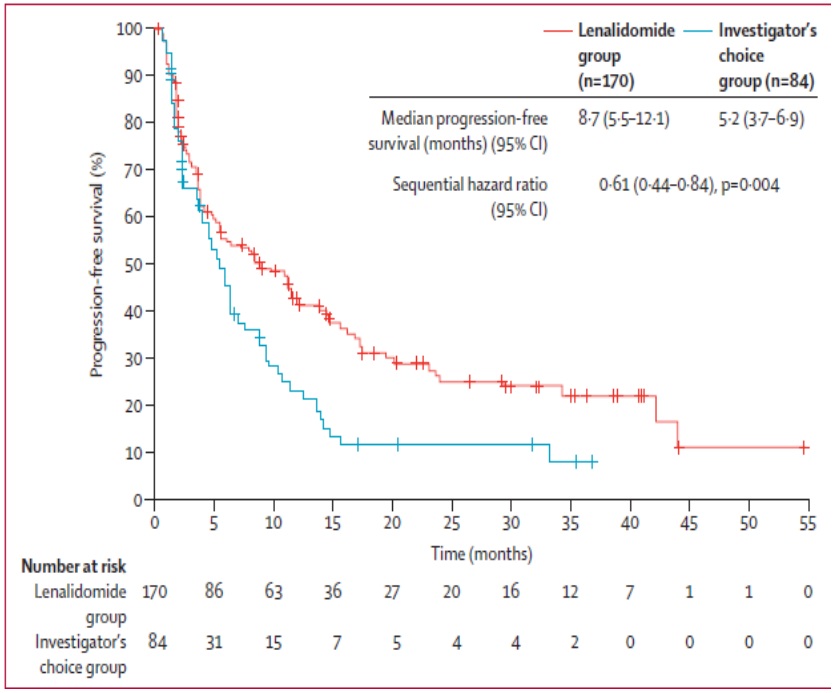
Lenalidomide vs investigator's choice in R/R MCL

Phase 2 randomized SPRINT trial

	Lenalidomide group (n=170)	Investigator's choice group (n=84)
Median age in years (range)	68·5 (44–88)	68·5 (49–87)
Age ≥ 65 years	115 (68%)	57 (68%)
Sex		
Male	123 (72%)	63 (75%)
Female	47 (28%)	21 (25%)
Mantle cell lymphoma stage at diagnosis		
I/II	13 (8%)	3 (4%)
III	30 (18%)	20 (24%)
IV	123 (72%)	59 (70%)
Missing	4 (2%)	2 (2%)
MIPI score at baseline		
Low	42 (25%)	21 (25%)
Intermediate	66 (39%)	37 (44%)
High	60 (35%)	25 (30%)
Missing	2 (1%)	1 (1%)
Ki-67 index >30%	31 (18%)	19 (23%)
Time from diagnosis to first dose‖		
<3 years	91 (54%)	44 (52%)
≥3 years	76 (45%)	39 (46%)
Median number of previous treatment regimens (IQR)	2 (1–3)	2 (1–3)

ORR 40% vs 11% (CR 5% vs 0%)

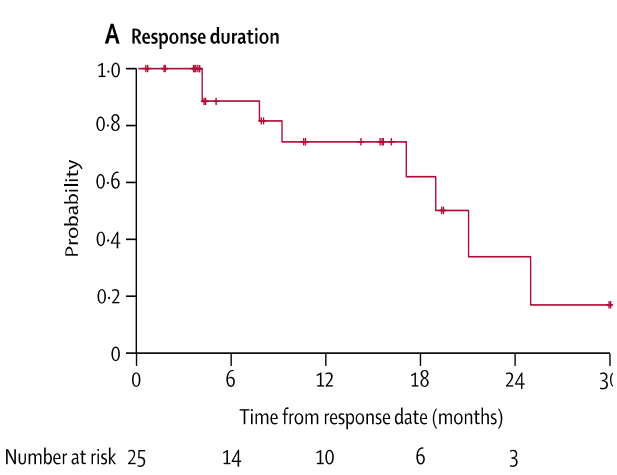




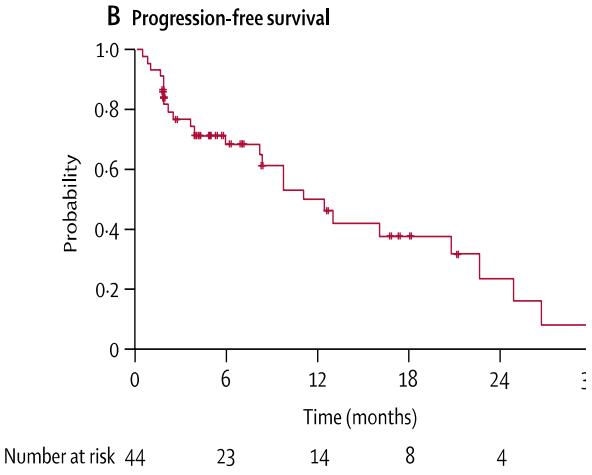
Trerny M et al, Lancet Oncol 2016

Lenalidomide with Rituximab in R/R MCL: phase 2

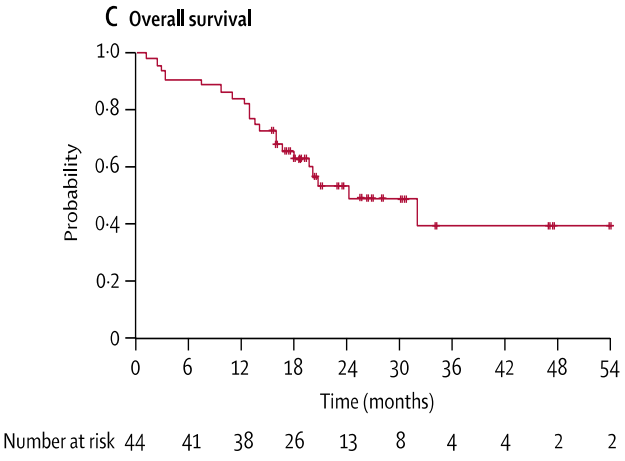
Response	N* 44 (%)
Overall response	25 (57)
Complete response	16 (36)
Partial response	9 (20)
Stable disease	10 (23)
Progressive disease	9 (20)



Median RD 18.9 months



Median PFS 11.1 months



Median OS 24.3 months

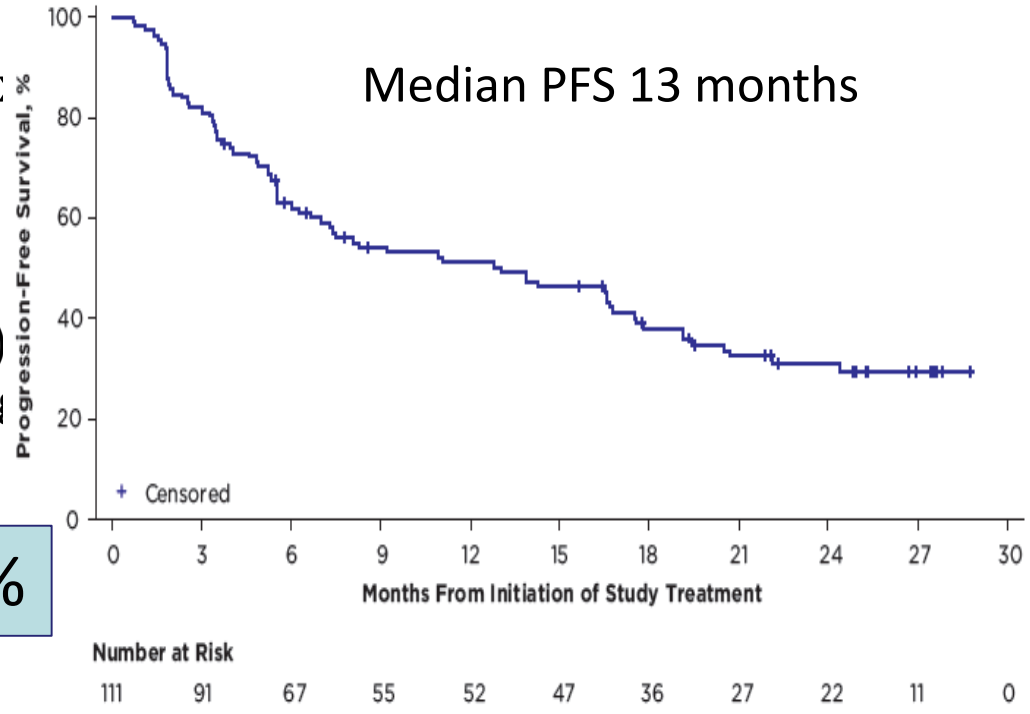
Wang et al, Lancet Oncology 2012

Single agent Ibrutinib in R/R MCL

Long-term follow-up: updated safety and efficacy results

111 pts, median 3 prior t:
Median f/u 27 months
Infection (78%, 28% gr ≥3)
Diarrhea (54%, 5% gr ≥3)
Bleeding (50.5%, 6% gr ≥3)
Atrial Fibrillation (11%, 6% g

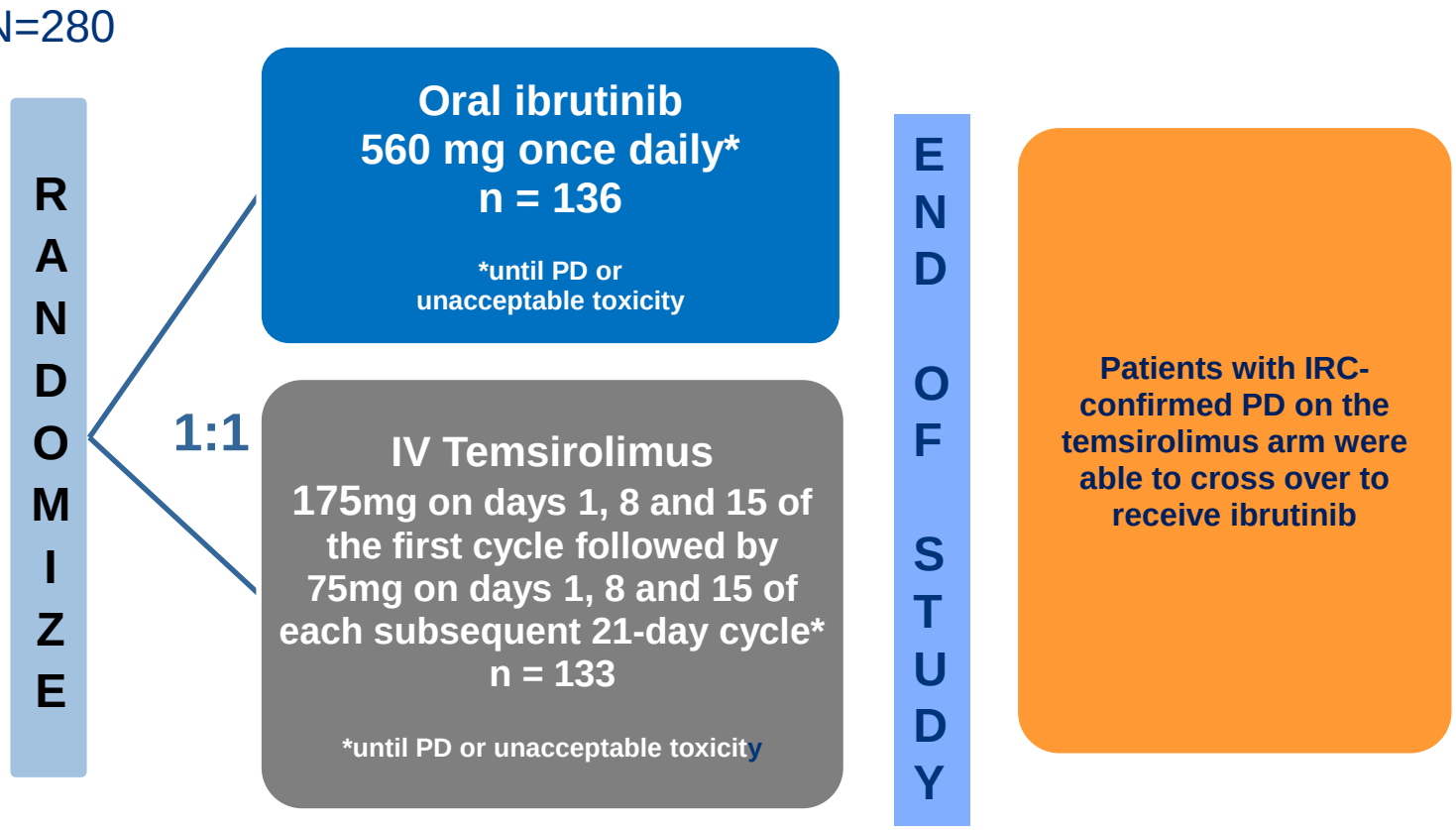
ORR 67%, CR 23%



Wang ML et al, Blood 2015

Ibrutinib Versus Temsirolimus in Patients With Relapsed or Refractory MCL: An International, Randomised, Open-Label, Phase 3 Study (MCL3001 Ray)

- Phase 3, International, open-label, randomized, multicenter study
- Relapsed or refractory MCL; at least 1 prior rituximab-containing therapy



Dreyling M et al, Lancet Oncol 2016

IRC, independent review committee;
PD, progressive disease.

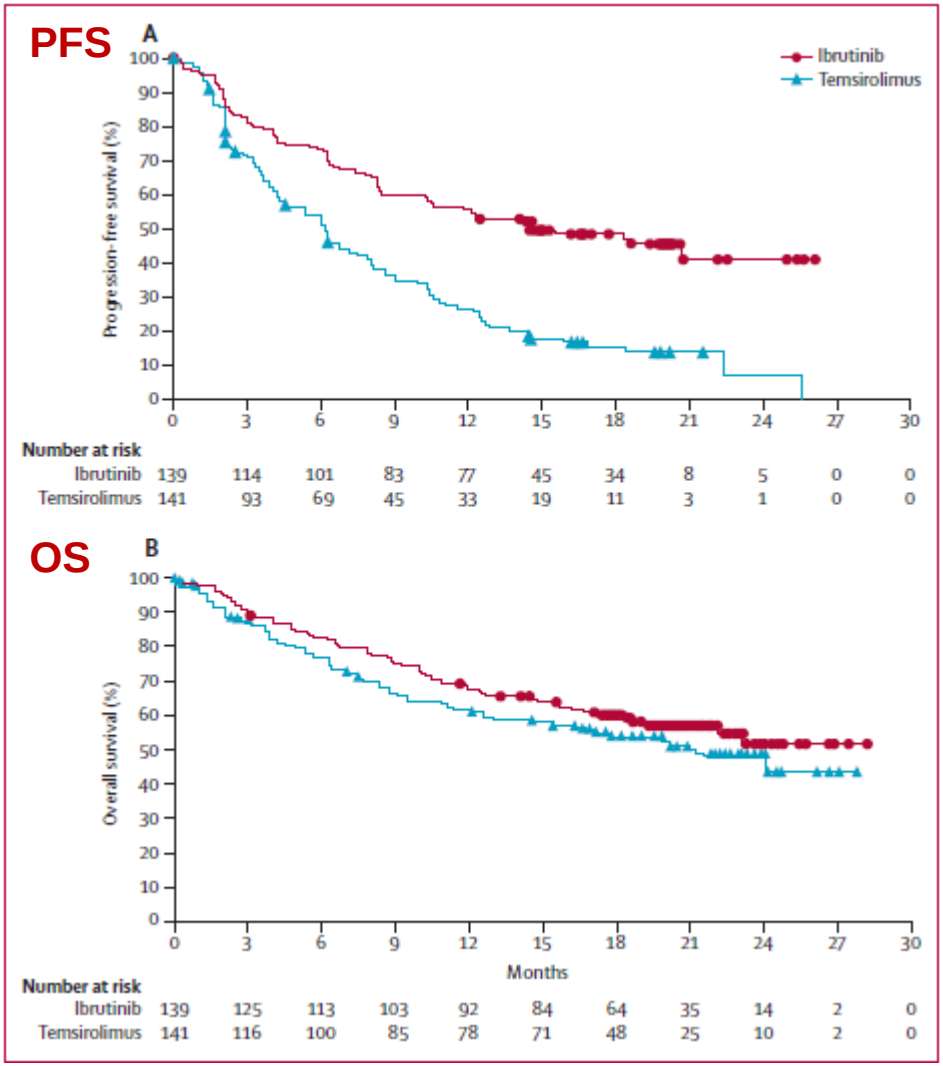
Open-Label, Phase 3 Study (MCL3001 Ray): Response and survival curves

Outcome, %	iBTK (n = 139)	Tems (n = 141)	*P* Value
ORR by IRC	71.9	40.4	< .0001
▪ CR	18.7	1.4	
▪ PR	53.2	39.0	
▪ SD	10.8	30.5	

✓ *23% of pts treated with temsirolimus crossed over to ibrutinib at progression*

Median DoR:

✓ Not reached (95% CI: 16.2-NE) with ibrutinib vs 7.0 mos (95% CI: 4.2-9.9) for temsirolimus.



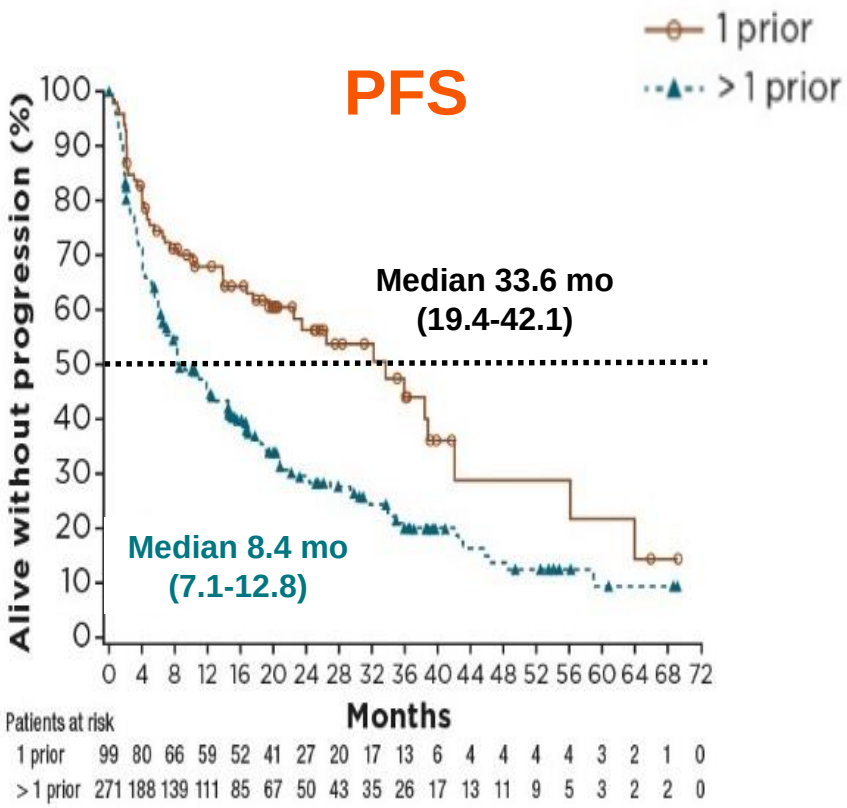
Median 3.5-year follow-up of Ibrutinib treatment in patients with relapsed/refractory MCL: A pooled analysis

	Total (Pooled) (N = 370)
Study, n (%)	
PCYC-1104	111
SPARK	120
RAY	139
Patients rolled over to CAN3001, n (%)	87 (23.5)
Median duration of follow-up, months (range)	41.1 (0.2-72.1)
Treatment discontinuation, n (%)	316 (85.4)
AE	37 (10.0)
Disease progression	218 (58.9)
Death	19 (5.1)
Other*	42 (11.4)

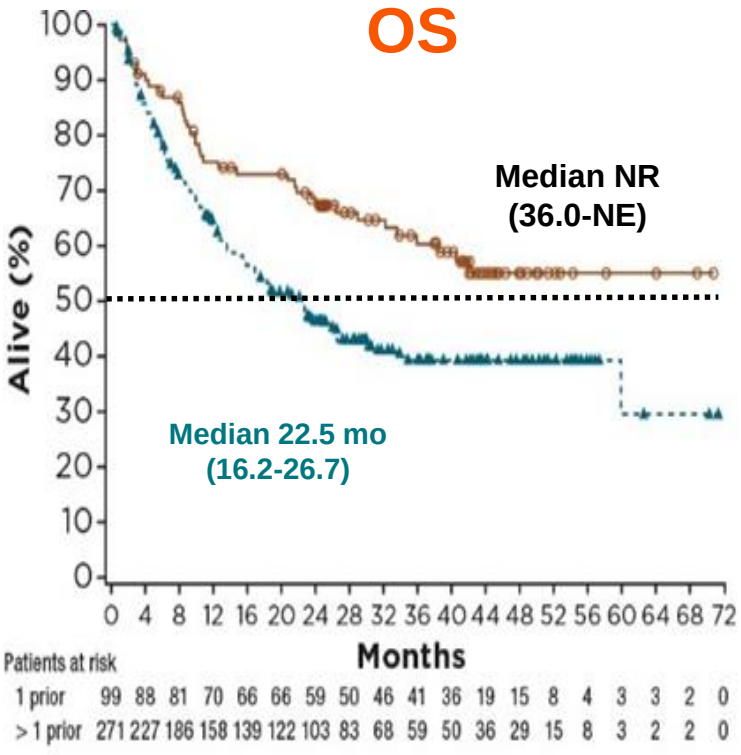
- Discontinuation rates due to AEs at time of primary analysis (median follow-up):
  - PCYC-1104 (15.3 months): 7%
  - SPARK (14.9 months): 7%
  - RAY (20 months): 6%

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: PFS and OS by prior line of therapy



Median PFS overall (95% CI): 13.0 (8.4-16.8) months

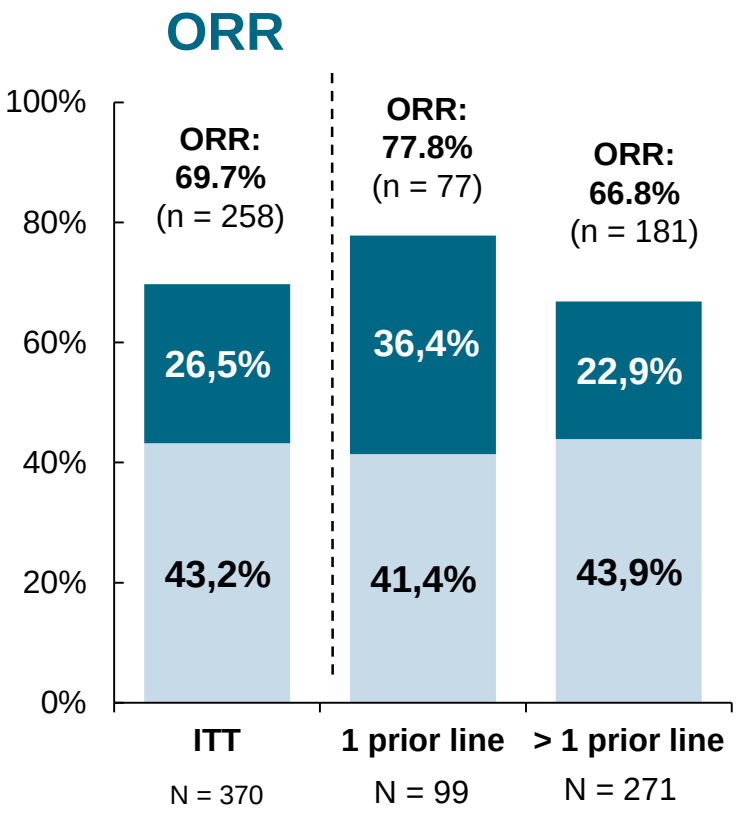


Median OS overall (95% CI): 26.7 (22.5-38.4) months

Median PFS was nearly 3 years in patients with 1 prior line of therapy

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: overall response and PFS/OS by best response



Median, Months (95% CI)	Best Response	
	CR (n = 98)	PR (n = 160)
PFS	46.2 (42.1-NE)	14.3 (10.4-17.5)
OS	NE (59.9-NE)	26.2 (21.6-34.7)

CR rate was 36% in patients with 1 prior line of therapy

Median PFS was nearly 4 years in patients who achieved a CR

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: cardiac risk factors and atrial fibrillation

- Studies enrolled patients with significant cardiac risk factors, including **53 patients with a history** of (or ongoing controlled) **AF/arrhythmia**

Patient History: Factors that May Increase Cardiac Risk, n (%)	Total (N = 370)
Hypertension	176 (47.6)
Hyperlipidemia	60 (16.2)
Atrial fibrillation/abnormal heart rhythm	53 (14.3)
Diabetes	48 (13.0)
Coronary artery disease	31 (8.4)

The majority (70%; 37 of 53) of patients who entered the study with a history of AF or arrhythmia did not have a recurrence

Rule et al., ASH 2017 (abstract 151, oral presentation)

Ibrutinib in MCL: management of ibrutinib in patients with bleeding or atrial fibrillation

Safety Population	Ibrutinib (N = 370)
Grade ≥ 3 bleeding	21 (5.7%)
Dose reduction	1 (0.3%)
Discontinuation*	3 (0.8%)
Grade ≥ 3 atrial fibrillation	22 (5.9%)
Dose reduction	2 (0.5%)
Discontinuation*	0

*Treatment discontinuation

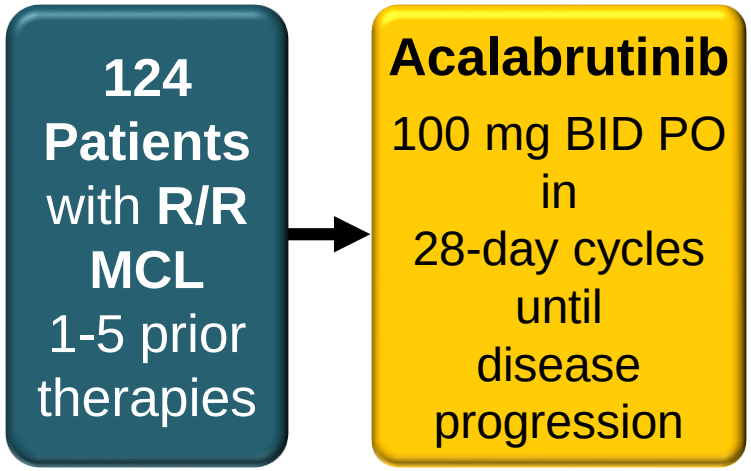
- **< 2% of 370 patients treated with ibrutinib discontinued or had a dose reduction due to grade ≥ 3 bleeding or AF**
- **No patients discontinued ibrutinib due to grade ≥ 3 AF**

Rule et al., ASH 2017 (abstract 151, oral presentation)

Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial

Michael Wang, Simon Rule, Pier Luigi Zinzani, Andre Goy, Olivier Casasnovas, Stephen D Smith, Gandhi Damaj, Jeanette Doorduijn, Thierry Lamy, Franck Morschhauser, Carlos Panizo, Bijal Shah, Andrew Davies, Richard Eek, Jehan Dupuis, Eric Jacobsen, Arnon P Kater, Steven Le Gouill, Lucie Oberic, Tadeusz Robak, Todd Covey, Richa Dua, Ahmed Hamdy, Xin Huang, Raquel Izumi, Priti Patel, Wayne Rothbaum, J Greg Slatter, Wojciech Jurczak

through January 5th, 2016, at 40 sites across, 9 countries



Data cutoff: February 28, 2017

Primary endpoint:

- ORR by investigator assessment based on the Lugano Classification[1]

Secondary endpoints:

- ORR by Independent Review Committee (IRC) assessment
- DOR, PFS, OS
- Safety
- Pharmacokinetics and pharmacodynamics

Exploratory endpoints:

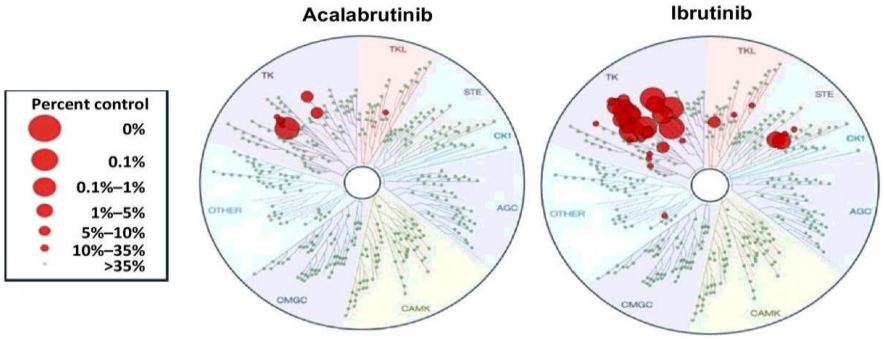
- Time to response
- IRC-assessed ORR per the 2007 International Harmonization Project criteria[2]

Wang et al., Lancet 2018

Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial

Michael Wang, Simon Rule, Pier Luigi Zinzani, Andre Goy, Olivier Casasnovas, Stephen D Smith, Gandhi Damaj, Jeanette Doorduijn, Thierry Lamy, Franck Morschhauser, Carlos Panizo, Bijal Shah, Andrew Davies, Richard Eek, Jehan Dupuis, Eric Jacobsen, Arnon P Kater, Steven Le Gouill, Lucie Oberic, Taduesz Robak, Todd Covey, Richa Dua, Ahmed Hamdy, Xin Huang, Raquel Izumi, Priti Patel, Wayne Rothbaum, J Greg Slatter, Wojciech Jurczak

Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared to Ibrutinib



Baseline characteristics	(n 124)
Median age (range)	68 (42-90)
Male gender	99 (80%)
ECOG ≤ 1	115 (93%)
MIPI low/interm/high	39%/44%/17%
AAS IV	93 (75%)
Median N prior Tx	2 (1-5)
Refractory disease	30 (24%)

Prior Tx:

- CHOP-based 64 (52%)
- BR 27 (22%)
- HyperCVAD 26 (21%)
- Bortezomib 24 (19%)
- SCT 22 (18%)
- Lenalidomide 9 (7%)

Wang et al., Lancet 2018

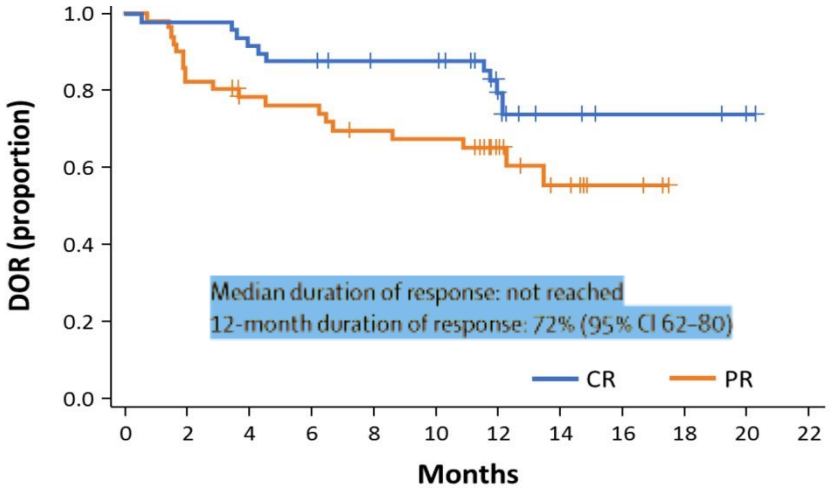
Acalabrutinib: results

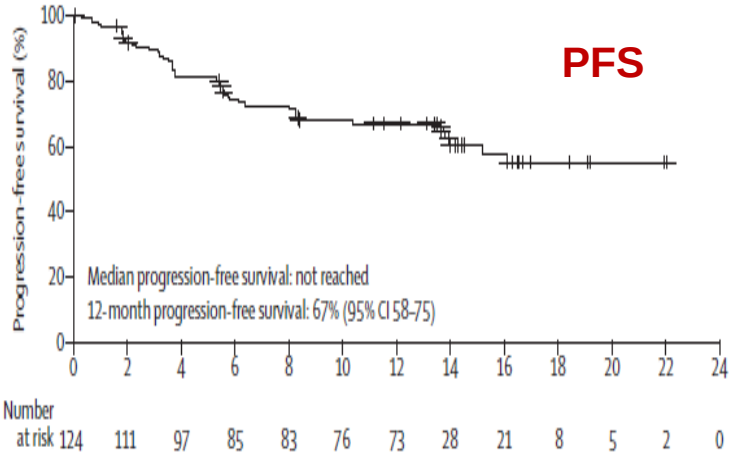
Table. Response by investigator assessment based on the Lugano Classification (Cheson, et al. 2014)

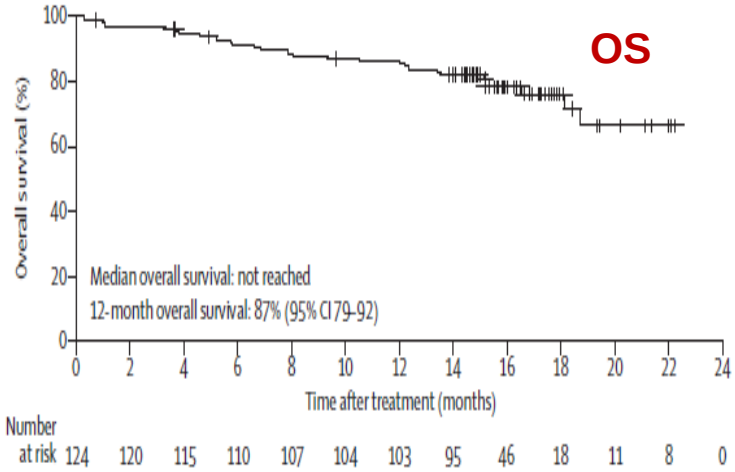
	All patients (N=124)	
	n (%)	95% CI, %
ORR (CR + PR)	100 (81)	73-87
Best response		
CR	49 (40)	31-49
PR	51 (41)	32-50
SD	11 (9)	5-15
PD	10 (8)	4-14
NE	3 (2)	1-7

Duration of Response

median time to initial response 1.9 months



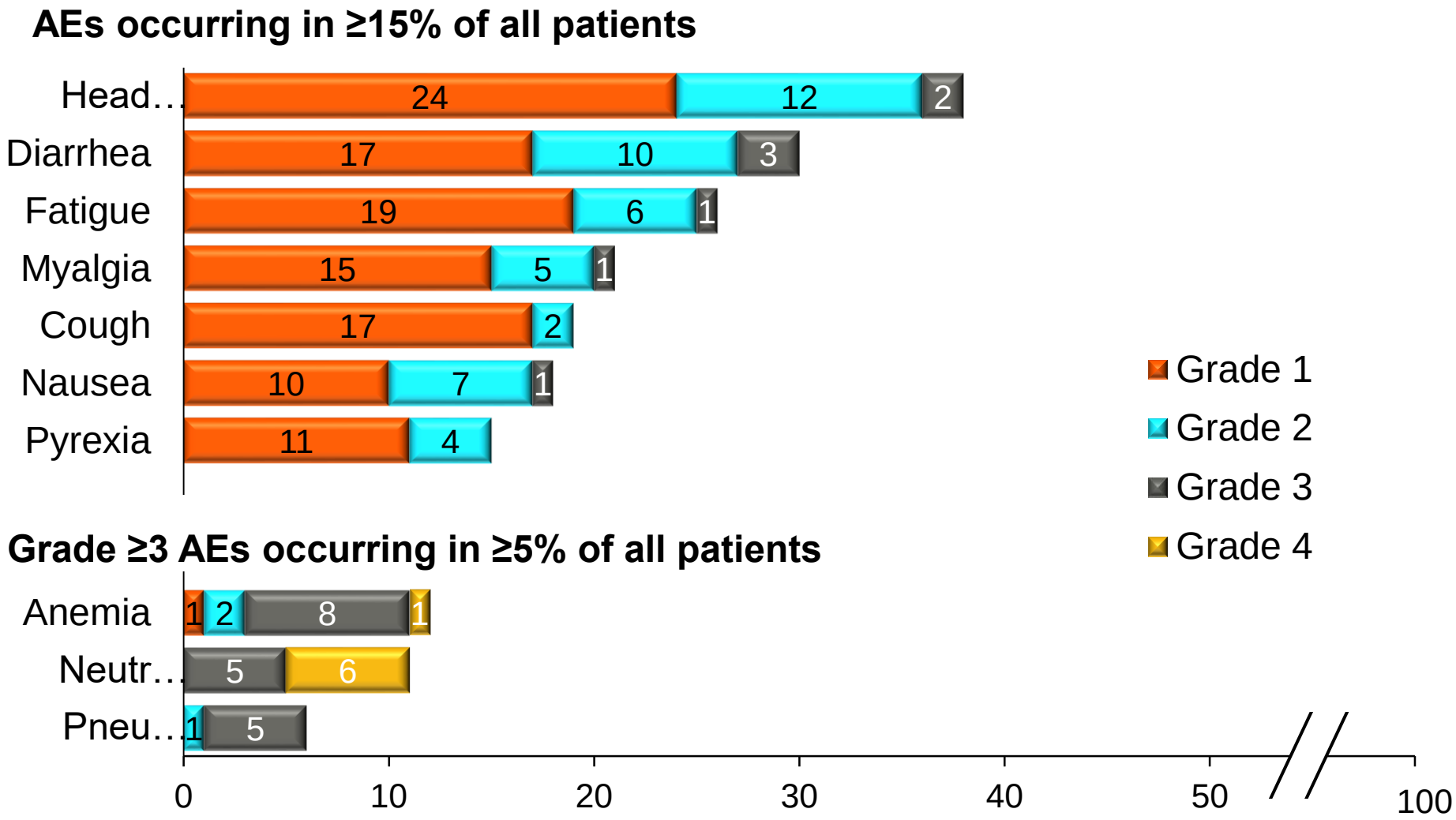




Wang et al, Lancet 2018

Acalabrutinib: safety

- At a median follow-up of 15.2 months, 56% of patients remain on treatment



Wang et al, Lancet 2018

Acalabrutinib vs Ibrutinib in R/R MCL

Agent	Ibrutinib 560mg/day	Acalabrutinib 100 mg 2x/day
N.patients	370	124
Median age	67.5	68
Median prior lines of therapy	2 (1-9)	2 (1-2)
SMIPI high	32%	17%
SMIPI int	45%	44%
SMIPI low	24%	39%
Blastoid	12%	NR
Prior SCT	34%	18%
Refractory	NR	24%

Compared to Ibrutinib (n=370) pooled data (3 trials), more favorable patient population in the Acalabrutinib trial (n=124)

Acalabrutinib vs Ibrutinib in R/R MCL

- Acalabrutinib appears to have better safety profile
  - very infrequent atrial fibrillation and bleeeding
    more headache
- Acalabrutinib was used in less heavily pre-treated patients
  - Head to head trial of ibrutinib vs acalabrutinib (ACE-CL-006) is pending

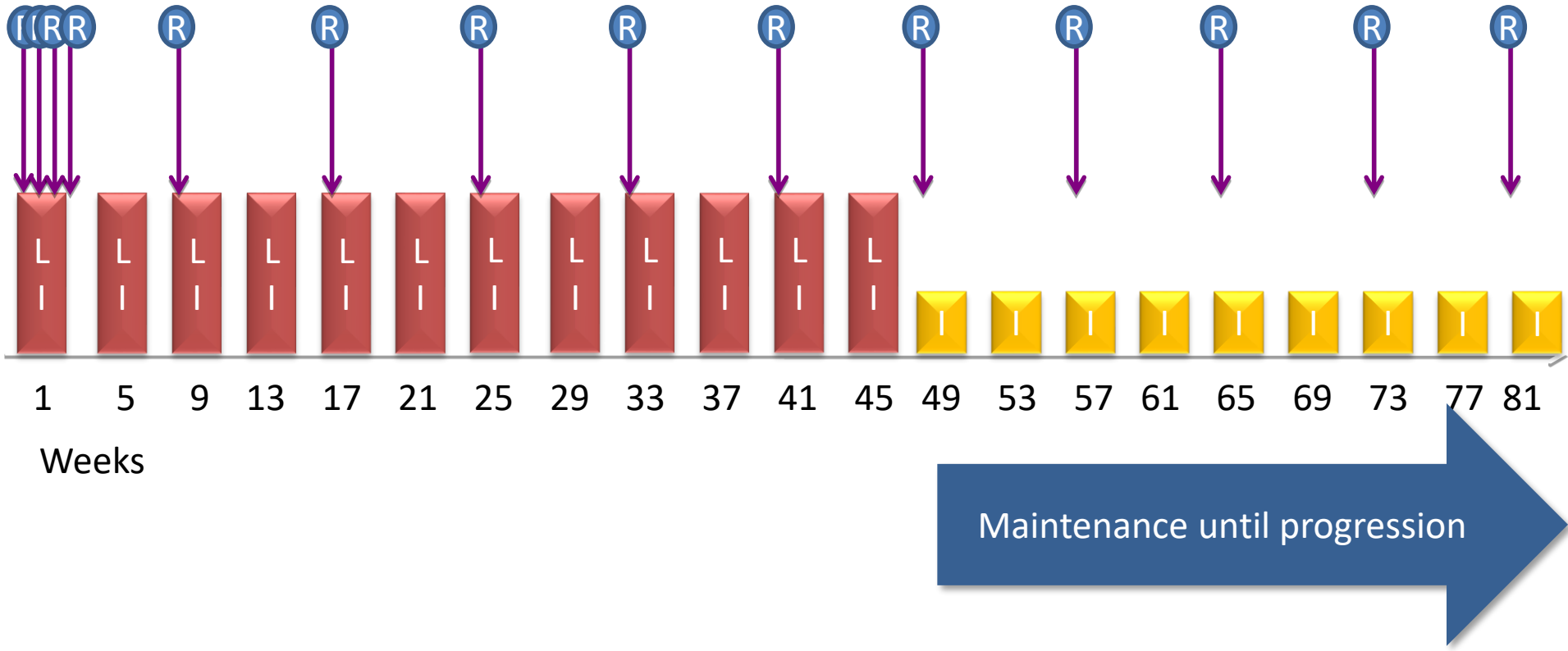
- In MCL , therapeutic chose based on patients factors
- If patients fails a BTK inhibitor, consider switch to Venetoclax
- If a BTK inhibitor is stopped for toxicity, use alternative BTK

- Acalabrutinib plus BR, and other combination,in current trials

Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial

Mats Jerkeman, Christian Winther Eskelund, Martin Hutchings, Riikka Räty, Karin Fahl Wader, Anna Laurell, Helle Toldbod, Lone Bredo Pedersen, Carsten Utoft Niemann, Christina Dahl, Hanne Kuitunen, Christian H Geisler, Kirsten Grønbæk, Arne Kolstad

Ibrutinib+Lenalidomide+Rituximab PHase II study



Jerkeman M Lancet Hematology 2018

Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial

Mats Jerkeman, Christian Winther Eskelund, Martin Hutchings, Riikka Räty, Karin Fahl Wader, Anna Laurell, Helle Toldbod, Lone Bredo Pedersen, Carsten Utoft Niemann, Christina Dahl, Hanne Kuitunen, Christian H Geisler, Kirsten Grønbæk, Arne Kolstad

Patient characteristics	
N^	50
Age >	69 (45-85)
Previous Tx (range)	2 (1-7)
ASCT Allo Ibrutinib Lenalidomide	21 (42%) 3 (6%) 4 (8%) 1 (2%)
Evaluable for genetic aberration	49

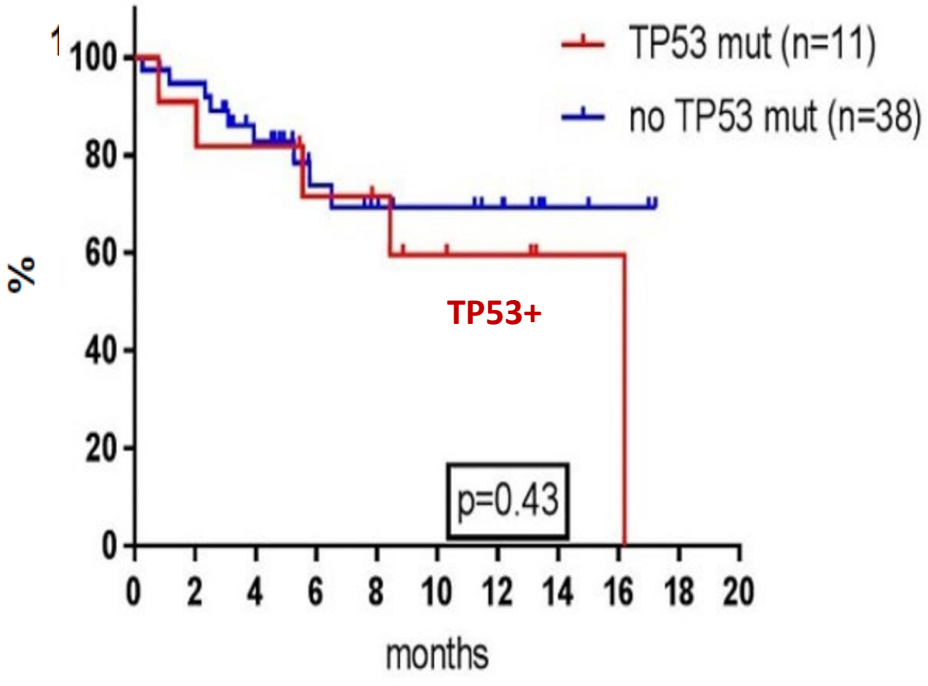
Response to treatment

	All patients (n=50)	*TP53* unmutated (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)

No difference in overall and CR rate among patients with and without TP53 mutation

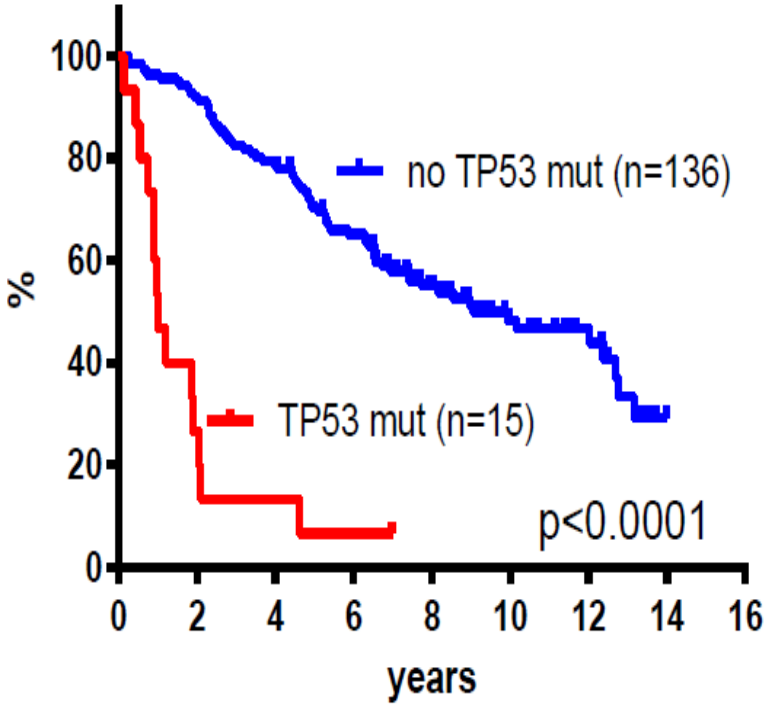
PFS according to TP53 mutation

NORDIC MCL6 PHILEMON



Jerkeman M et al, ASH 2016, ABSTR 148

NORDIC MCL2/3



Eskelund C et al, Blood 2017

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma

Matthew S. Davids, Andrew W. Roberts, John F. Seymour, John M. Pagel, Brad S. Kahl, William G. Wierda, Soham Puvvada, Thomas J. Kipps, Mary Ann Anderson, Ahmed Hamed Salem, Martin Dunbar, Ming Zhu, Franklin Peale, Jeremy A. Ross, Lori Gressick, Monali Desai, Su Young Kim, Maria Verdugo, Rod A. Humerickhouse, Gary B. Gordon, and John F. Gerecitano

Characteristic, n (%)		All N=106	MCL n=28	FL n=29	DLBCL n=41 [a]	Other [b] n=8
Age, years	Median (range)	66 (25–86)	72 (35–85)	64 (46–75)	67 (25–86)	63 (56–73)
Prior therapies	Median (range)	3 (1–10)	3 (1–7)	3 (1–10)	3 (1–8)	4 (2–6)
	Rituximab-refractory	33 (31)	8 (29)	8 (28)	16 (39)	1 (33)
Bulky nodes	>5 cm	49 (48)	16 (59)	8 (29)	22 (54)	3 (38)
	>10 cm	14 (14)	3 (11)	2 (7)	8 (20)	1 (13)
LDH	> Upper Limit of Normal	45 (44)	7 (27)	10 (35)	27 (68)	1 (13)

[a] Includes 7 patients DLBCL-Richter's transformation

[b] Includes n=4 WM, n=3 MZL, n=1 MM

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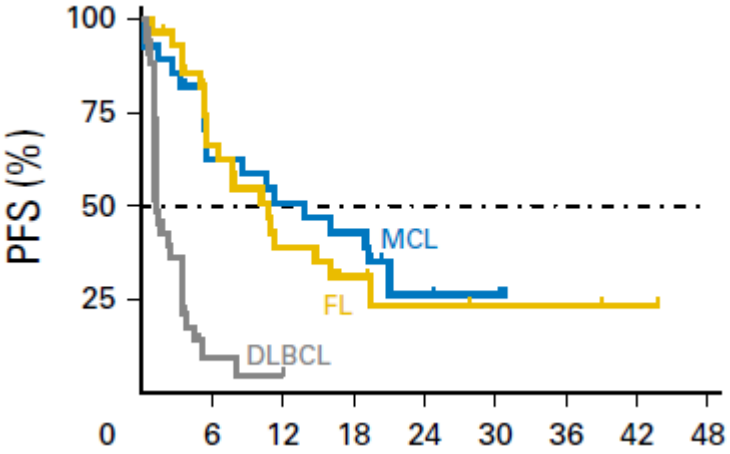
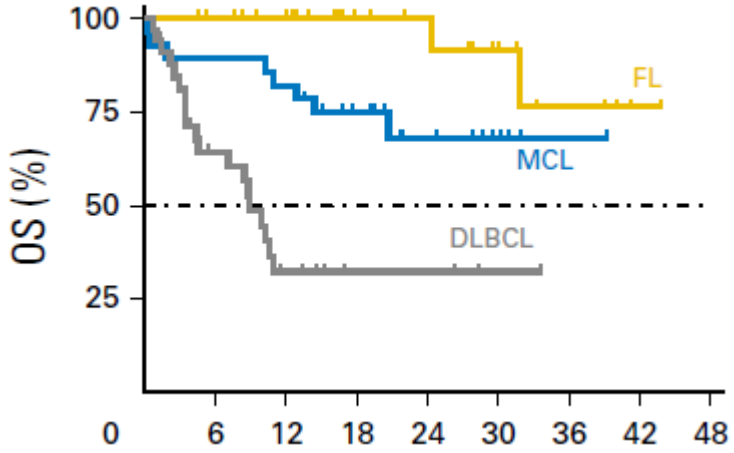
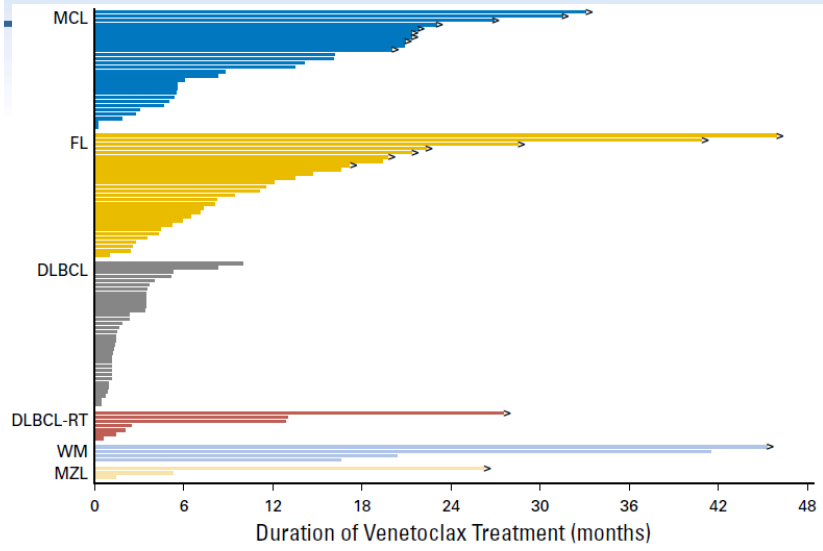
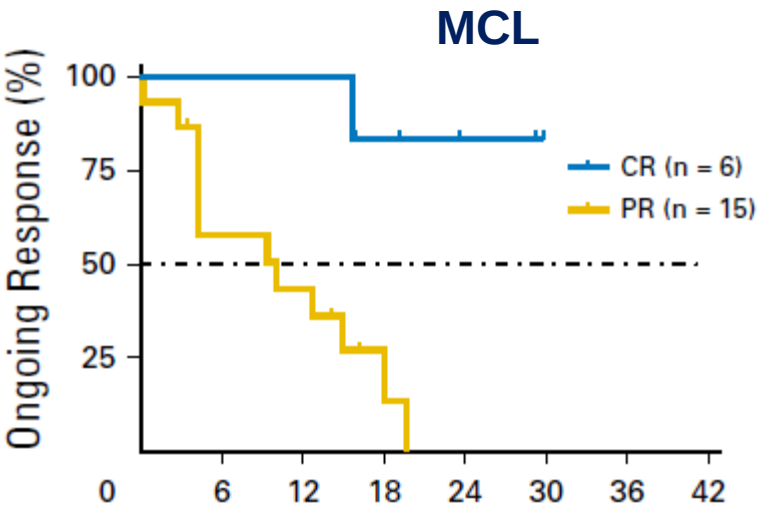




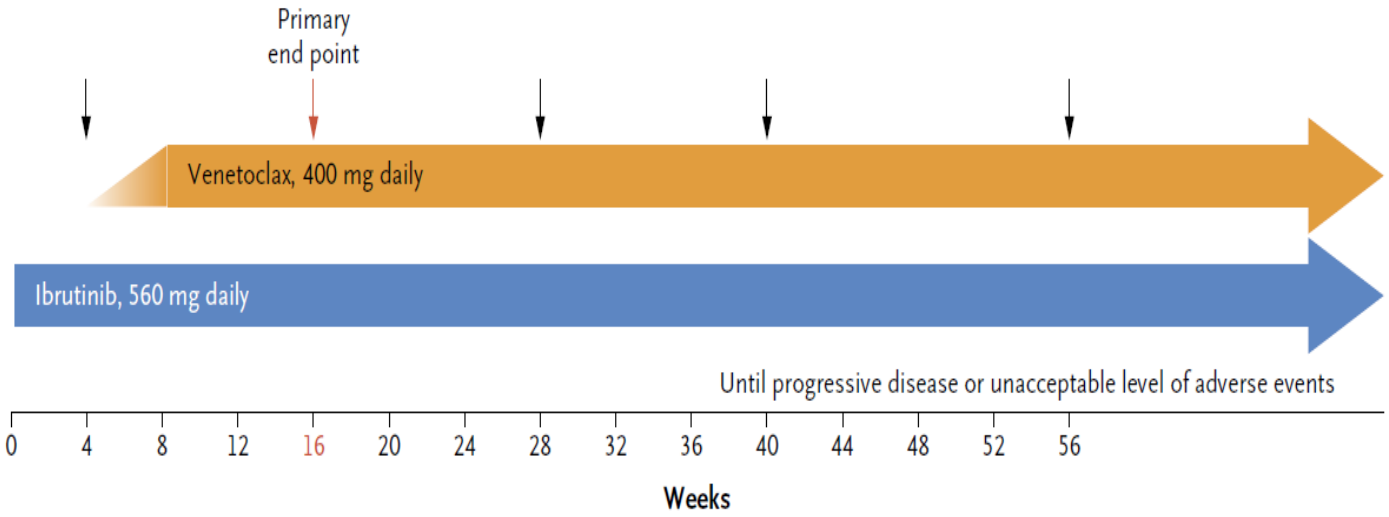




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma



Tam CS et al, NEJM 2018

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

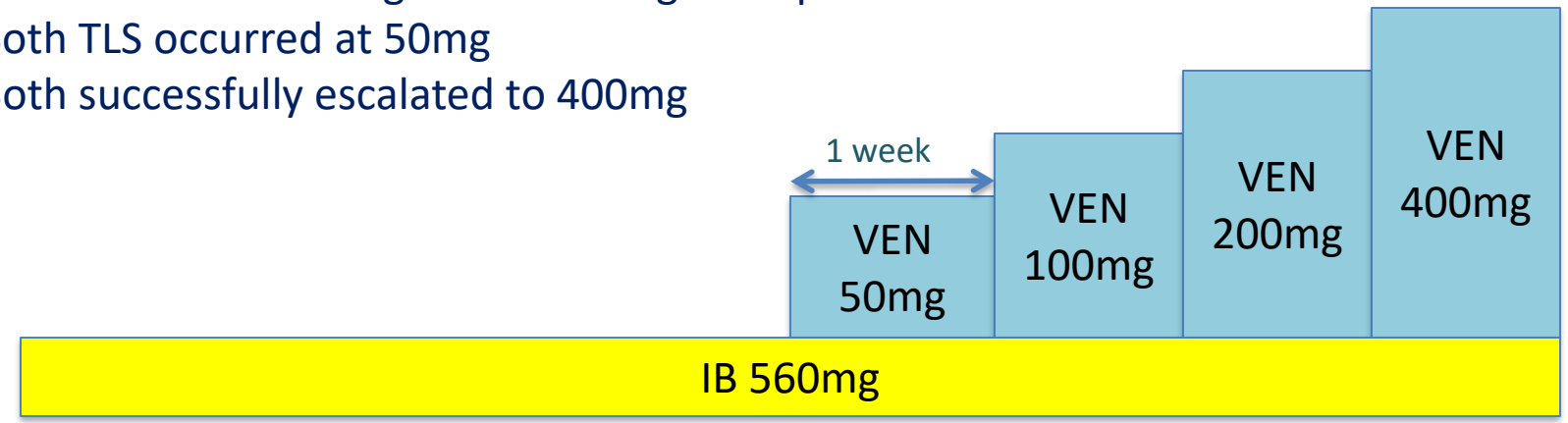
24 pts

Characteristic	Value
Median age (range) — yr	68 (47–81)
Sex — no. (%)	
Female	3 (12)
Male	21 (88)
Previous treatment for mantle-cell lymphoma — no. (%)	
Yes	23 (96)
No†	1 (4)
No. of previous therapies among patients who had received therapy — median (range)‡	2 (1–6)
Previous therapy — no./total no. (%)‡	
Autologous transplantation	7/23 (30)
Rituximab	23/23 (100)
Anthracycline	21/23 (91)
High-dose cytarabine	11/23 (48)
Bendamustine	4/23 (17)
Blastic or pleomorphic mantle-cell lymphoma — no./total no. (%)	1/21 (5)
Ki-67 ≥30% — no./total no. (%)	9/21 (43)
TP53 status — no. (%)	
Mutated with deletion	4 (17)
Mutated without deletion	7 (29)
Deletion without mutation	1 (4)

Tam CS et al, NEJM 2018

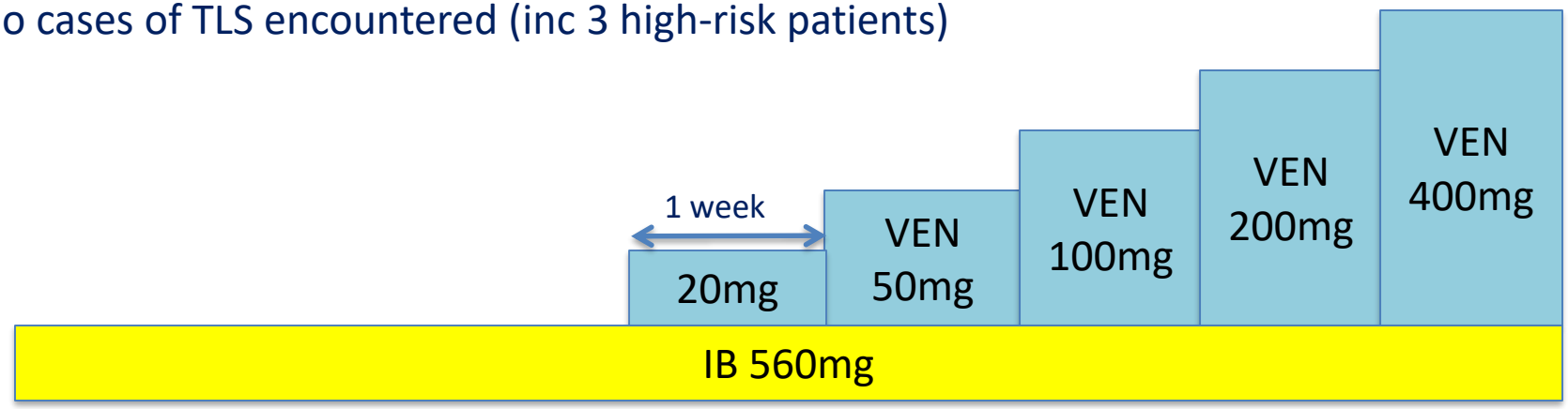
Tumour Lysis Syndrome

N = 16 treated using initial schedule
2 cases of TLS* among 4 baseline high-risk patients
Both TLS occurred at 50mg
Both successfully escalated to 400mg



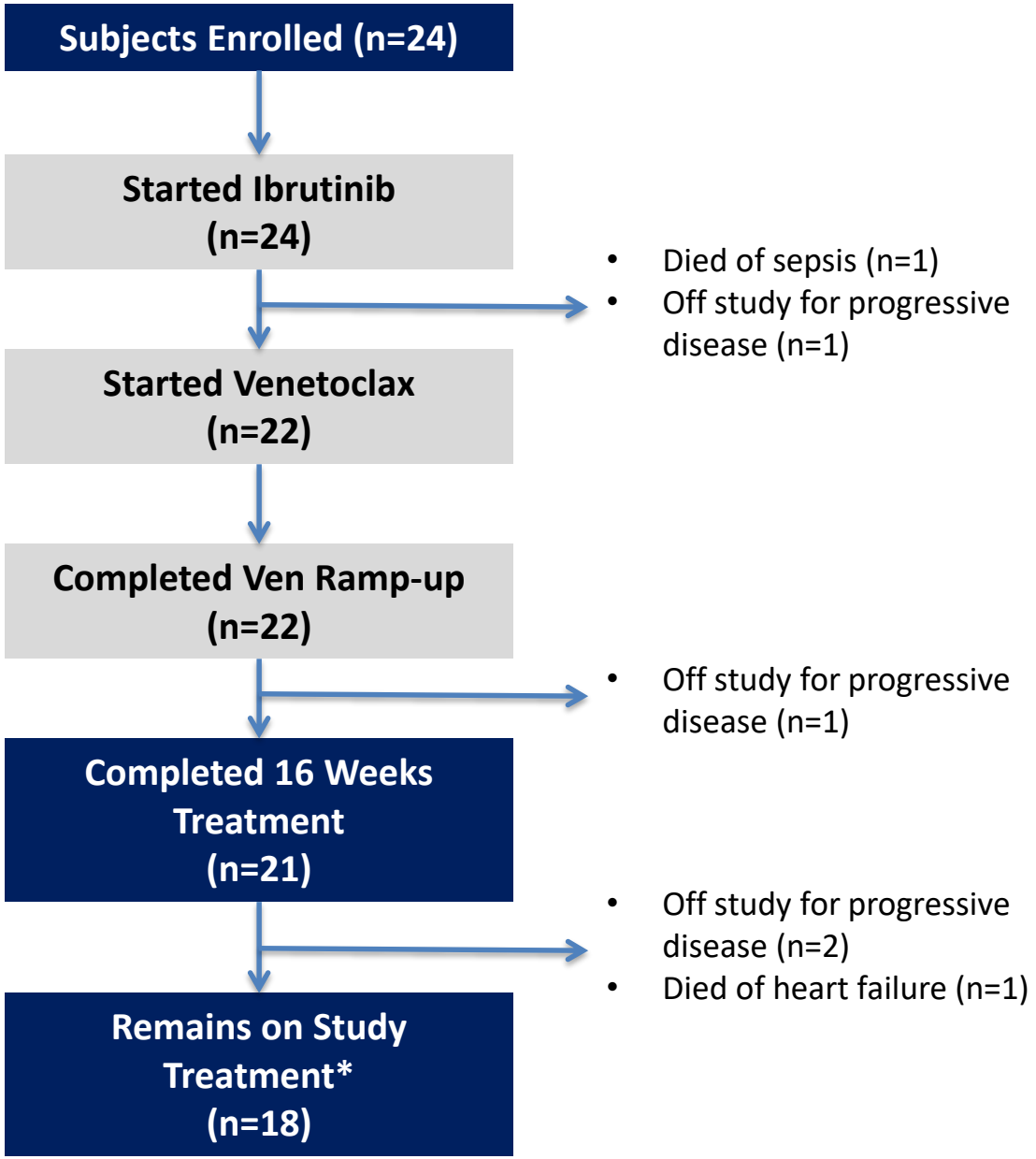
one case of grade 3 clinical TLS (acute renal impairment); one case of self-limiting fever, hyperphosphataemia and 400% elevation in LDH, regarded as grade 3 biochemical TLS in absence of alternative explanation.

N = 8 treated using revised schedule (20mg start)
No cases of TLS encountered (inc 3 high-risk patients)



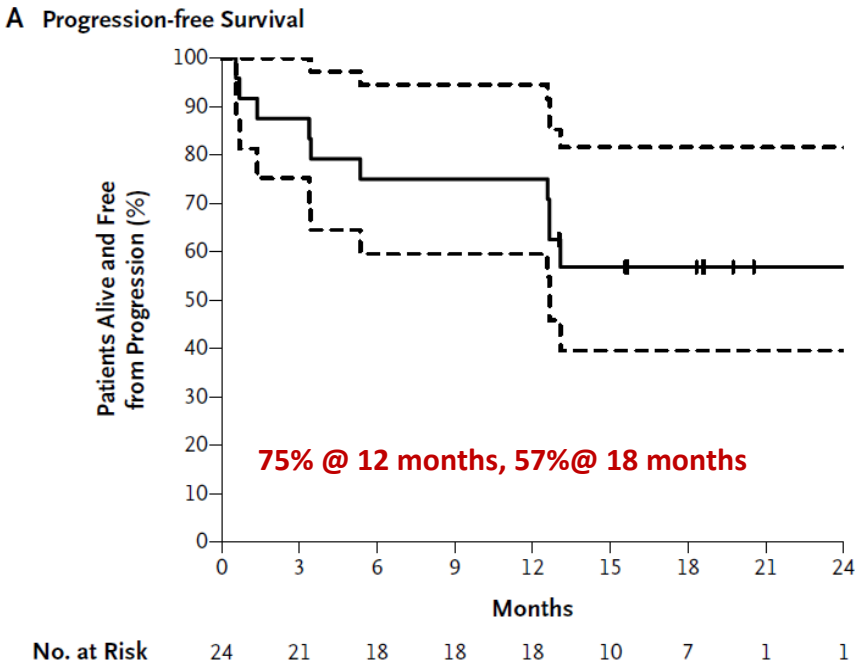
Data-Cutoff 10-Jan-2017

Median Follow-up 8.3 months (1.4 to 17.7+ months)



Venetoclax & ibrutinib in relapsed MCL

PFS



75% @ 12 months, 57%@ 18 months

Response@ wk 16	No PET (N= 24)	PET (N = 24)
CR (%)	10 (42)	15 (62)
PR (%)	4 (17)	2 (8)
PD (%)	3 (12)	4 (17)

Toxicity

Toxicity mostly Grade 1-2

diarrhea, fatigue

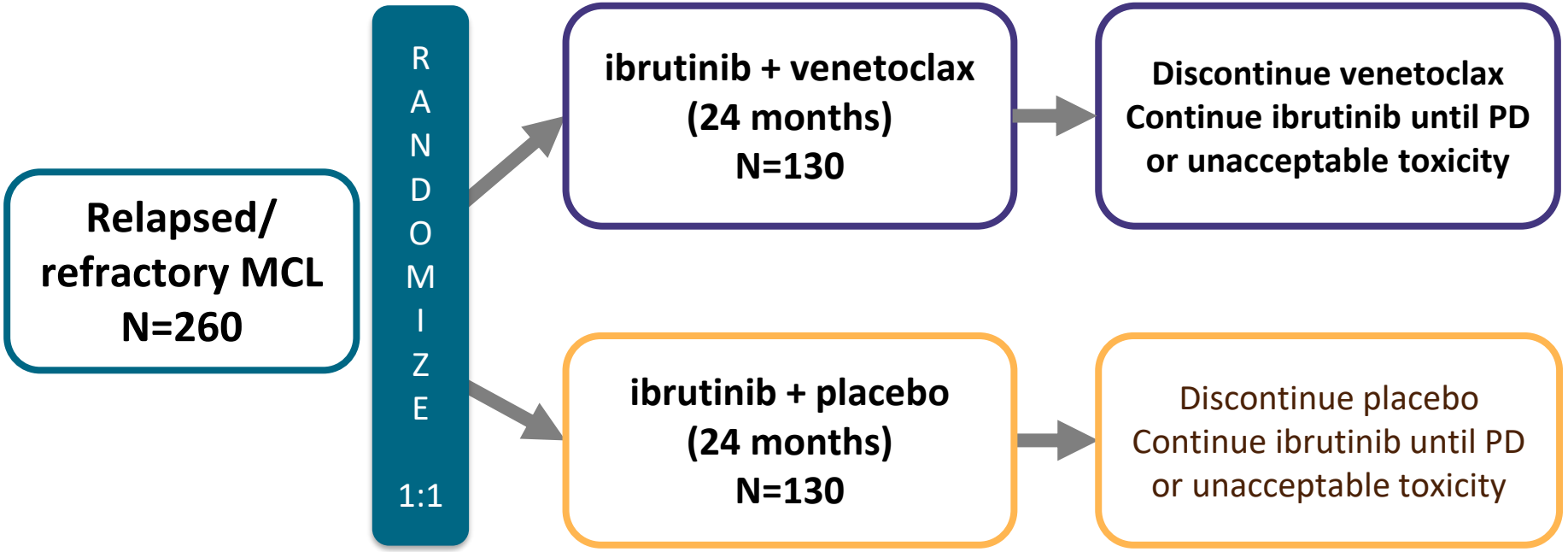
Grade 3-4

- 33% neutropenia
- 12% diarrhea
- 4% bleeding
- 8% atrial fibrillation
- 8% tumor lysis

Tam et al, NEJM 2018

Phase 3 Study Design of PCYC-1143: SYMPATICO

Randomized Post-Safety Run-In Period



Primary Endpoint

- PFS*

*Investigator-assessed.

KLIMT phase II study: R/R MCL

Lenalidomide (maximum period of treatment= *24 cycles*)

- Lenalidomide: 25* mg/daily on day 1 to 21 of a 28 days course

* For patients with creatinine clearance ≥ 30 mL/min but < 50 mL/min the dosage of R will be 10 mg/daily on day 1 to 21 of a 28 days course;

Carfilzomib (maximum period of treatment= *24 cycles*)

- *Cycles 1-12*: Carfilzomib: on days 1, 2, 8, 9, 15, 16

  The dosage of Carfilzomib will be 20 mg/m^2 on days 1 and 2 during cycle 1 and then Carfilzomib 27 mg/m^2 thereafter;
- *Cycles 13-24*: Carfilzomib: on days 1, 2, 15, 16

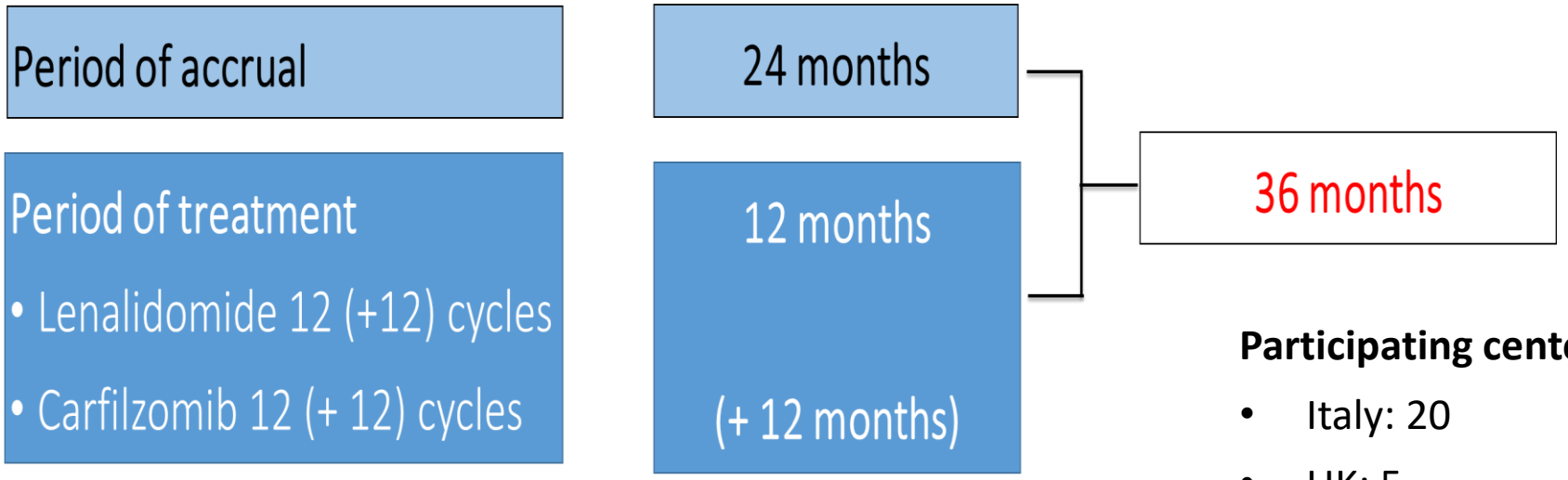
  The dosage of Carfilzomib will be 27 mg/m^2

Dexamethasone (maximum period of treatment= *24 cycles*)

- Dexamethasone 20 mg on days 1-2, 8-9, 15-16, 22-23
- Dexamethasone 10 mg on days 1-2, 8-9, 15-16, 22-23 (age > 75)

Francesco Zaja Principal Investigator

KLIMT study: timing centers



Participating centers:

- Italy: 20
- UK: 5
- Spain: 4
- Poland: 3
- The Netherlands : 2

The anticipated study dates (start/end) are:

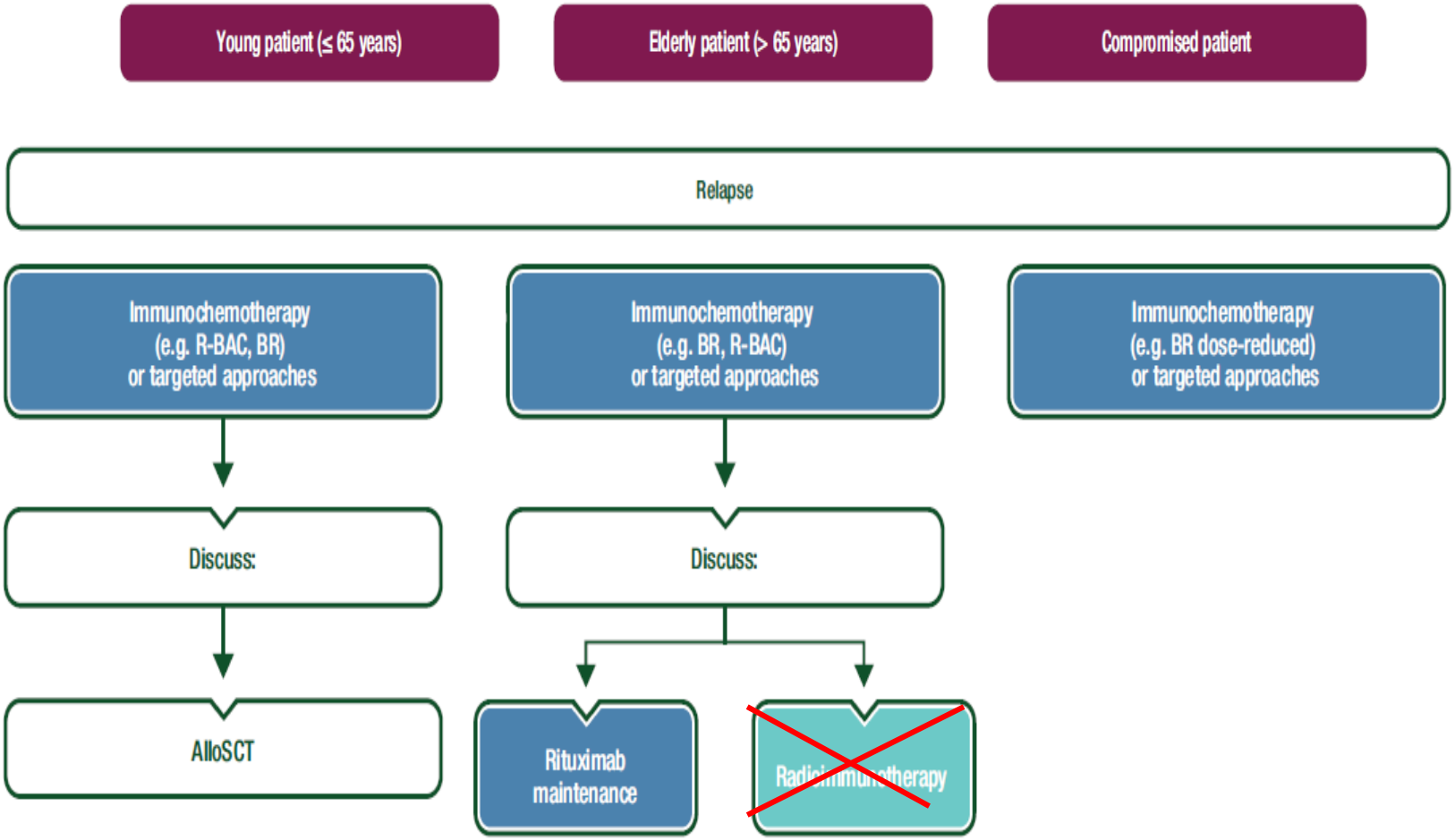
- 1st patient enrolled (FPFV): January 2018 (?)
- Last patient enrolled (LPLV): December 2019 (?)

Patients will be evaluated at 12 cycles after the start of treatment of the last patient

Responsive patients (CR, PR, SD) may continue to receive KL until to 24 cycles.

Francesco Zaja Principal Investigator

ESMO Guidelines 2017: relapse



Dreyling M, et al. Ann Oncol 2017

Ringraziamenti

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