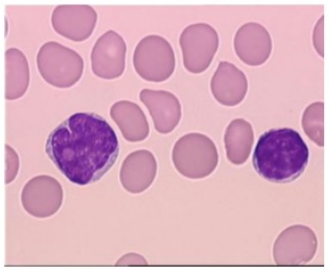
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
MEDIZINISCHE KLINIK UND POLIKLINIK III
DIREKTOR: PROF. DR. M. VON BERGWELT

MANTLE CELL LYMPHOMA:
OTHER AGENTS



German Lymphoma Alliance

European MCL Network

Mantle Cell Lymphoma
Disclosures

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https://bureaucracyincts.eu

Research Support (institution)	**Abbvie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Amgen, Astra Zeneca, Bayer, BMS/Celgene, Gilead/Kite, Incyte, Janssen, Novartis, Roche**
Scientific Advisory Board	**Astra Zeneca, Bayer, Beigene, BMS/Celgene, Genmab, Gilead/Kite, Incyte, Janssen, Lilly/Loxo, Morphosys, Novartis, Roche**

European MCL Network
Study generation 2022

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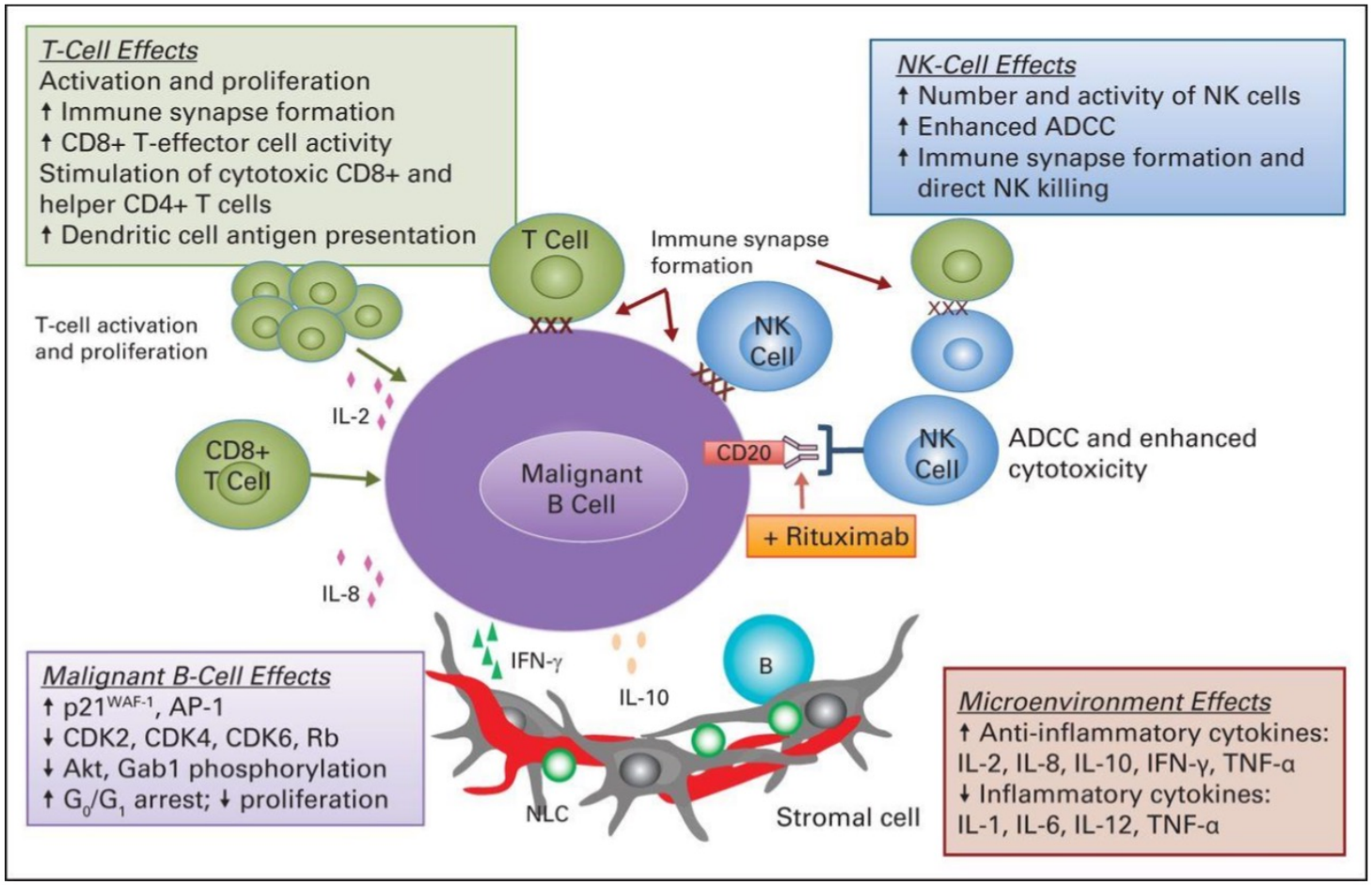
	< 65 years	> 60 years	> 65 years		
+ chemo	*MCL younger:* R-CHOP/DHAP =>ASCT R-CHOP+I/DHAP =>ASCT => I R-CHOP+I/DHAP => I	*MCL elderly R2:* R-CHOP vs R-CHOP/Ara-C => Rituximab M +/- Lenalidomide	BR +/- BTK ⇒ Rituximab M +/- BTK	*VR-BAC:* R-BAC ⇒ Venetoclax ⇒ (only high risk)	
vs. chemo ?		*ENRICH:* R-CHOP/Benda vs R-Ibrutinib	BR vs. BTK-R	*OASIS 2:* R-Ibrutinib +/- Venetoclax	*MCL elderly 3:* BR (Ibrutinib) vs R-Venetoclax-Ibrutinib

Relapse

R-HAD +/- Bortezomib	Ibrutinib/ Bortezomib	Ibrutinib/ R-Lenalidomide	Venetoclax/ R-Lenalidomide	Ibrutinib +/- ABT-199

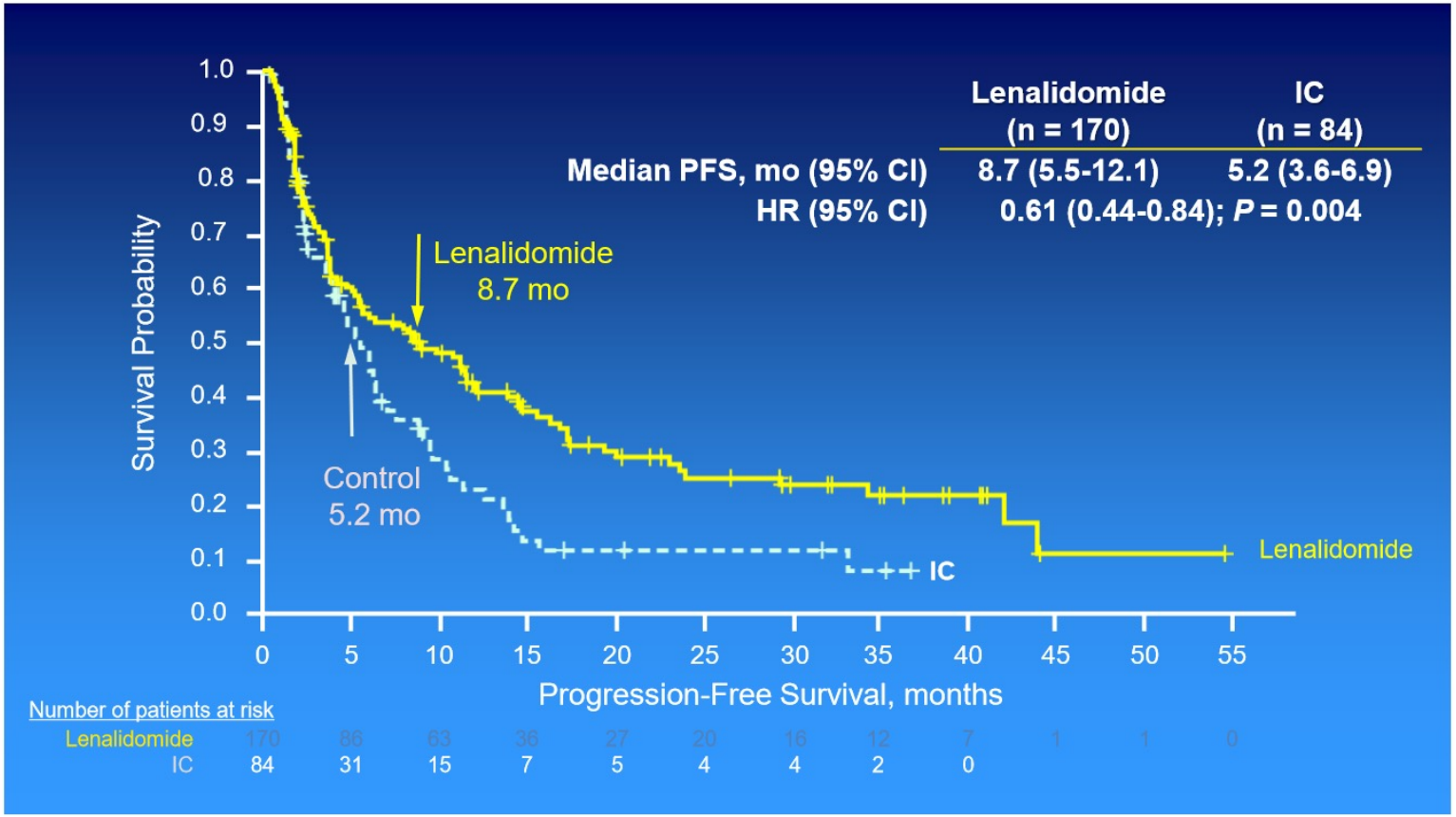
Lenalidomide
Mechanisms of action



Gribben, JCO 2015

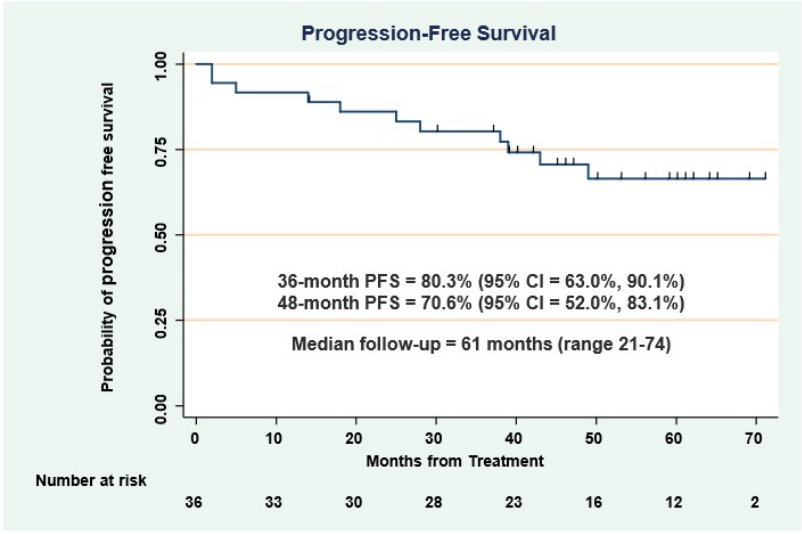
Relapsed Mantle cell lymphoma

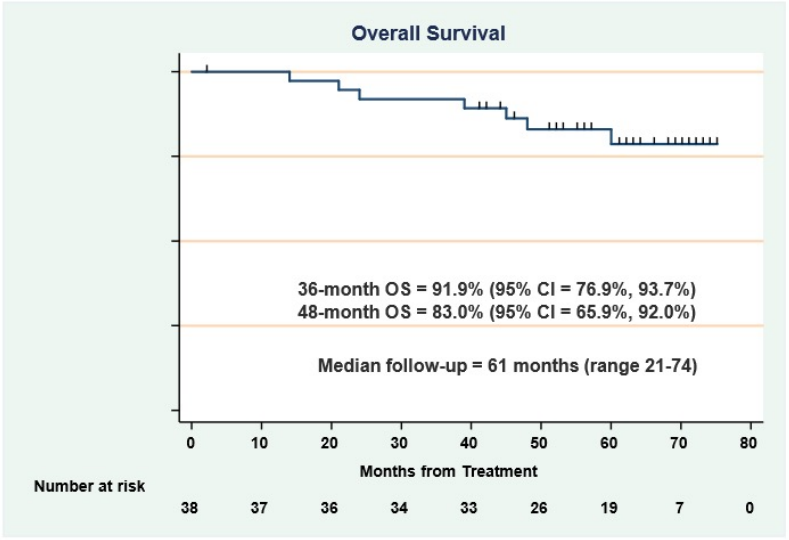
Lenalidomide



Trneny, Lancet Oncol 2016

Mantle cell lymphoma
Rituximab-Lenalidomide (first line)





Ruan, Blood 2018

Mantle cell lymphoma (first line)
MCL elderly R2

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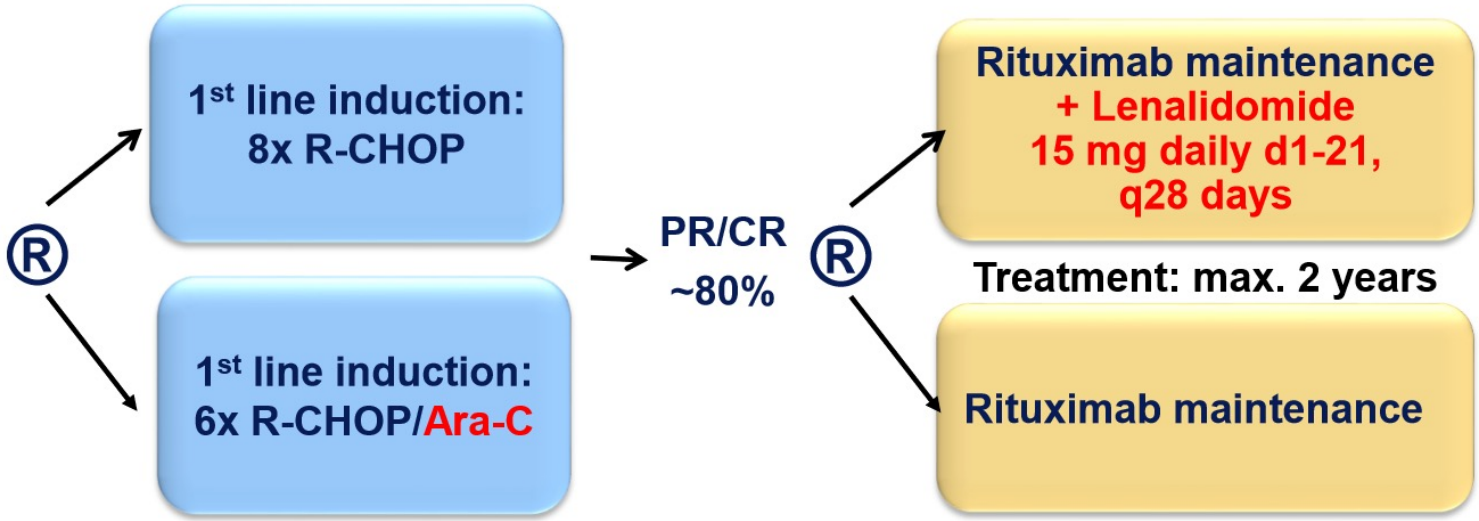
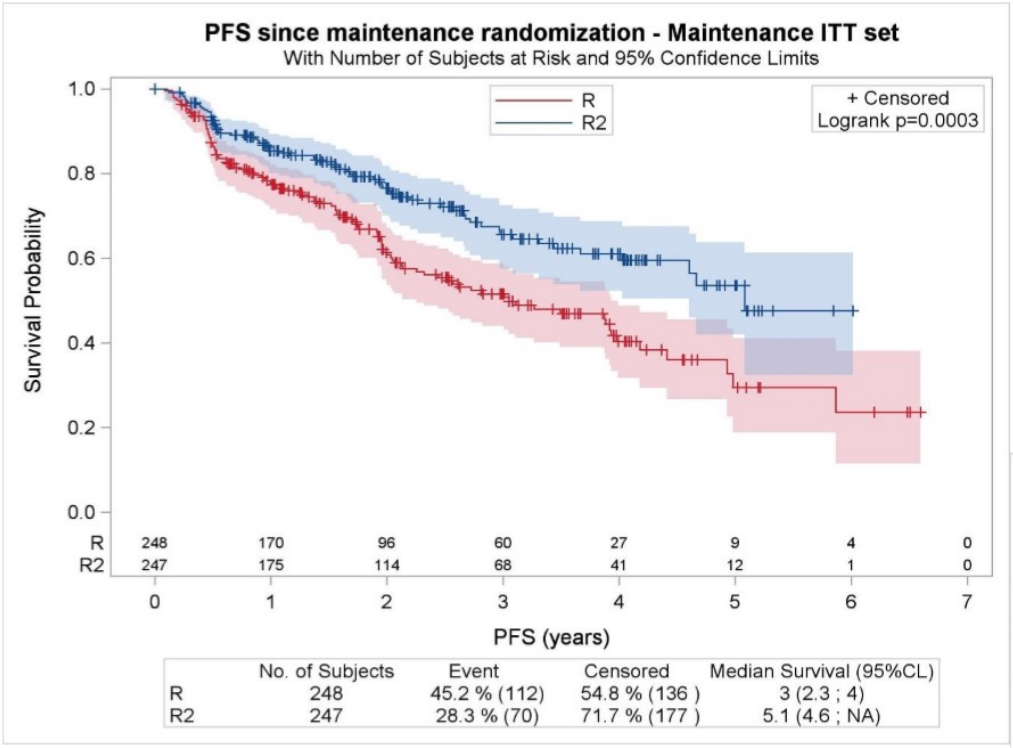
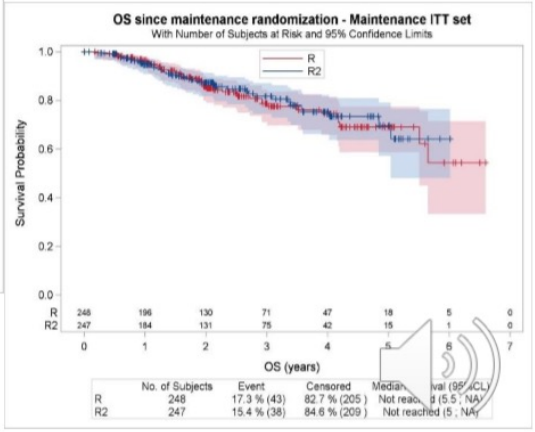


sponsor: LYSARC
central pathology: W. Klapper
MRD diagnostics: M. Ladetto, C. Pott, MH Delfau

MCL-R2 Elderly: survival analysis





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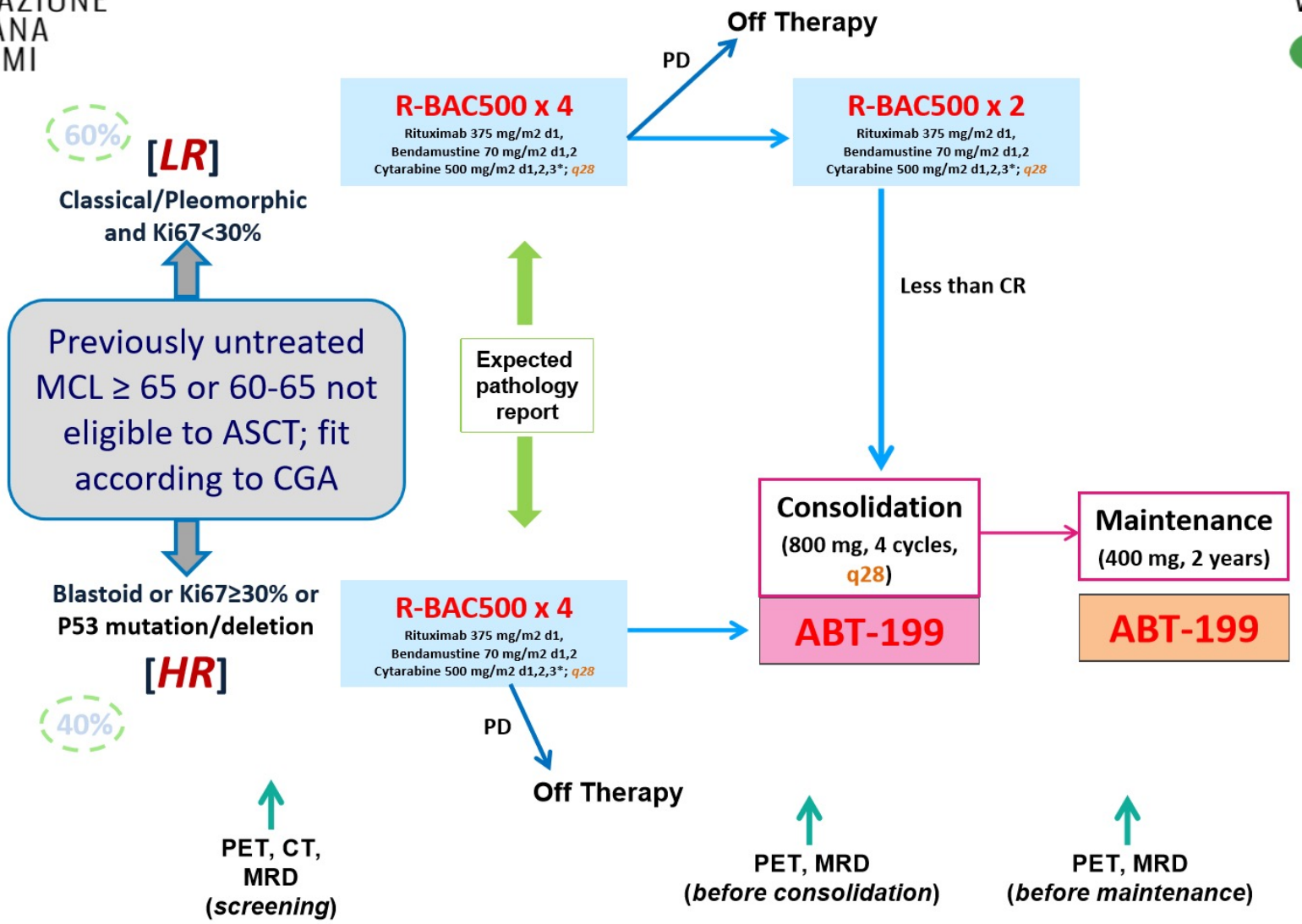
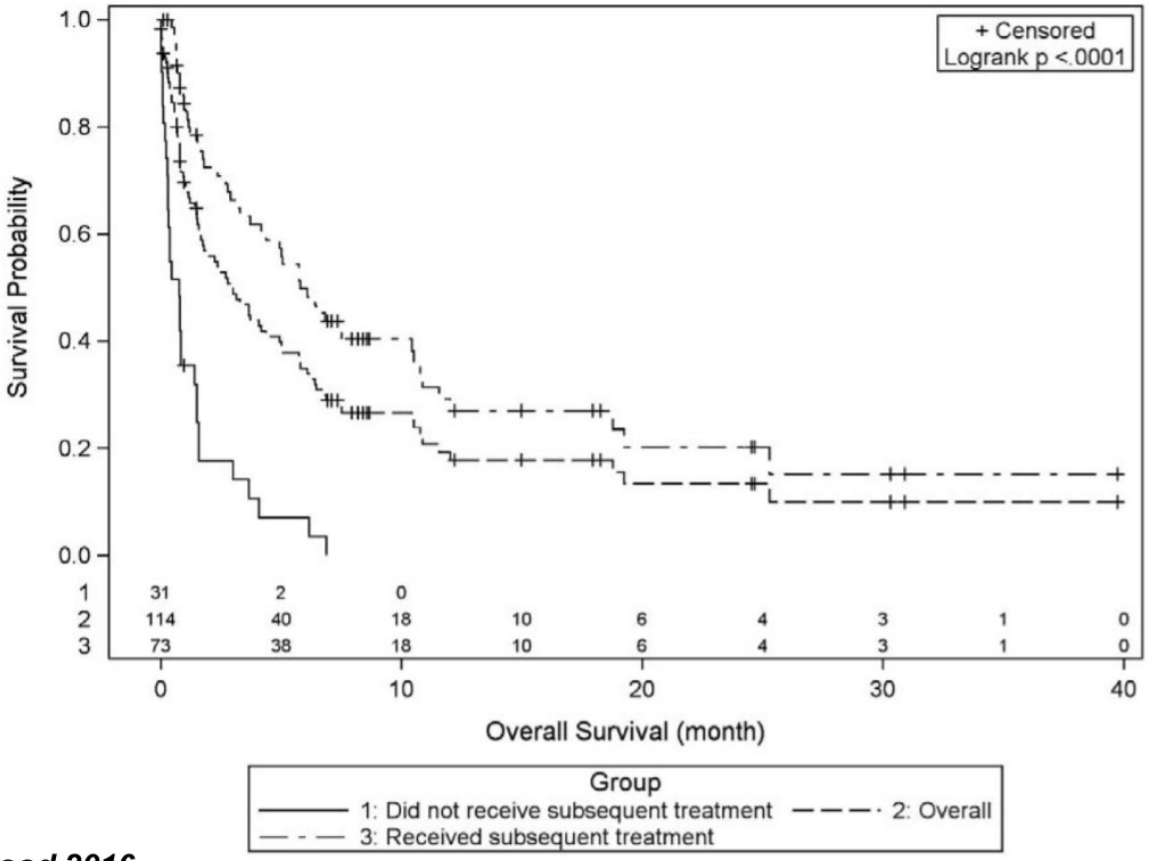
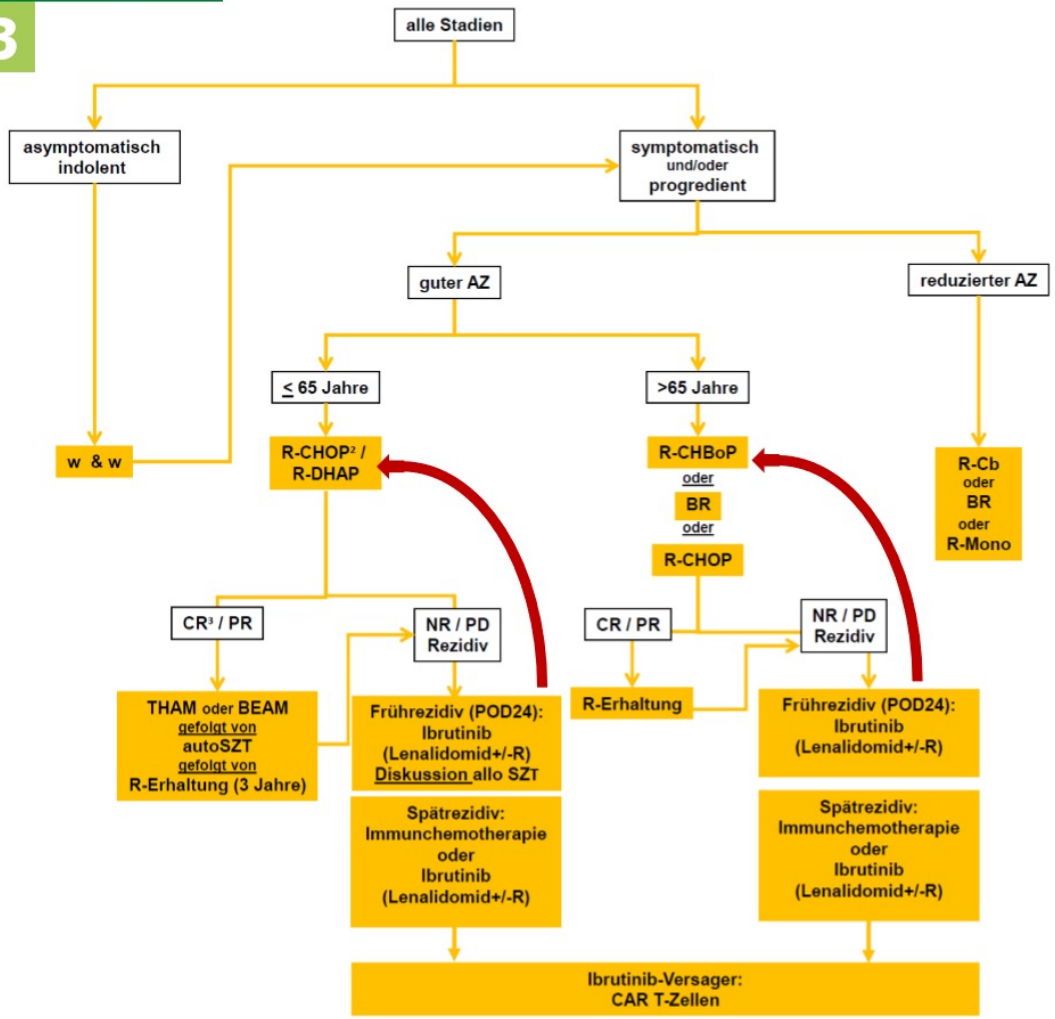


Relapsed mantle cell lymphoma
Failure under ibrutinib



Martin, Blood 2016

Mantle cell Lymphoma
Onkopedia 2023



Interdisciplinary CAR-T Taskforce LMU
Immunotherapy in Lymphoma

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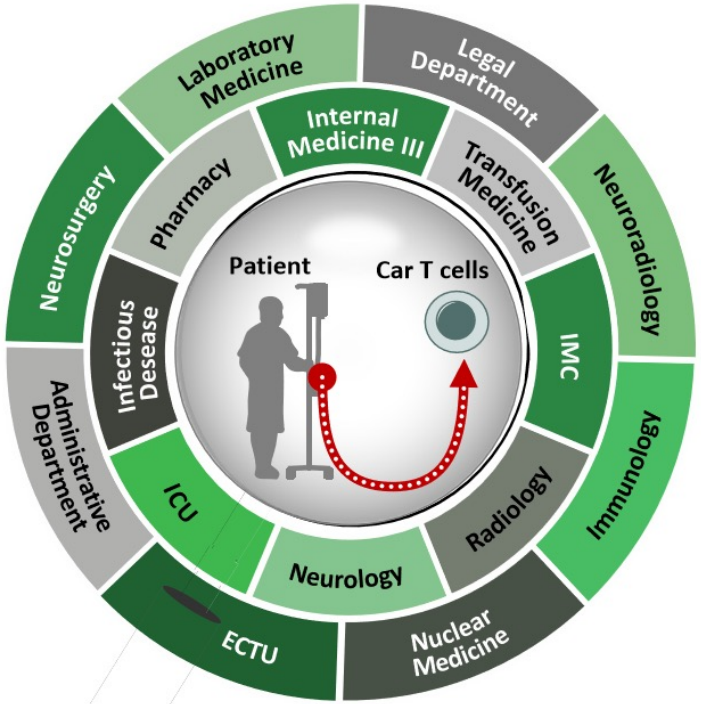
Building on a MEDIII Immuno-Taskforce based on T cell bispecifics Experience

IMP

- IMMune effector cells as Potent Actors of Cancer Therapy

A Smartphone Application for the Mangement of CAR T and BiTE associated Toxicites



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CAR-T cells in mantle cell lymphoma
Zuma 2: BTK failures

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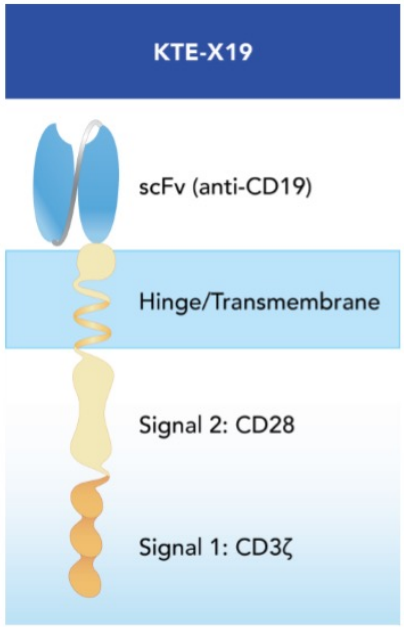
- Patients with R/R MCL have very poor outcomes
  - In patients who progress after BTK inhibitor therapy, ORR is 25% – 42% and OS is 6 – 10 months,[1-3] and few patients proceed to alloSCT
- KTE-X19 is a new anti-CD19 CAR T cell therapy containing a CD3ζ T cell activation domain and CD28 signaling domain
  - Manufacturing process removes circulating tumor cells[4]
- ZUMA-2 is a Phase 2, pivotal, multicenter, international study evaluating KTE-X19 in patients with R/R MCL



CAR T-cells in MCL
Survival rates

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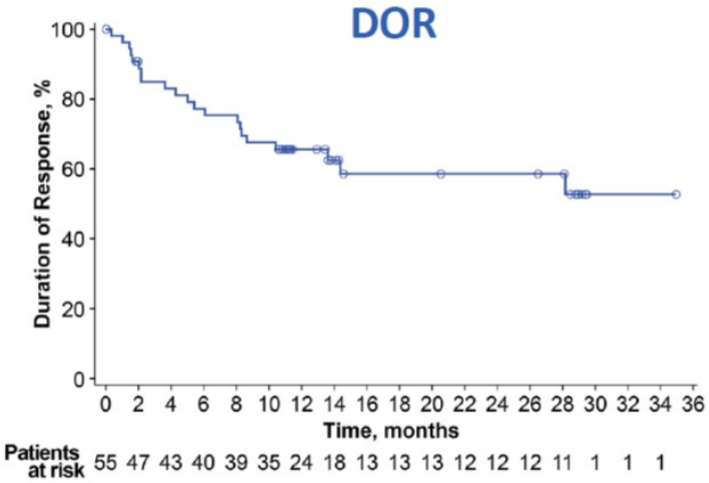
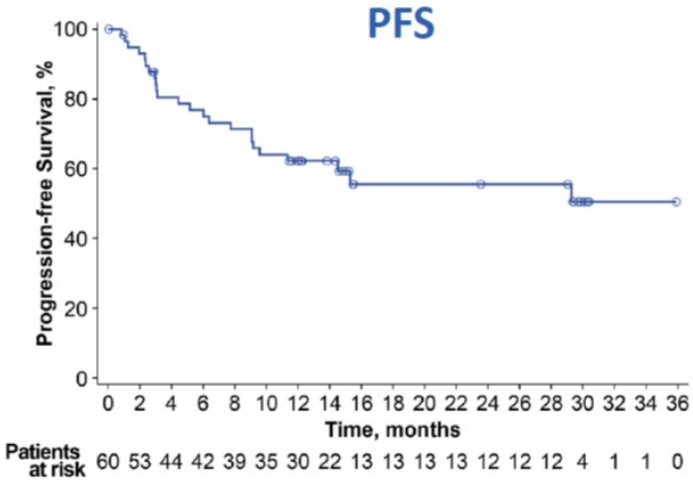
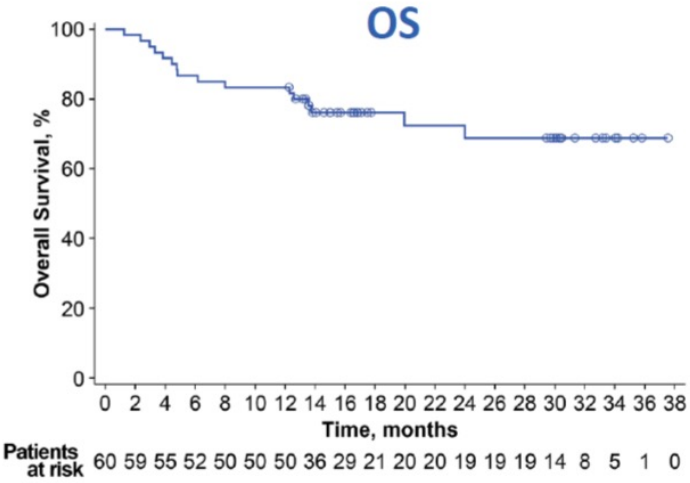
- The medians for DOR, PFS, and OS were not reached after a median follow-up of 17.5 months







Wang, ASH 2020

EUROPEAN HEMATOLOGY ASSOCIATION

KTE-X19 versus Standard of Care for Relapsed/Refractory Mantle Cell Lymphoma Previously Treated with Bruton Tyrosine Kinase Inhibitors: Real-World Evidence from Europe

EHA-1751

Georg Hess* [1], Martin Dreyling[2], Lucie Oberic[3], Eva Gine[4], Pier Luigi Zinzani[5], Kim Linton[6], Adam Vilmar[7], Mats Jerkeman [8], Jenny MH Chen[9], Anke Ohler[1], Stephan Stilgenbauer [10], Catherine Thieblemont[11], Jonathan Lambert[12], Vittorio Ruggero Zilioli[13], Juan Manuel Sancho[14], Ana Jimenez Ubieto[15], Luca Fischer[1], Sam Keeping[8], Julie E Park[8], Gregory A. Maglinte[16], Liliosa Nyamutswa[16], Rubina Siddiqi[16], John Reitan[17], Sally Wade[18], Gilles Salles[19]

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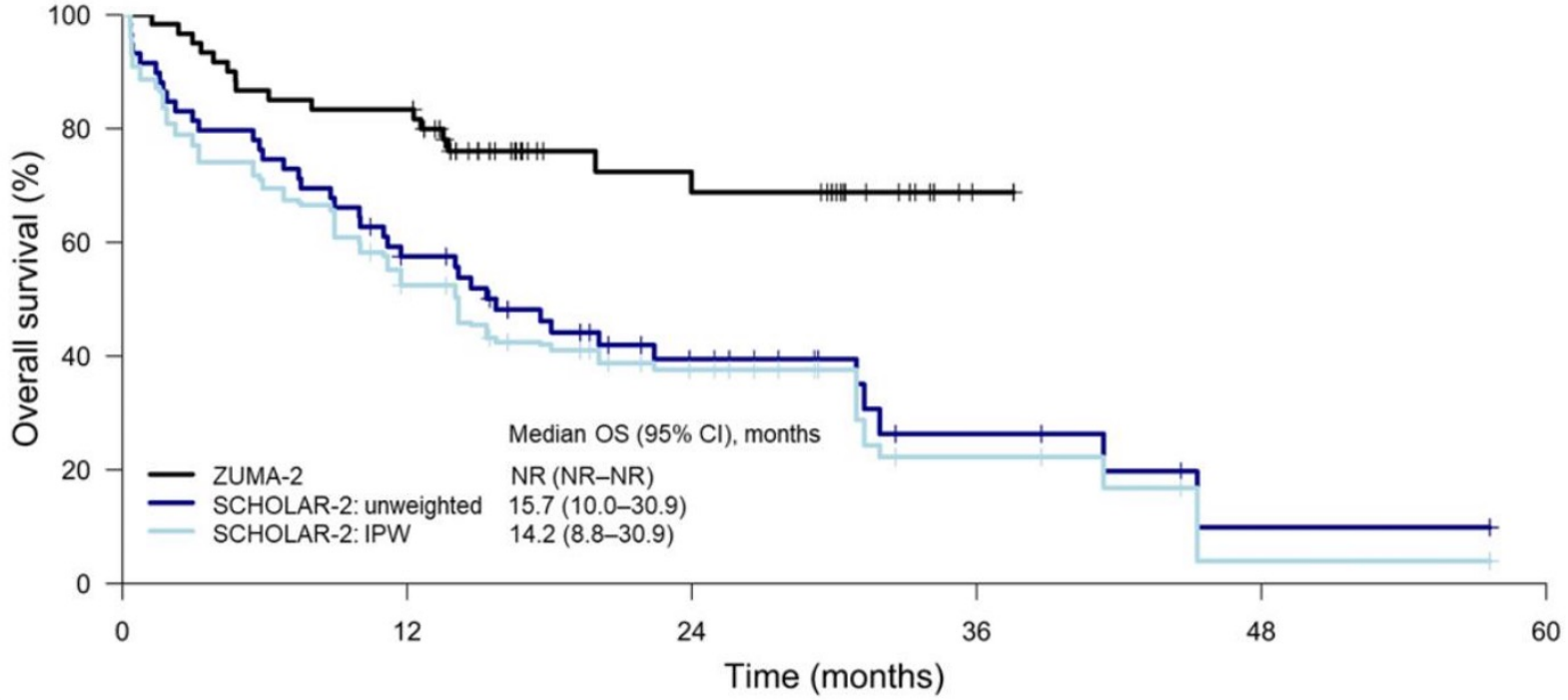
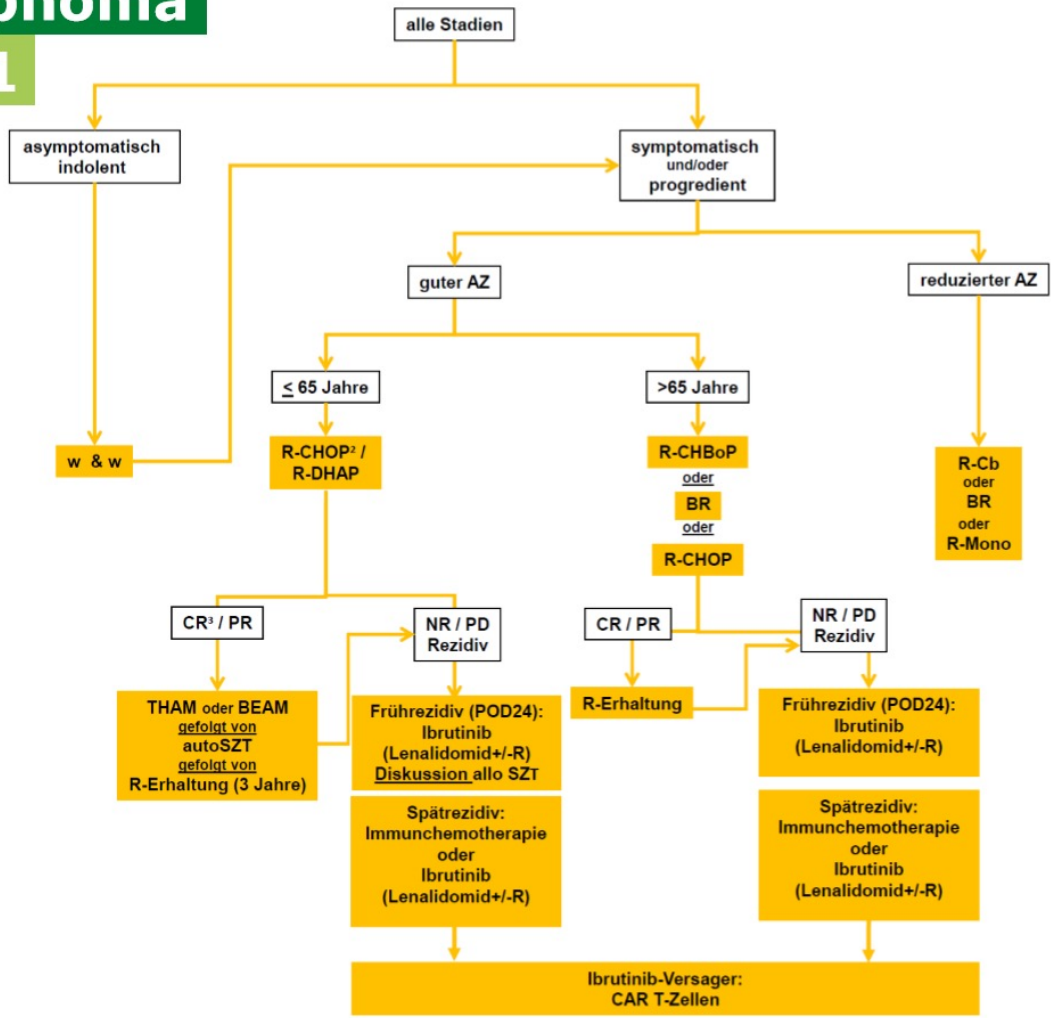


Number at risk (number censored)

ZUMA-2	60 (0)	50 (0)	19 (25)	1 (43)	0 (44)	0 (44)
SCHOLAR-2 (unweighted)	59 (0)	32 (2)	15 (10)	5 (17)	1 (19)	0 (20)
SCHOLAR-2 (IPW)	59 (0)	30 (1)	15 (8)	4 (16)	0 (18)	0 (19)

Hess, Dreyling, EHA 2021

Mantle cell lymphoma
Onkopedia 2021



Brexu-Cel RWE: Patient demographics

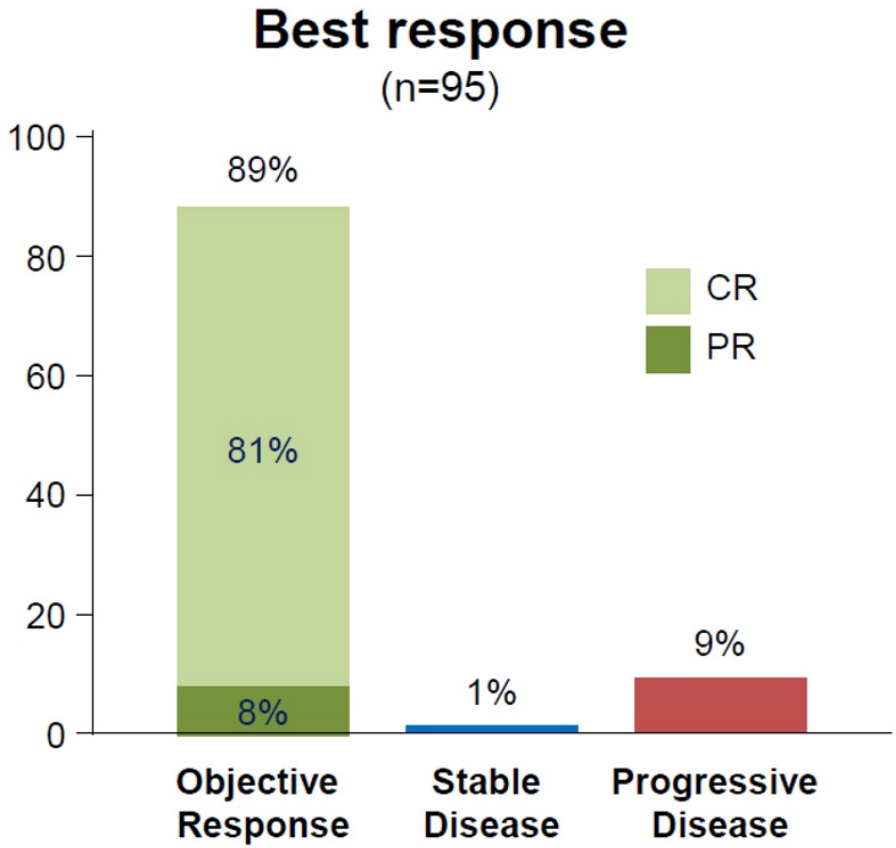
Variables	Number	Variables	Number
Age, median (range)	67 (34-89)	**Prior therapies**	
Sex, male	76 (80%)	Total lines, median (range)	3 (1-10)
ECOG PS ≥2	8 (8%)	Prior CD20 antibody	94 (99%)
Simplified MIPI		Prior anthracycline or bendamustine	82 (86%)
Low risk (0-3)	30 (32%)	Prior cytarabine	43 (45%)
Intermediate risk (4-5)	54 (57%)	Prior AutoSCT	27 (28%)
High risk (6-11)	11 (12%)	Prior rituximab maintenance	41 (43%)
Ki-67, ≥50%	50/88 (57%)	Prior BTKi	78 (82%)
Blastoid/pleomorphic	39 (41%)	BTKi-refractory n=69 (73%), BTKi-intolerant n=5 (5%)	
***TP53* mutation or deletion**	31/70 (44%)	Prior lenalidomide	22 (23%)
Complex karyotype	8/28 (29%)	Prior venetoclax	33 (35%)
Stage III-IV	83 (87%)	**Disease status**	
CNS involvement	7 (7%)	Relapsed after last line	53 (56%)
Bone marrow involvement	30/67 (45%)	Refractory to last line	42 (44%)
Bulky disease (≥10 cm)	10 (11%)	**Total (received CAR T infusion)**	**95**

U.S. CAR-T Lymphoma CONSORTIUM

Wang Y et al. ASH 2021, Abstr #744.

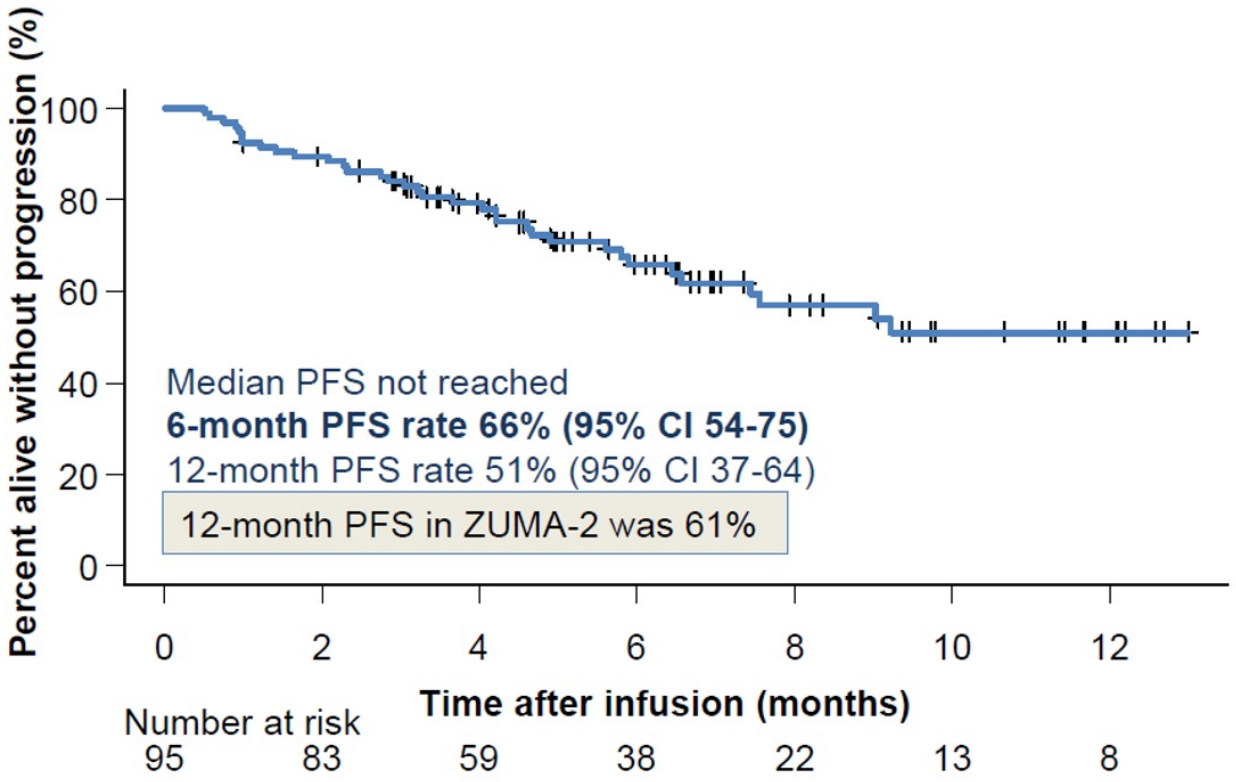
Brexu-Cel RWE: Clinical response

- **Median time to initial response was 30 days (range 16-104).**
- Day 30 ORR (n=92 evaluated) was 88%, including 66% CR and 22% PR.
- 12 of 20 patients with PR and 1 of 2 patients with SD at day 30 achieved CR after a median of 64 days (range 22-135).
- Median time to best response was 30 days (range 16-168).
- **The best ORR was comparable to that reported in ZUMA-2 (93%).**



Wang Y et al. ASH 2021, Abstr #744.

Brexu-cel RWE: Progression-free survival



U.S. CAR-T Lymphoma CONSORTIUM

Wang Y et al. ASH 2021, Abstr #744.

Baseline characteristics

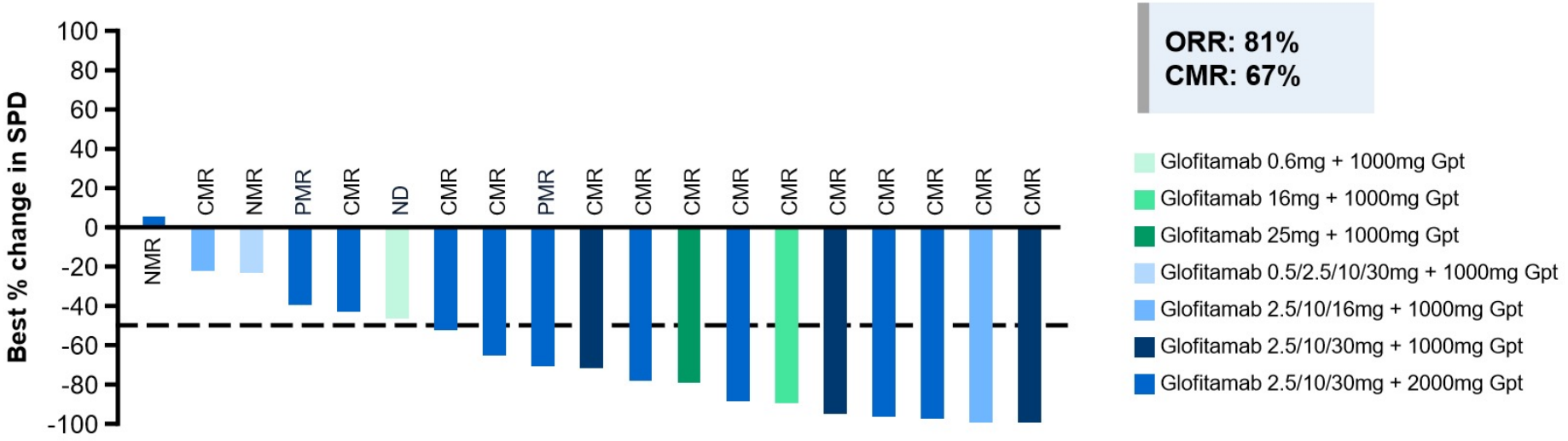
n (%) of patients unless stated		Glofitamab fixed dosing + 1000mg Gpt (n=3)	Glofitamab SUD + 1000mg Gpt (n=7)	Glofitamab SUD + 2000mg Gpt (n=19)	All patients (N=29*)
Median age, years (range)		81.0 (66–84)	69.0 (64–75)	66.0 (41–84)	69.0 (41–84)
Male		2 (66.7)	6 (85.7)	12 (63.2)	20 (69.0)
Ann Arbor stage III–IV at study entry		2 (66.7)	6 (85.7)	16 (84.2)	24 (82.8)
MCL IPI score ≥6 at study entry		3 (100)	3 (42.9)	12 (63.2)	18 (62.1)
Prior therapy	Median time since last therapy, months (range)	1.1 (1.0–8.5)	3.4 (1.2–53.2)	1.6 (0.1–107.5)	1.7 (0.1–107.5)
	Prior lines of therapy, median (range)	3 (2–5)	4 (3–5)	3 (1–6)	3 (1–6)
	BTKi	3 (100)	6 (85.7)	11 (57.9)	20 (69.0)
	Lenalidomide	0	1 (14.3)	3 (15.8)	4 (13.8)
	Chemotherapy	3 (100)	7 (100)	18 (94.7)	28 (96.6)
	Alkylator	0	6 (85.7)	7 (36.8)	13 (44.8)
	Anti-CD20 monoclonal antibody	3 (100)	6 (85.7)	14 (73.7)	23 (79.3)
Refractory status	Refractory to any prior therapy	3 (100)	7 (100)	16 (84.2)	26 (89.7)
	Refractory to prior anti-CD20 therapy	2 (66.7)	3 (42.9)	10 (52.6)	15 (51.7)
	Refractory to first-line therapy	2 (66.7)	2 (28.6)	11 (57.9)	15 (51.7)
	Refractory to last prior therapy	2 (66.7)	5 (71.4)	13 (68.4)	20 (69.0)

Philips, ASH 2021, #130

Antitumor activity

Zoom video location

Best percentage change from baseline SPD*

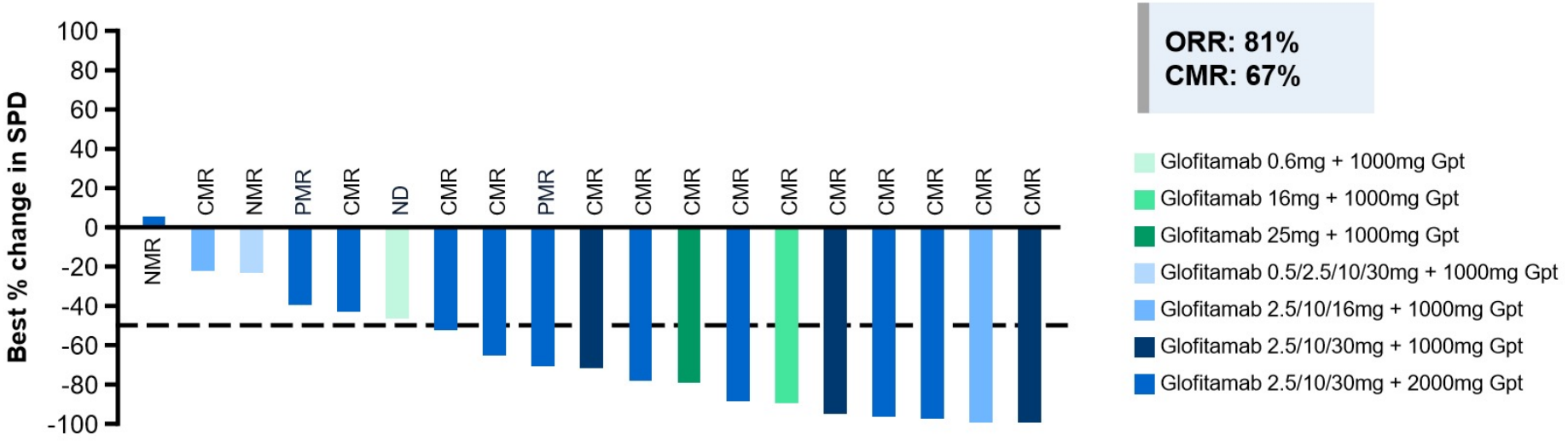


Philips, ASH 2021, #130

Antitumor activity

Zoom video location

Best percentage change from baseline SPD*



Philips, ASH 2021, #130

LOXO-305 Patient Characteristics

Characteristics	MCL (n=134)
Median age (range), years	70 (46, 88)
Female / Male, n (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)
Median number prior lines of systemic therapy (range)	3 (1, 9)
Prior therapy, n (%)	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant[b]	30 (22)
IMiD	23 (17)
BCL2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTKi[a]	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

Wang, ASH 2021, #381

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

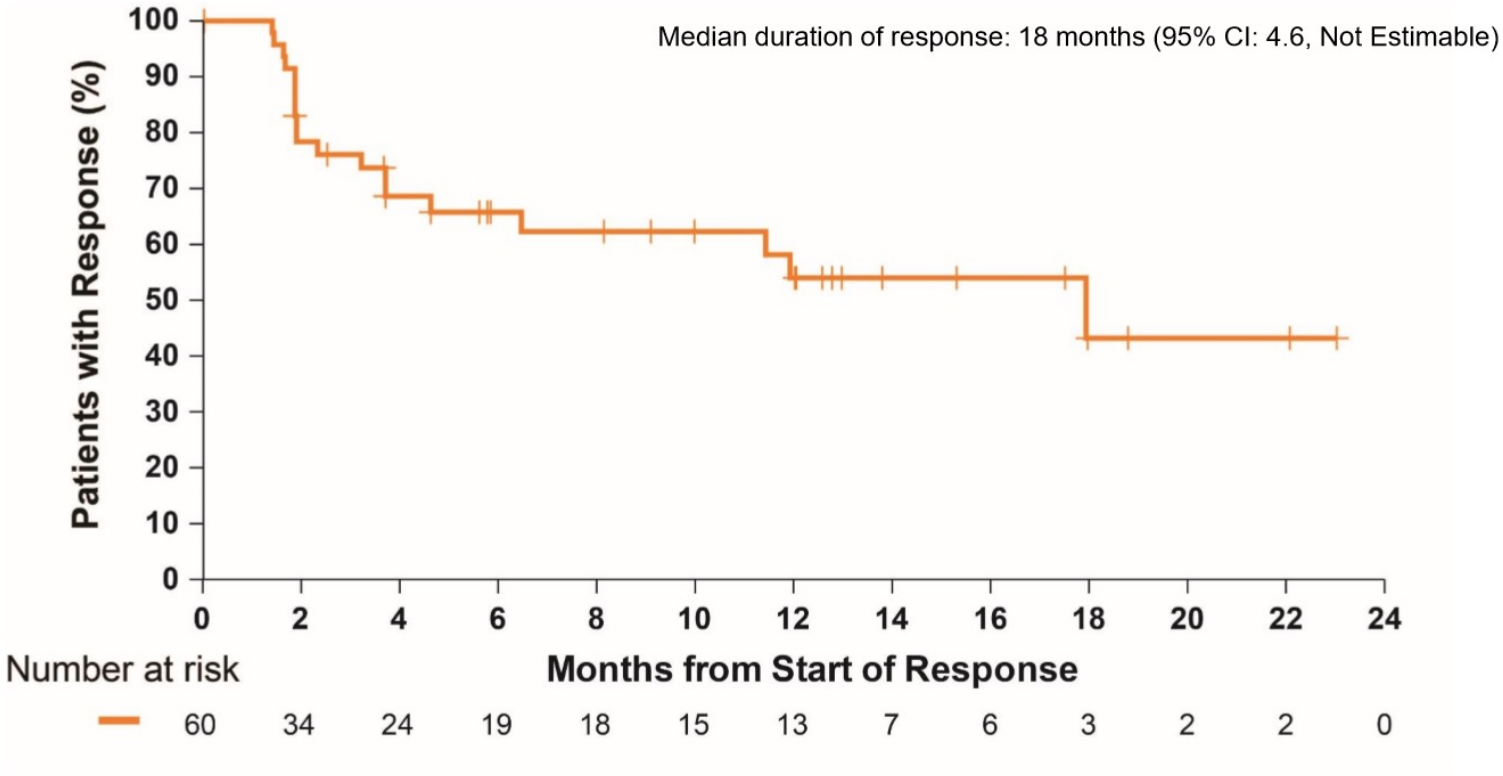
No DLTs reported and MTD not reached

96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily

1% (n=6) of patients permanently discontinued due to treatment-related AEs

Wang, ASH 2021, #381

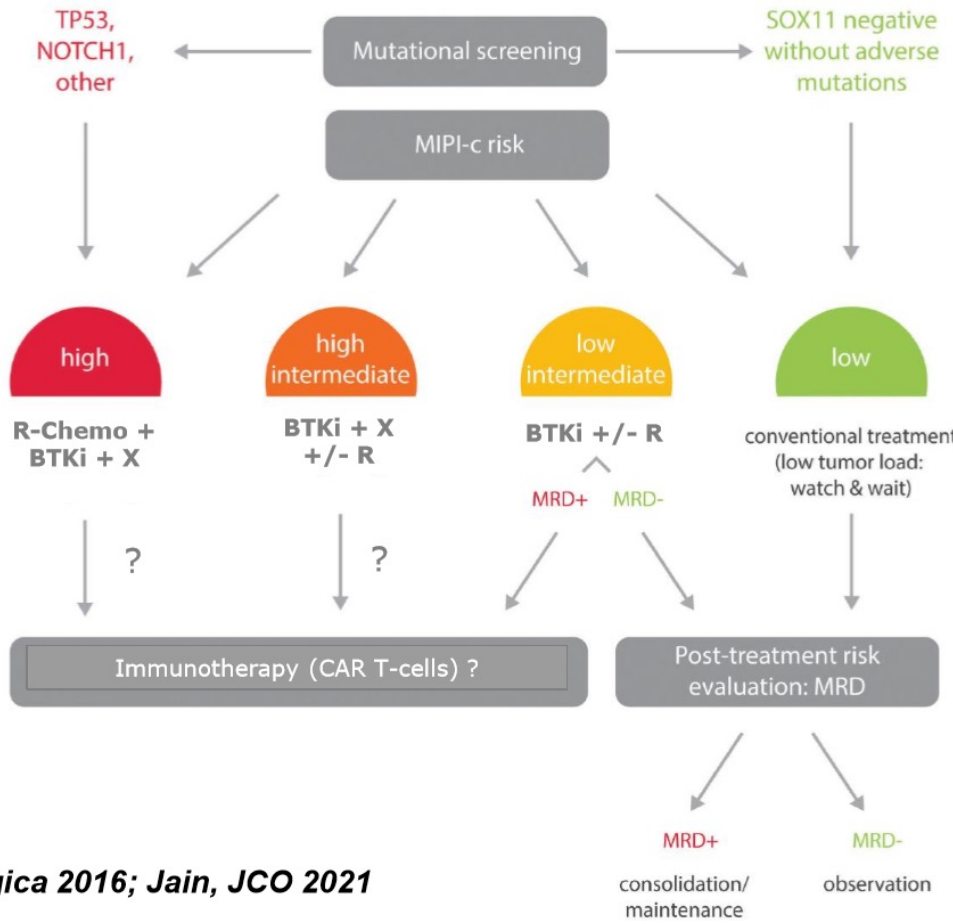
Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Wang, ASH 2021, #381

European MCL Network
Potential future therapeutic algorithm ?



modified from: Dreyling, Haematologica 2016; Jain, JCO 2021

Mantle cell Lymphome
Novel treatments 2022

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- high risk in clinical routine: Ki-67, p53 mut, blastoid

- first line: - younger: R/DHAP-autologous SCT- R-maintenance ?

  Elderly: IR-CHOP/Benda **(+ I)** + R-maintenance

  in studies: **non-chemo (combined) approaches**

- in early relapses: BTKi (combinations?)

  - in studies: **non-covalent BTKi, CAR –T cells, bispecific antibodies (combinations?)**

Acknowledgement