Sequencing of therapies in R/R MCL

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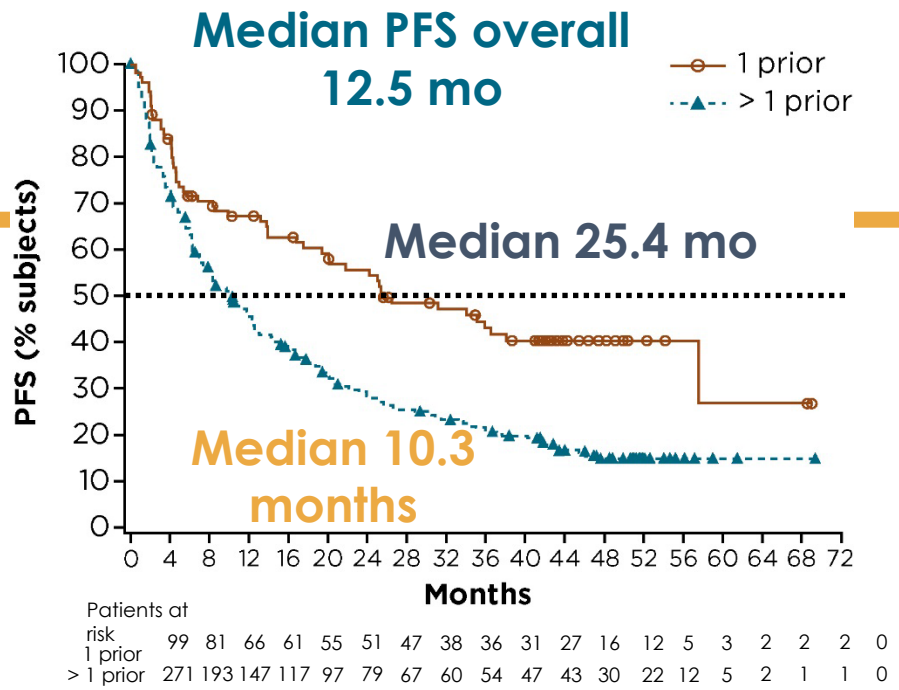
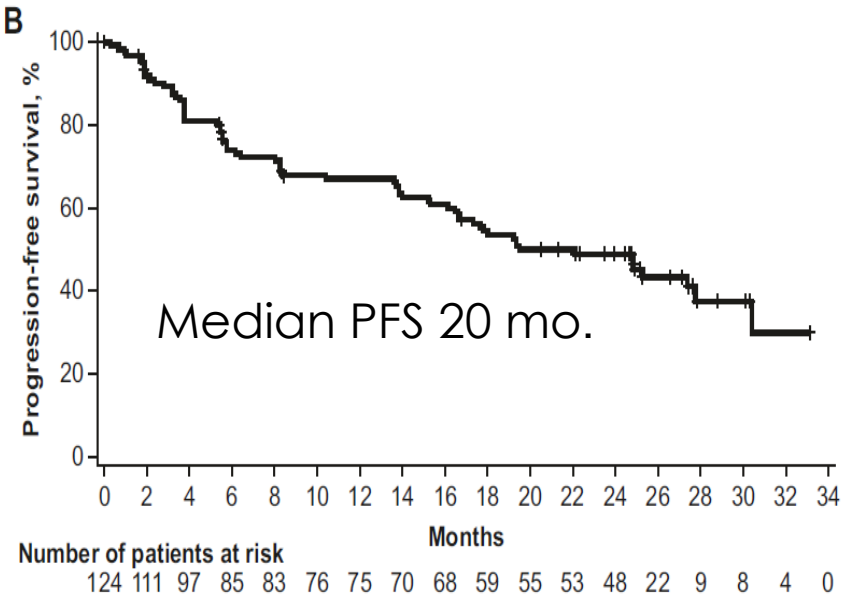
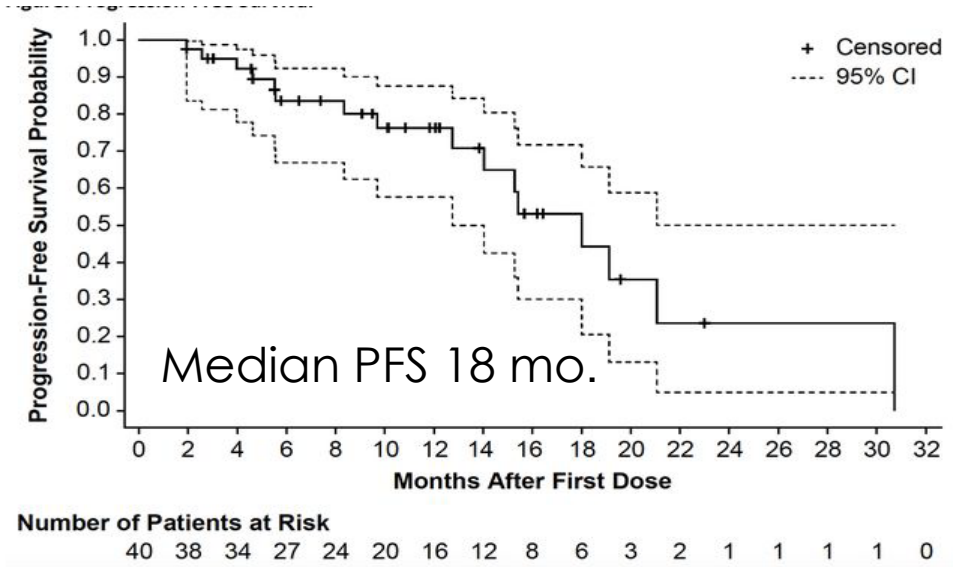


Ibrutinib
November 2013



Acalabrutinib
October 2017



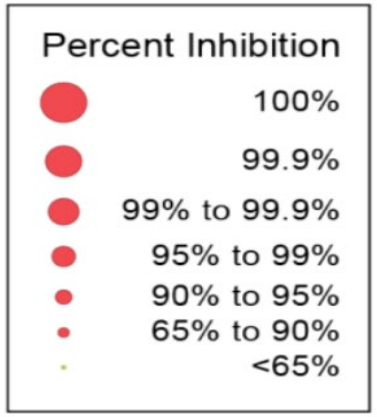
Zanubrutinib
November 2019

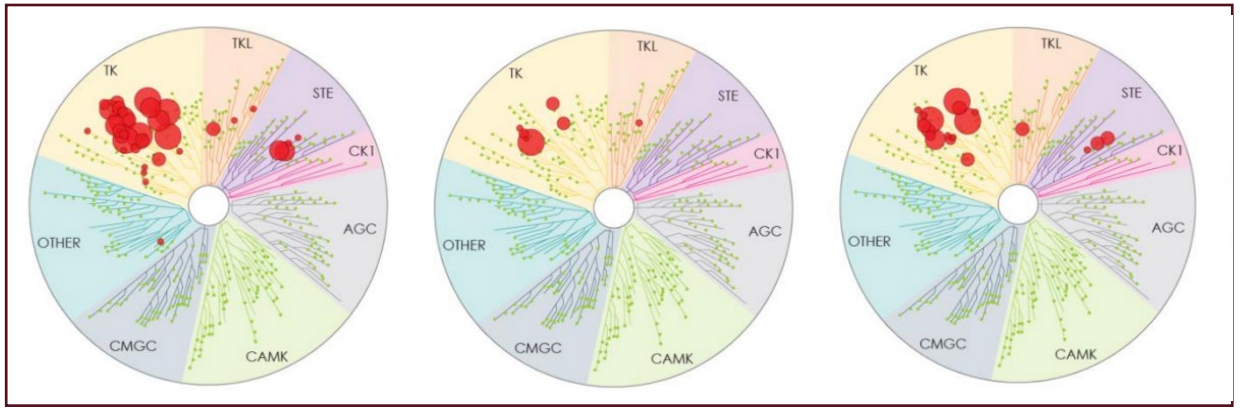
Rule et al *Lancet* 2018; Wang et al. Lancet Oncol 2018, Wang et al. Leukemia 2019; Tam et al. Blood 2018;132:1592

Covalent BTK-inhibitors

Table 2. Grade > 3 toxicities observed in clinical trials of single agent ibrutinib, acalabrutinib, and zanubrutinib

IBRUTINIB*	ACALABRUTINIB	ZANUBRUTINIB
Hypertension (5-29%) Neutropenia (10-22%) Infections (20%) Pneumonia (7-15%) Diarrhea (13%) Thrombocytopenia (6-11%) Anemia (5-9%) Atrial fibrillation (7-9%) Second cancers (6%) Fever (5%) Sinusitis (5%) Urinary tract infection (5%) Hyponatremia (5%)	Neutropenia (11%) Pneumonia (1-10%) Hypertension (3-7%) Syncope (3%) Atrial fibrillation (2%)	Neutropenia (6%) Infections (3%) Anemia (2%) Hypertension (2%) Atrial fibrillation (1%) Bleeding (1%)
A different incidence of side effects has been reported in unselected real-world patients treated with commercial ibrutinib (see manuscript for details) (*) only toxicities observed in > 5% of patients are reported for ibrutinib		



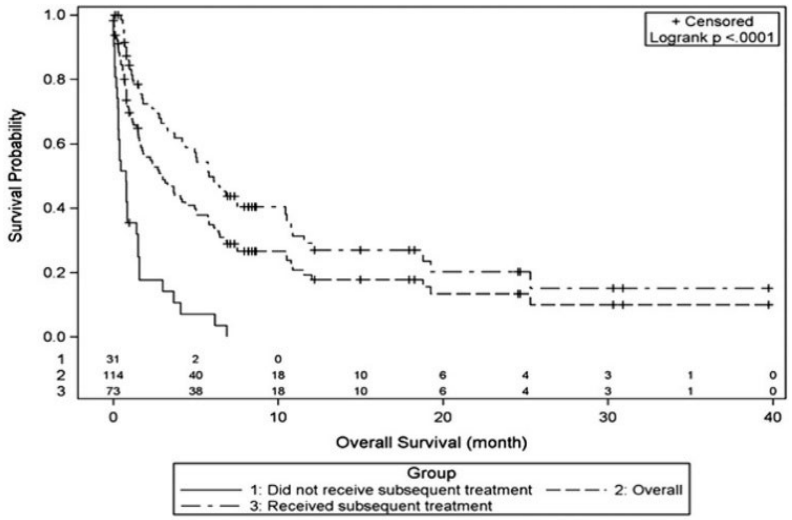


Ibrutinib Acalabrutinib Zanubrutinib

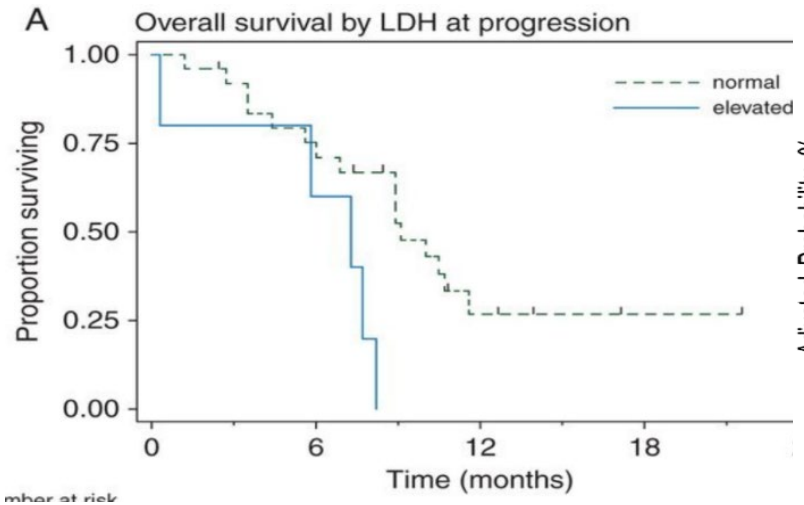
Kaptein et al, ASH 2018; Abstract 1871; Strati P, et al. Oncology Times. September 2019.

BTKi Failure

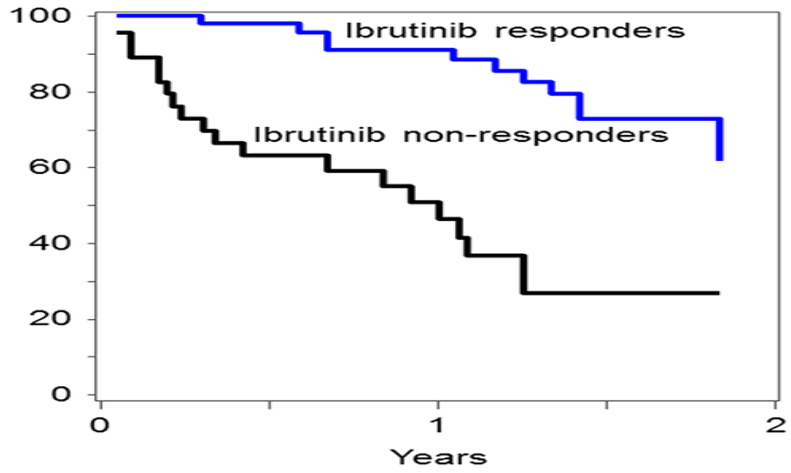
mOS 2.9 mo.
mOS^{Tx} 5.8 mo.



mOS^{Tx} 8.4 mo.



mOS 2.5 mo.
mOS^{Tx} 5 mo.



Martin et al. Blood 2016;127:1559; Cheah et al. Ann Oncol 2015;26:1175; Epperla et al. Hematological Oncol 2017;16:1099

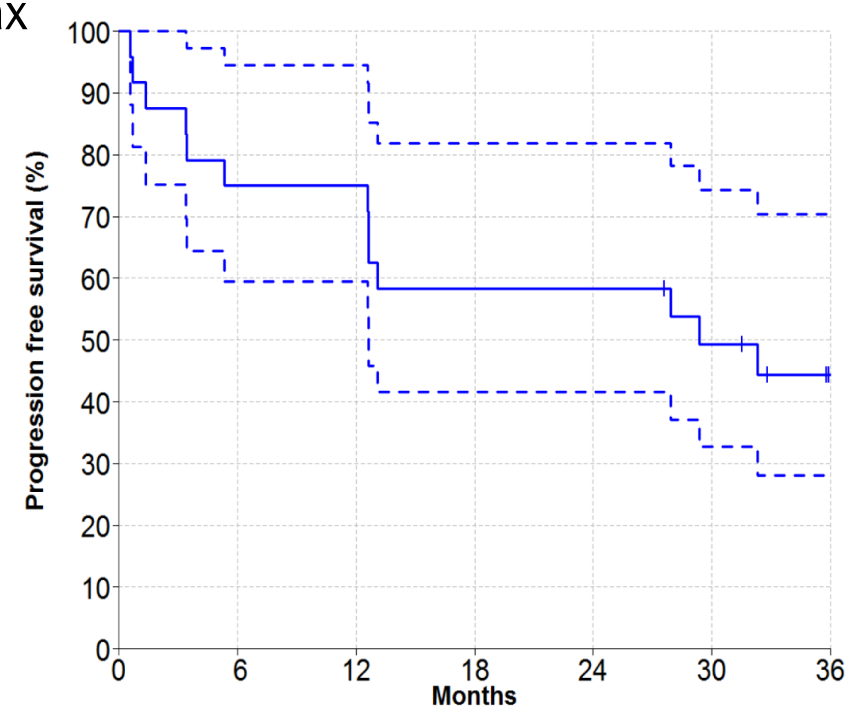
Ibrutinib plus venetoclax

- AIM Trial: Ibrutinib + Venetoclax
  - 23 patients
  - CR Rate of 71%
  - Median PFS 29 months

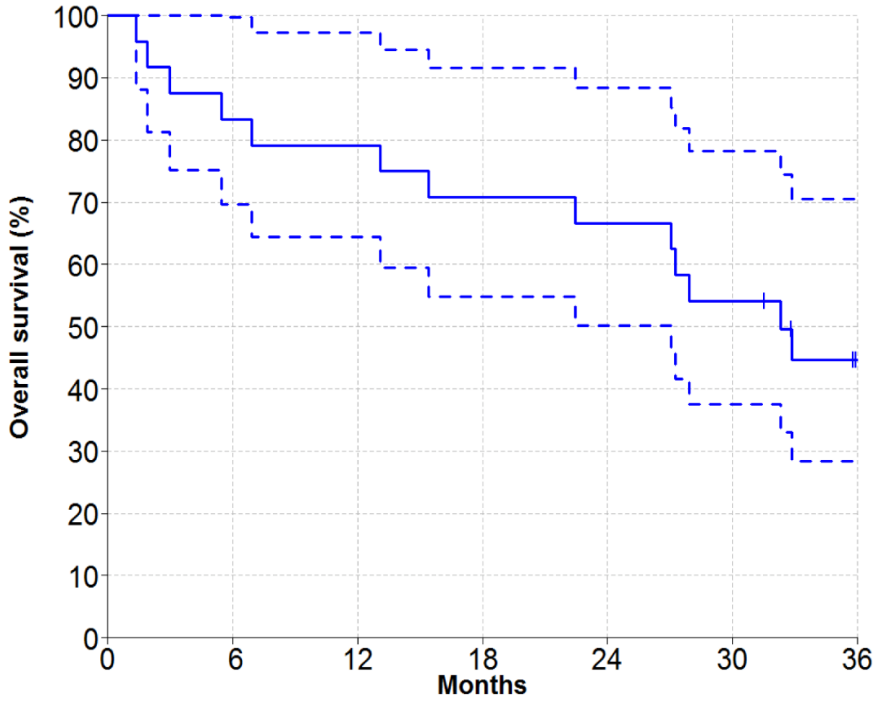
SYMPATICO: Safety Run-In

- 21 patients
- ORR 81%, CR 62%
- Estimated 75% PFS at 18 months

Median PFS 29 months



Median OS 32 months



- 50% TP53 patients responded, all CR
- 5 off treatment in MRD negative CR after median 18.5 months treatment (range 18 – 33)
- 4 remain free of clinical or MRD progression after 6, 13, 17 and 18 months off treatment
- One patient developed radiologic progression after 7 months

Handunetti et al ASH 2019, Tam ASH 2020

Brexucabtagene autoleucel (Brexu-cel/KTE-X19)

- Autologous anti-CD19 chimeric antigen receptor T cells (CART)
- ZUMA-2, a phase II international, multi-center study r/r MCL
- Accelerated approval from FDA for treatment of adults with r/r MCL July 2020

Characteristic	N = 68
Median age (range), years	65 (38 – 79)
≥ 65 years, n (%)	39 (57)
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
ECOG 0/1, n (%)	100 (100)
Intermediate/high-risk MIPI, n (%)	38 (56)
Ki-67 proliferation index ≥ 50%, n/n (%)[a]	34/49 (69)
TP53 mutation, n/n (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease, n (%)[b]	38 (56)
Blastoid Morphology, n(%)	17 (25)

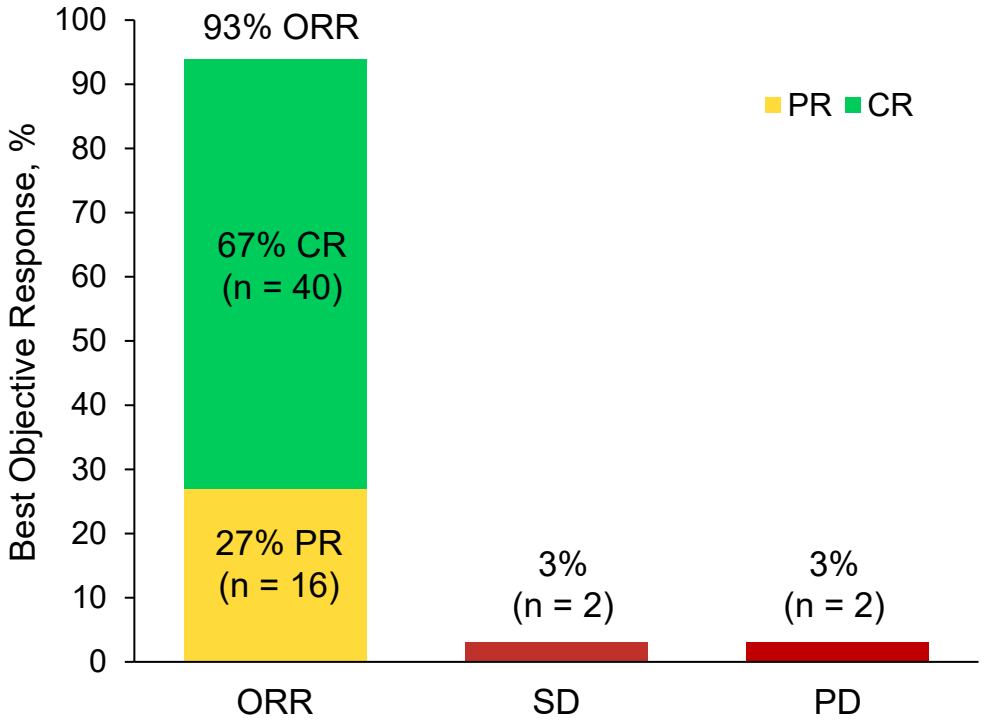
Bridging Therapy

Characteristic	N = 68
Any bridging therapy, n (%)	25 (37)
Ibrutinib	14 (21)
Acalabrutinib	5 (7)
Dexamethasone	12 (18)
Methylprednisolone	2 (3)
Both BTKi and steroids, n (%)	6 (9)
Ibrutinib + steroid	4 (6)
Acalabrutinib + steroid	2 (3)

[a] Ki-67 data were available for 49 patients at diagnosis. [b] Excludes bone marrow and splenic involvement. [c] Morphology was unknown for 10 patients.
BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index.

Wang et al, NEJM 382:1331-42, 2020

ZUMA-2, KTE-X19 Responses

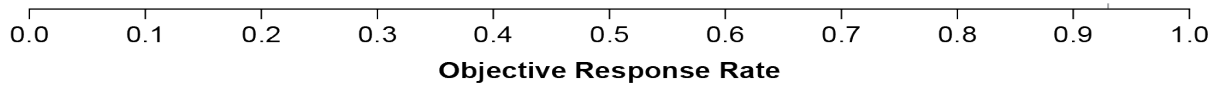


	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

Wang et al, NEJM 382:1331-42, 2020

High Risk Subgroups

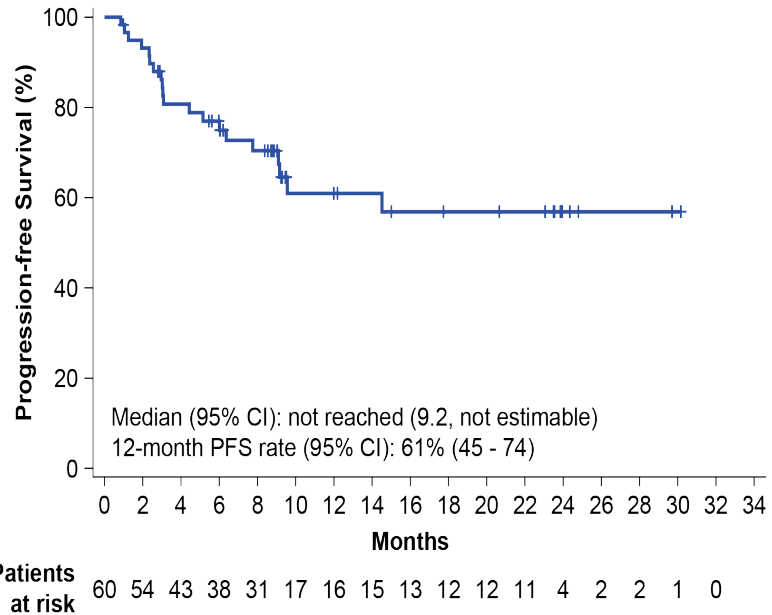
	Evaluable Patients	Responding Patients	ORR (95% CI)
Overall	60	56	0.93 (0.84, 0.98)
Age			
< 65 Years	28	26	0.93 (0.76, 0.99)
≥ 65 Years	32	30	0.94 (0.79, 0.99)
MCL morphology			
Classical MCL	35	32	0.91 (0.77, 0.98)
Pleomorphic	4	4	1.00 (0.40, 1.00)
Blastoid	14	13	0.93 (0.66, 1.00)
Ki-67 index			
< 50%	14	14	1.00 (0.77, 1.00)
≥ 50%	32	30	0.94 (0.79, 0.99)
Disease stage			
I-II	2	2	1.00 (0.16, 1.00)
III-IV	58	54	0.93 (0.83, 0.98)
Simplified MIPI			
Low risk	25	23	0.92 (0.74, 0.99)
Intermediate/high risk	33	31	0.94 (0.80, 0.99)
Steroid use for AE management			
Yes	35	33	0.94 (0.81, 0.99)
No	25	23	0.92 (0.74, 0.99)
Tocilizumab use			
Yes	42	40	0.95 (0.84, 0.99)
No	18	16	0.89 (0.65, 0.99)
Bridging therapy use			
Yes	21	19	0.90 (0.70, 0.99)
No	39	37	0.95 (0.83, 0.99)



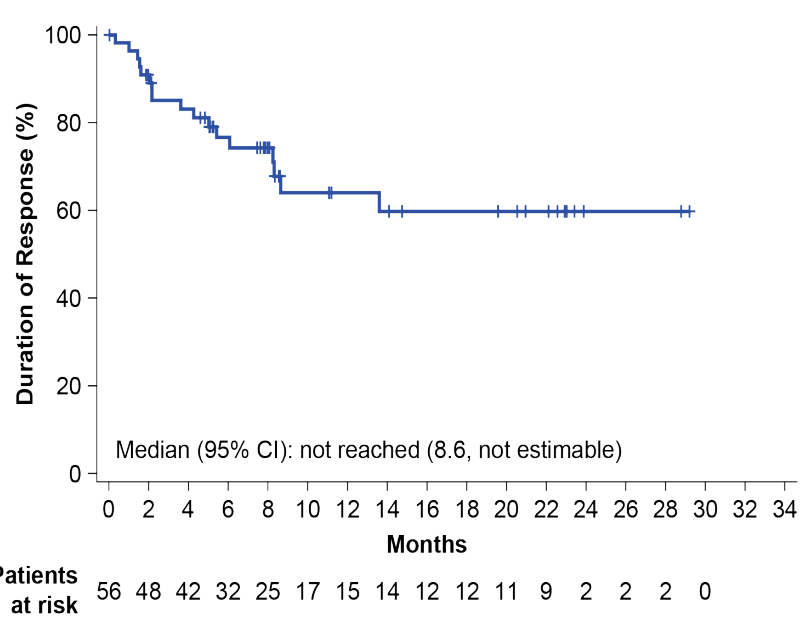
Wang et al, NEJM 382:1331-42, 2020

ZUMA-2, KTE-X19

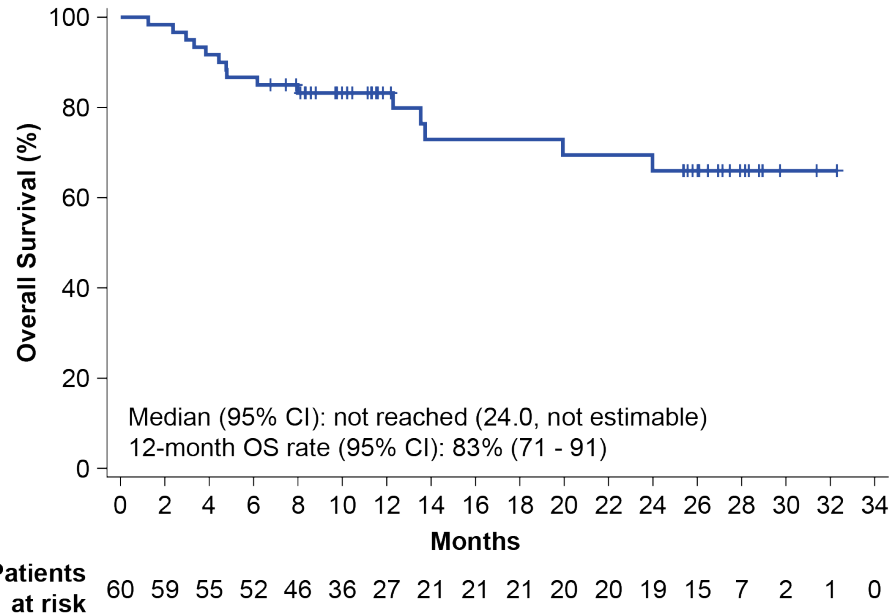
Progression Free Survival



Duration of Response



Overall Survival



- The medians for DOR, PFS, and OS were not reached after a median follow-up of 17.5 months
- 48% of patients remain in ongoing response, 70% of patients in CR remain in response

Wang et al ASH 2020

ZUMA-2, KTE-X19

Parameter	N = 68
CRS, n (%)[a]	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Most common any grade symptoms of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
AE management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to onset (range), days	2 (1 – 13)
Median duration of events, days	11
Patients with resolved events, n (%)	62/62 (100)

Parameter	N = 68
Neurologic events, n (%)[a]	
Any grade	43 (63)
Grade ≥ 3	21 (31)
Most common any grade symptoms, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
AE management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	26 (38)
Median time to onset (range), days	7 (1 – 32)
Median duration of events, days	12
Patients with resolved events, n (%)	37/43 (86)[b]

Wang et al, NEJM 382:1331-42, 2020

Toxicities of Brexu-cel

- Cytopenias
  - Grade 3 or higher – 94%
  - Persistent grade 3 – 26% beyond 90 days of treatment
- Infections – 32%
- Grade 5 Toxicities
  - 2 patients (3%) – likely from lymphodepletion
  - 1 organizing pneumonia
  - 1 septicemia (Staph bacteremia)

Wang et al, NEJM 382:1331-42, 2020

Brexu-Cel RWE

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**

- 74 (78%) patients would not have met ZUMA-2 eligibility criteria.
- Main reasons included prior therapies, renal dysfunction, cytopenias, ECOG PS, CNS involvement.
- 64 (67%) patients received bridging therapy
- 22 chemoimmunotherapy, 13 radiation, 9 venetoclax, 3 lenalidomide

Wang Y et al, ASH 2021

Brexu-Cel: CRS and ICANS

	CRS, n (%)	ICANS, n (%)	ZUMA-2 CRS (%)	ZUMA-2 NE (%)
Total	86 (91%)	57 (60%)	91%	63%
Max Grade*				
1-2	78 (82%)	24 (25%)	76%	32%
3-4	8 (8%)	33 (35%)	15%	31%
Days to onset	4 (0-11)	6 (1-15)	2 (1-13)	7
Days to max Grade	5 (0-7)	7 (3-15)	-	-
Duration	5 (1-33+)	6 (2-144+)	11	12

*CRS grading: ASTCT (n=11), Lee (n=2), CARTOX (n=1); ICANS grading: ASTCT (n=12), CTCAE (n=1), CARTOX (n=1)
CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; NE = neurological events.

- The incidences of CRS and ICANS were comparable to those reported in ZUMA-2.
- Tocilizumab and corticosteroids use appeared to be more frequent in this Consortium study cohort.

Management	Number	ZUMA-2 (%)
Tocilizumab	75 (79%)	CRS: 59% NE: 26%
Tocilizumab doses, median	2 (1-4)	
Steroid	66 (69%)	CRS: 22% NE: 38%
Anakinra	16 (17%)	
ICU admission	20 (21%)	
ICU days, median	3 (1-12)	
Vasopressors	10 (11%)	16%
Mechanical ventilation	4 (4%)	
Dialysis	3 (3%)	

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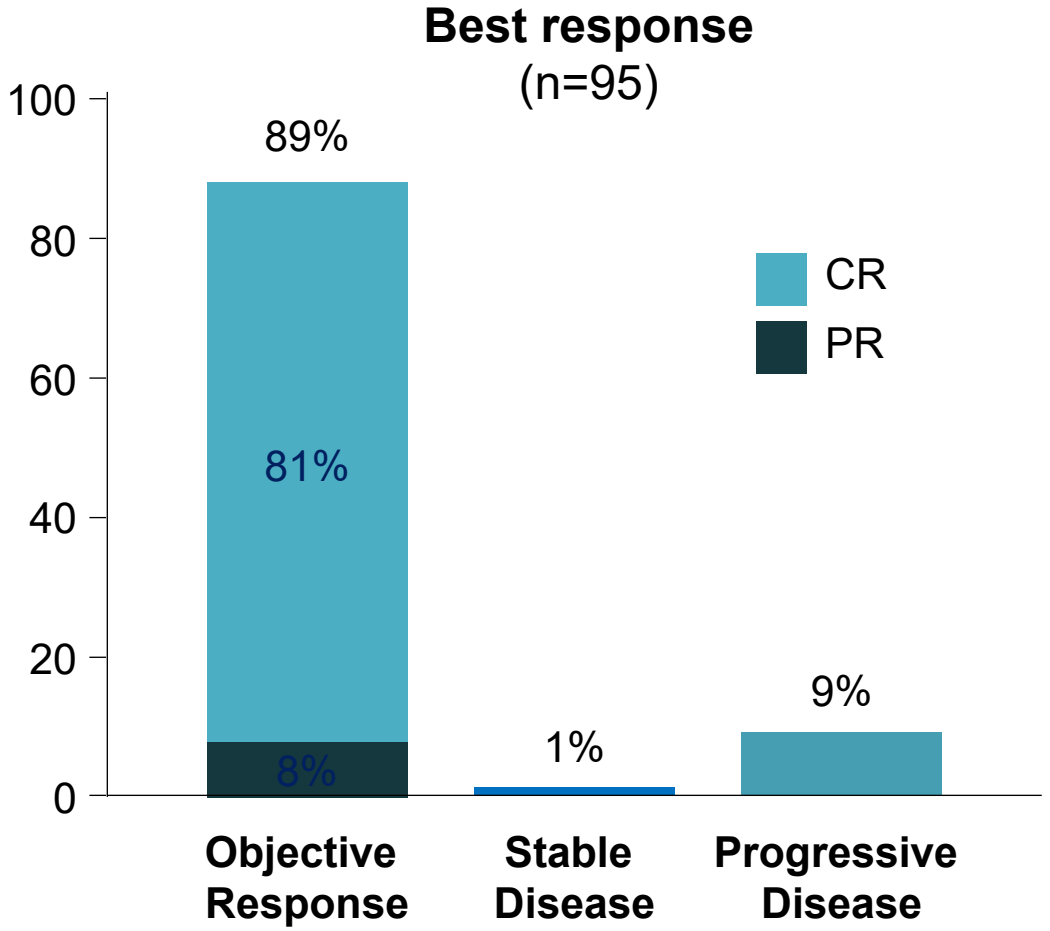
Brexu-Cel RWE: Clinical response

- 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).
- No difference in response across high-risk subgroups (blastoid, ki-67 > 50%, TP53 mutation, BTKi exposure, ZUMA eligible/inelgibile)



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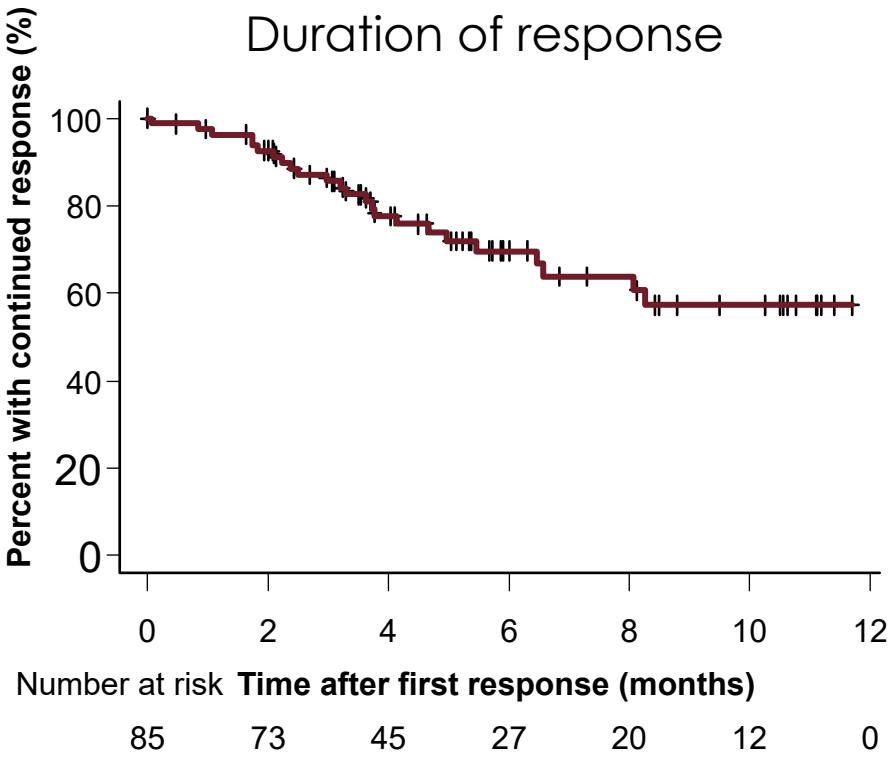
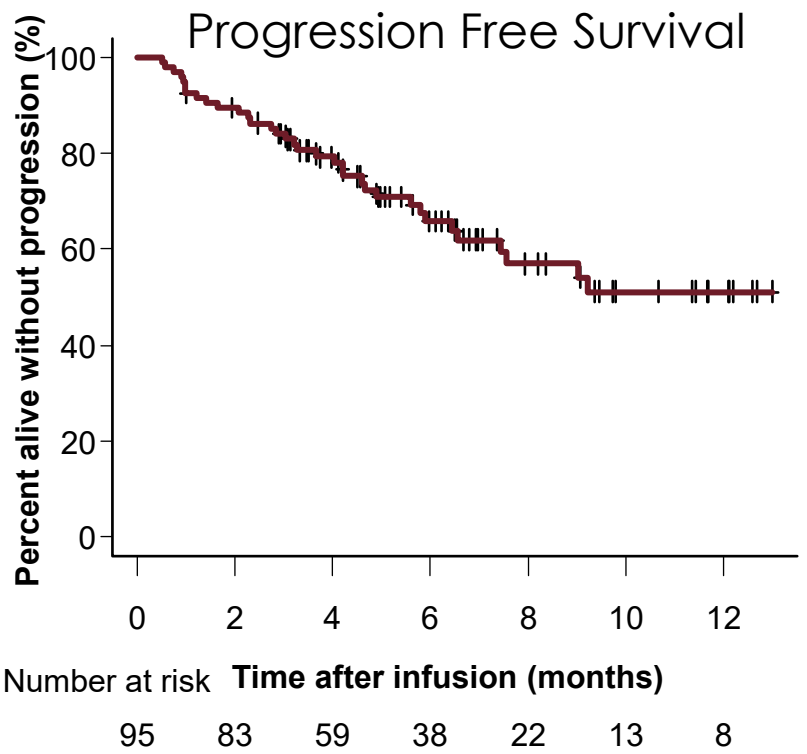
Brexu-Cel RWE: Median follow-up = 6.7 months (range 0.5-13.6)



Median DOR not reached

6-month rate 70% (95% CI 57-80)

6-month DOR comparable to that in ZUMA-2

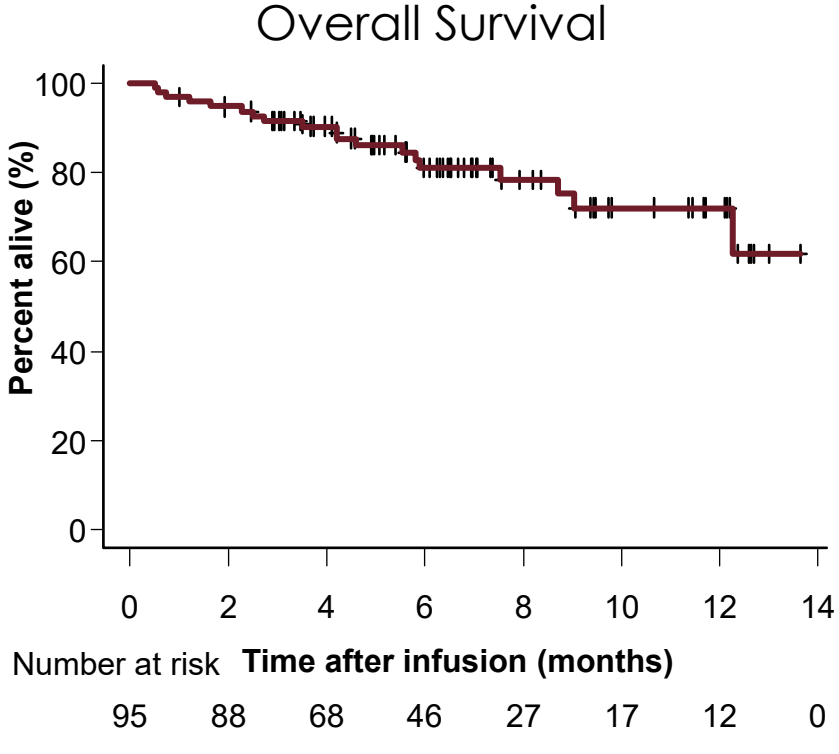


Median PFS not reached

6-month PFS rate 66% (95% CI 54-75)

12-month PFS rate 51% (95% CI 37-64)

12-month PFS in ZUMA-2 was 61%



Median OS not reached

6-month OS rate 81% (95% CI 70-88)

12-month OS rate 72% (95% CI 57-82)

12-month OS in ZUMA-2 was 83%

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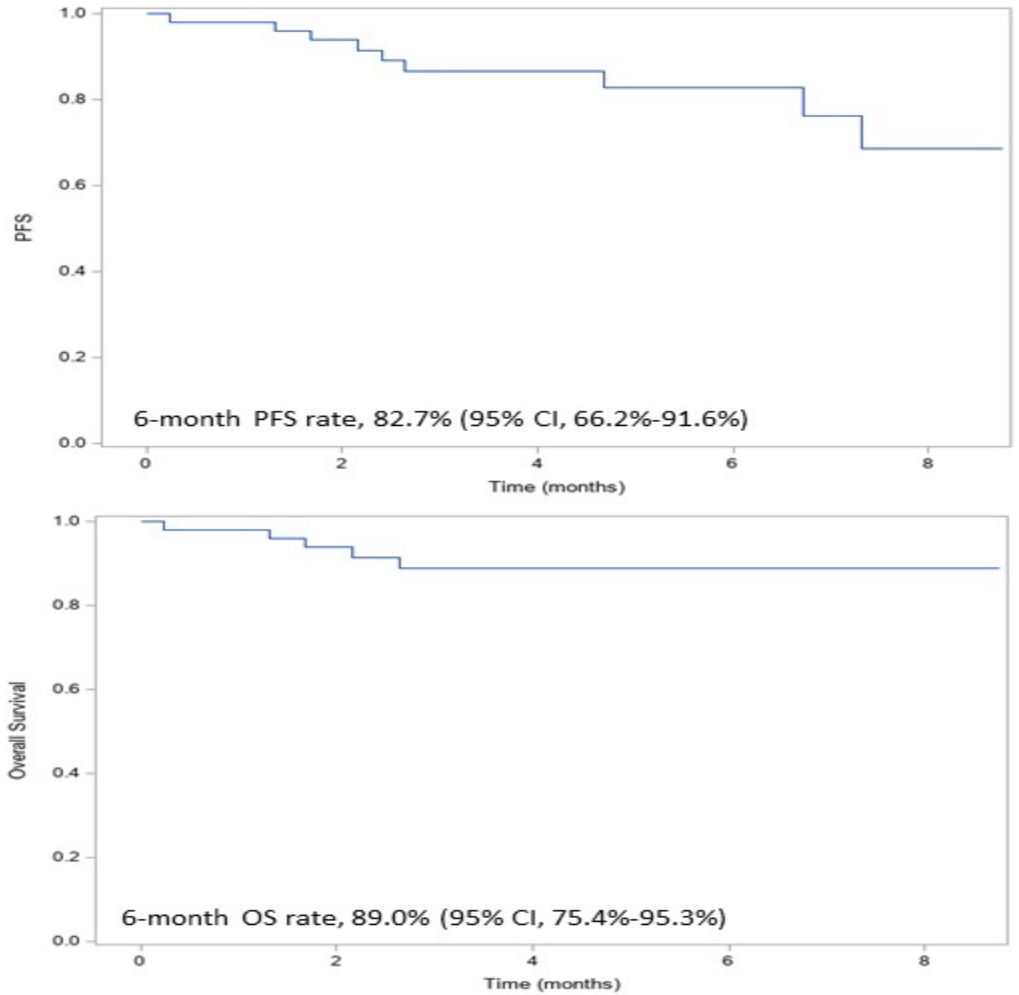
Brexu-Cel RWE:2nd Cohort

Table 1. Baseline characteristics of patients who received brexu-cel

Characteristic	Patients (n = 52)
Median Age (range) – yr	66 (47-79)
Male gender – n (%)	43 (82)
Ann Arbor stage 4 at diagnosis – n (%)	41 (78)
Baseline pathology and cytogenetic characteristics – n/total n (%)*	
Blastoid/pleomorphic histology present	12/39 (30)
Ki67 ≥ 30%	30/36 (83)
TP53 mutation present	3/9 (33)
Deletion 17p present	9/23 (39)
≥ 3 cytogenetic abnormalities	13/29 (44)
Baseline MIPI – n/total n (%)*	
Low	9/29 (31)
Intermediate	10/29 (34)
High	10/29 (34)
ECOG performance status prior to lymphodepleting chemo – n (%)	
0-1	47 (90)
2	4 (8)
3	1 (2)
Relapse within 24 months of first-line therapy – n (%)	26 (50)
Median no. therapies prior to CAR T (range)	3 (2-8)
Prior autologous transplant – n (%)	21 (40)
Prior allogeneic transplant – n (%)	2 (4)
Previously treated with BTKi – n (%)	52 (100)
Disease progression on BTKi – n (%)	29 (56)
Best response to most recent treatment prior to leukapheresis – n/total n (%)*	
CR	13/41 (32)
PR	14/41 (34)
SD	3/41 (7)
PD	11/41 (27)

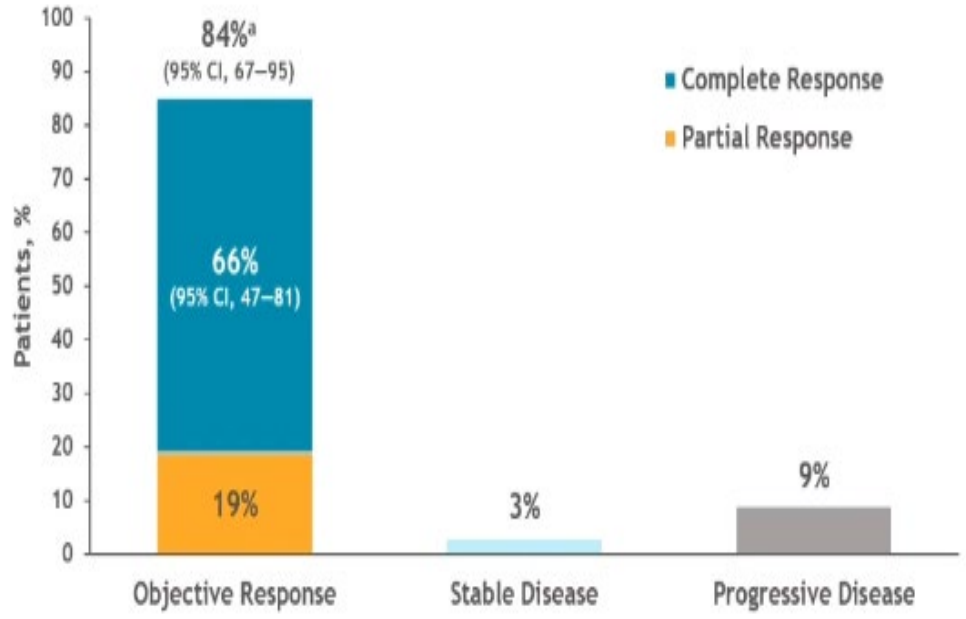
*number of positive cases out of number of patients with data available

Figure 1. Progression-free survival and overall survival in patients who received brexu-cel



Ramancik et al, ASH 2021

TRANSCEND, Liso-cel



- ORR and CR rate, respectively, for patients with high-risk features:
  - Ki67 ≥30% (n = 23): 83% and 65%
  - Blastoid morphology (n = 13): 77% and 54%
  - *TP53* mutations (n = 7): 100% and 57%

	All liso-cel–Treated Patients (N = 32)
CRS or NE, n (%)	
Any grade	19 (59)
Grade ≥3	5 (16)
CRS	
Any grade, n (%)	16 (50)
Grade ≥3, n (%)	1 (3)
Time to onset, median (range), days	6 (2–10)
Time to resolution, median (range), days	4 (2–9)
NE	
Any grade, n (%)	11 (34)
Grade ≥3, n (%)	4 (12.5)
Time to onset, median (range), days	8 (2–25)
Time to resolution, median (range), days	4 (1–27)
ICU admissions, n (%)	3 (9)
CRS and/or NE	3 (9)
Other reasons	0

Palomba et al ASH 2020

Non-CART Therapies

TREATMENT	Overall Response Rate	Median Progression Free Survival	Median Duration of Response	Median Overall Survival
Lenalidomide	29		20 weeks	
Venetoclax	53	3.2 months	8.1 months	9.4 months
R-BAC (Rituximab, Bendamustine, Cytarabine)	83%	10.1 months		12.5 months

DR2IVE treatment schedule

Dexamethasone	20–40 mg PO or IV 1, 8, 15, 22
Rituximab	375 mg/m2 IV 1, 8, 15, 22
Lenalidomide	15–20 mg PO 1–21
Bortezomib	1.3 mg/m2 SC 1, 8, 15, 22

Wang et al J Hematol Oncol 2017 Nov 2;10(1):171; Eyre et al Hematologica 2019 Feb;104(2):e68-e71McCulloch et al BJH 2020 May;189(4):684-688; Wang BJH 2017

Conclusions

- BTKi preferred treatment at initial relapse
  - Continue at progression
- Brexu-cel highly active patients with prior BTKi exposure
  - Early prioritization of high-risk patients for evaluation
- Targeted therapies options for patients not candidates for brexu-cel or clinical trials