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# Treatment of Richter Transformation

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@SylvesterCancer



# Disclosures

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- AdBoard
  - Genentech, Lilly, Amgen, TG Therapeutics, Incyte, BeiGene, Janssen, Epizyme, SeaGen, Kite, ADC Therapeutics
- Research Funding
  - Lilly, Incyte, BeiGene, BostonGene, ONO Therapeutics

# Richter Transformation

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- Transformation of CLL to aggressive lymphoma, mainly DLBCL
  - 2-10% of CLL natural history
  - 0.5-1%/yr
- Constitutional symptoms, elev LDH, hyperCa, fast growing lymph nodes
- PET/CT
  - Cutoff SUV 5 (NPV 92%, PPV 38%)
- Excisional lymph node biopsy
- Programmed at birth
  - Underlying disease biology, not treatment received
  - No difference in randomized studies
  - Greater in R/R from clonal evolution

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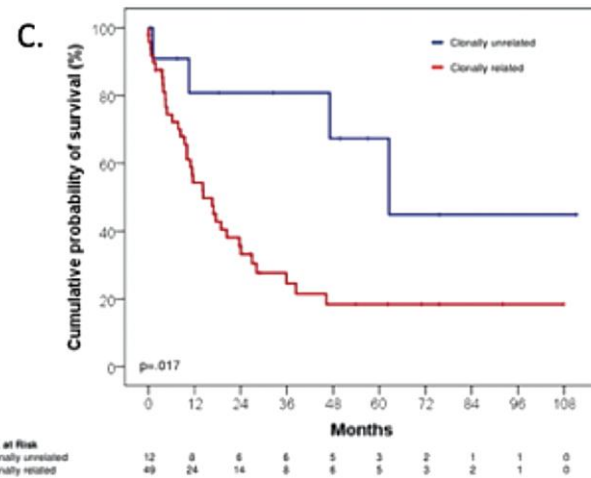
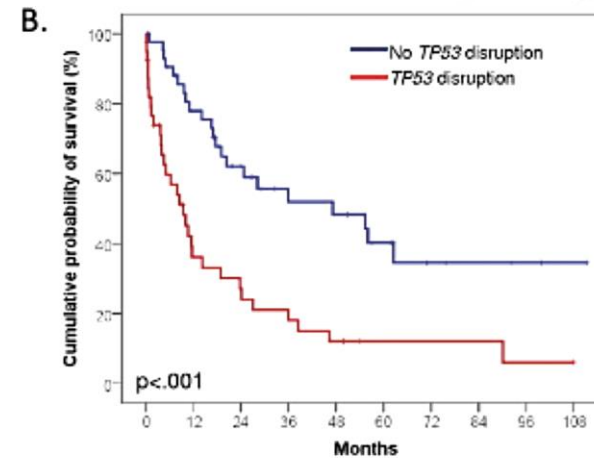
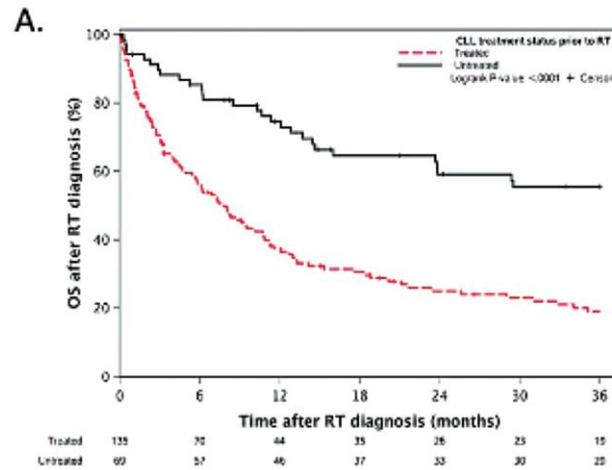
Blood (2014) 123 (11): 1647–1657; Blood. 2014;123(18):2783-2790

# RT – molecular features

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- High-risk genomic characteristics
  - unmutated IGHV status
  - activating NOTCH1 mutations
  - TP53 deletion and/or mutation
  - Del11q
- Clonal relationship - IGH gene sequencing in transformed & CLL cells
  - Clonally related
    - a little better if untreated, no TP53
    - Immunologically distinct from CLL/de novo DLBCL - PD-1 expression up to 80%
  - Clonally unrelated – similar prognosis to de novo DLBCL
- Most common genomic alterations in clonally related
  - TP53 mutation (60%-80%)
  - MYC overexpression (40%)
  - CDKN2A deletion (30%)
  - Activating NOTCH1 mutation (~30%)

# RT – molecular features



# RT – molecular features

Study and years of patient recruitment	Regimen	n	Median age (years)	Results		
				ORR	CRR	Median OS
<b>Anthracycline-containing regimens</b>						
Langerbeins et al <sup>16</sup> (2003–2008)	R-CHOP	15	69 (N/A)	67%	7%	21 months
Dabaja et al <sup>17</sup> (published 2000)	HyperCVXD	29	61 (36–75)	41%	38%	10 months
Tsimberidou et al <sup>18</sup> (1999–2001)	Rituximab and GM-CSF with alternating hyperCVAD and MTX/cytarabine	30	59 (27–79)	43%	18%	8.5 months
Rogers et al <sup>19</sup> (2006–2014)	R-EPOCH	46	67 (38–83)	39%	N/A	5.9 months
<b>Platinum-containing regimens</b>						
Tsimberidou et al <sup>20</sup> (2004–2006)	OFAR1	20	59 (34–77)	50%	20%	8 months
Tsimberidou et al <sup>21</sup> (2007–2010)	OFAR2	35	63 (40–81)	43%	8.6%	6.6 months
<b>Fludarabine-containing regimens</b>						
Giles et al <sup>22</sup> (1992–1996)	PFA or CFA	12	59 (49–74)	45%	N/A	17 months
Tsimberidou et al <sup>23</sup> (1997–2001)	FACPGM	15	62 (42–74)	5%	5%	2.2 months

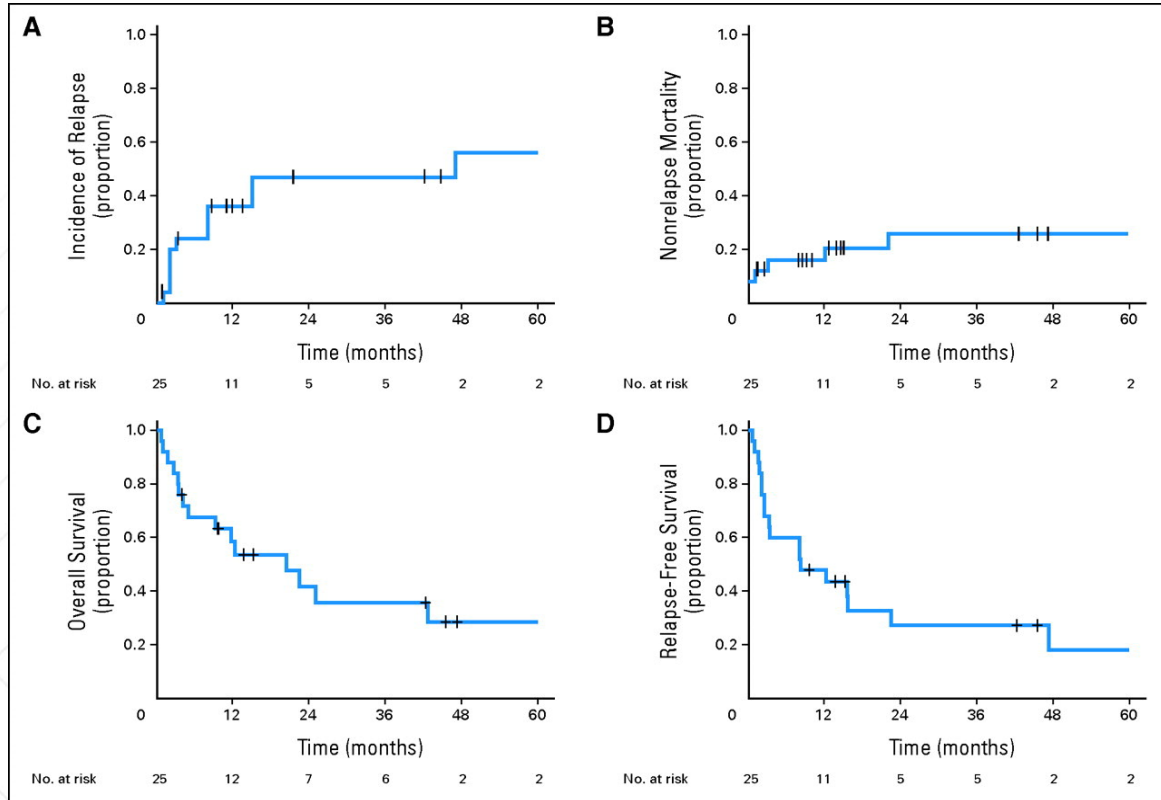
# RT – allo HSCT

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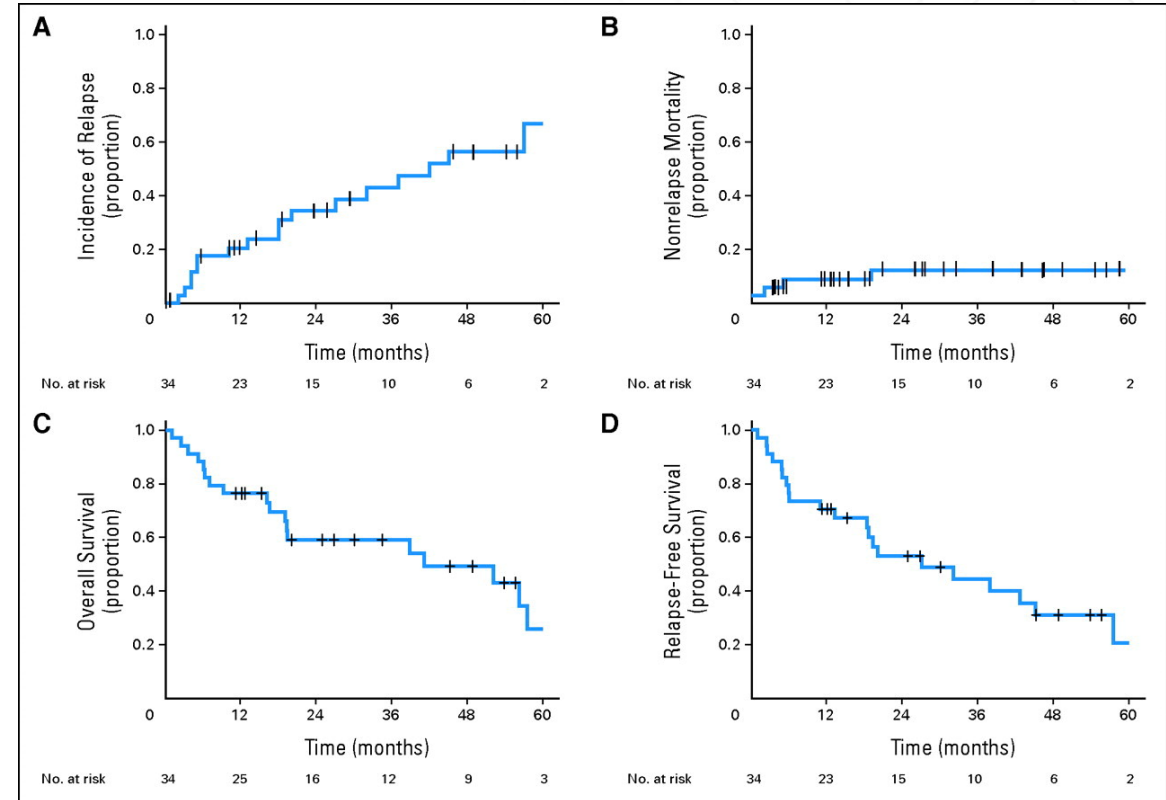
- EBMTR review
  
- Allo-HCT
  - N=25
  - plateau on long-term relapse-free survival
  - 3-year RFS 27% post alloSCT
    - Chemosensitive disease
    - Reduced-intensity conditioning
  - 47% relapse (10 DLBCL-RS, 2 CLL)
  - 26% NRM @ 3 yrs
  
- ASCT
  - N=34
  - No plateau on relapse-free survival
  - 3-year RFS 45% (11 relapses with DLBCL-RS and 6 with CLL)

# RT – allo HSCT

## Allo SCT



## ASCT





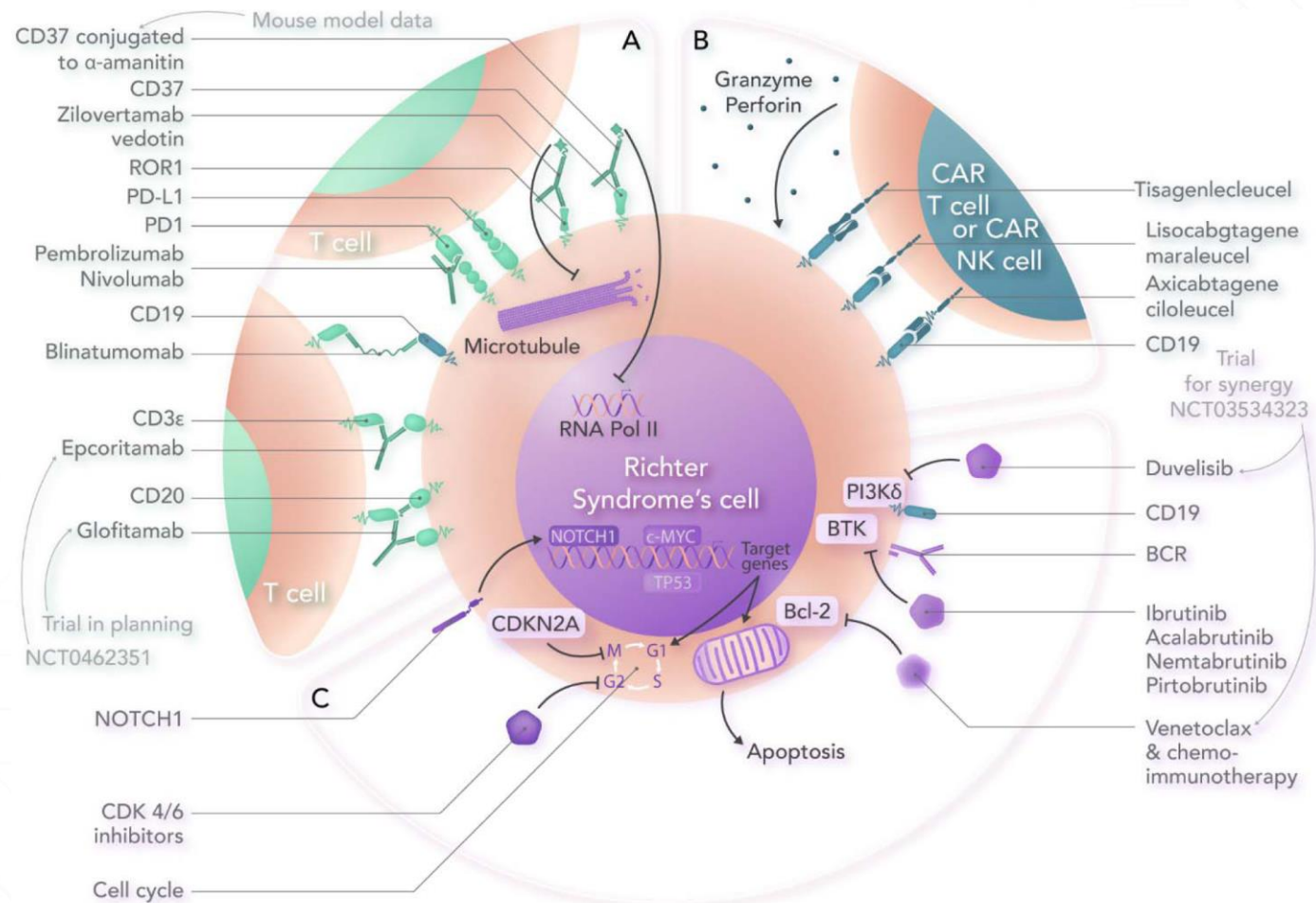
# RT – allo HSCT

- EBMTR review
- N=66 allo-HCT (2008-2018)
  - Median age 56.2 yrs (51.3-63.1)
  - Median time RT to allo-HCT 6.9 months (4.9-11)
  - CR=28 (42.4%)
  - reduced intensity conditioning (66.2%)
    - N=18 (27.3%) matched sibling donor
    - N=24 (36.4%) matched unrelated donor
    - Remaining mismatched
- Median follow-up 6.6 years
  - 1-yr OS 65% (54-77)
  - 1-yr PFS 39% (27-51)
  - 3-yr OS 53% (41-65)
  - 3-yr PFS 29% (18-40)
- CR - superior 3-yr PFS (39% vs. 21%,  $p = 0.032$ )
- Cumulative gr II-IV aGVHD at D+100 41% (95% CI 29-53)
- Chronic GVHD at 3 years 53% (95% CI 41-65)
- Non-relapse mortality at 3 yrs 38% (95% CI, 26-50)

# Novel agents

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# Novel agents



# Venetoclax + CIT

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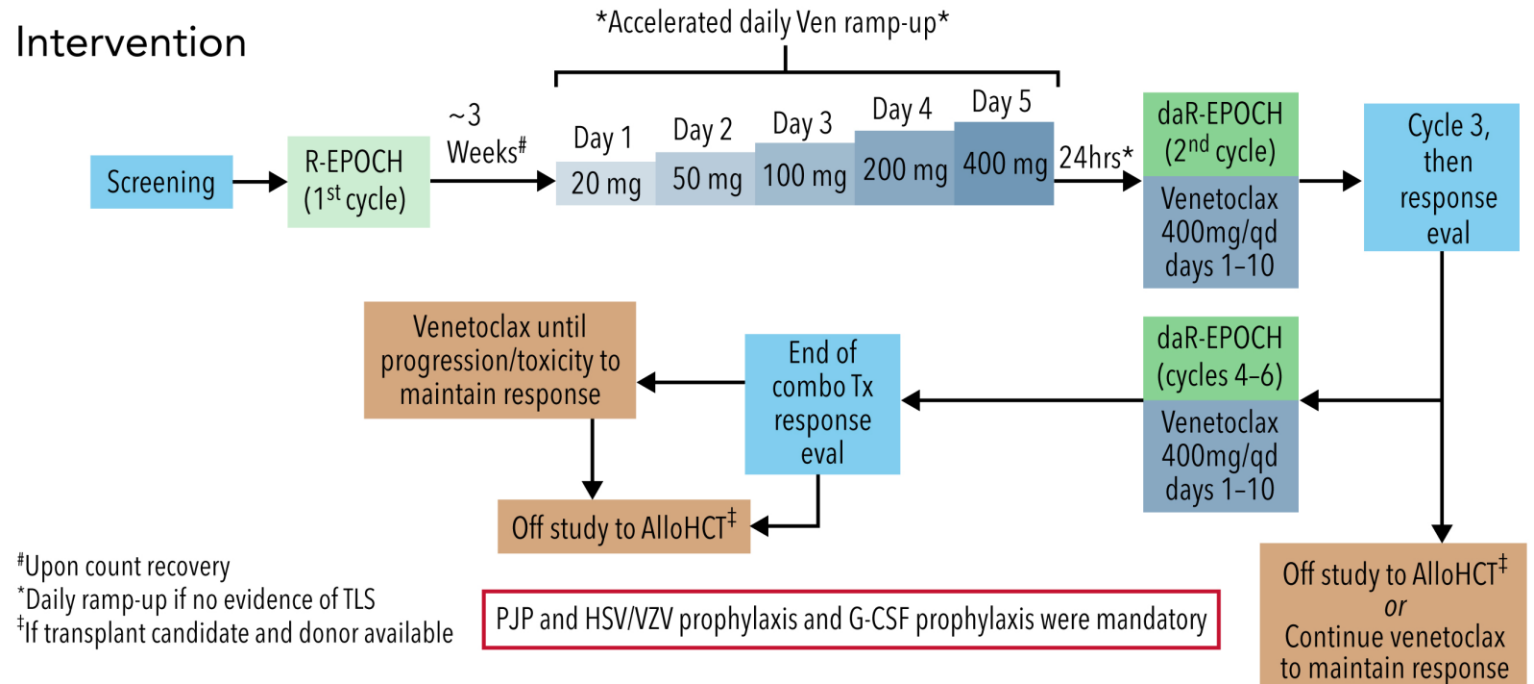
- Retrospective study
- N=62 patients
  - BTKi; n=28
  - R-CHOP; n=13
  - Intensive chemoimmunotherapy; n=21
- ORR/CR
  - BTKi - 36%/25%
  - R-CHOP 54%/46%
  - Intensive therapy 52%/38%
- Median PFS/OS
  - BTKi - 4.9/14.3 months
  - R-CHOP - 14.9 months/not reached
  - Intensive therapy 3.3/9 months
- del(17p)/TP53 - lower CR
- Gr 3-4 cytopenia - most frequent intensive chemoimmunotherapy
- Gr 3-4 infection - similar across groups

# Venetoclax + CIT

## Venetoclax plus dose-adjusted R-EPOCH (VR-EPOCH) for Richter's syndrome

### Patients (n=26 treated)

- Biopsy-proven RS
- Median age 63 years
- 78% with prior CLL treatment
- 52% with complex karyotype
- 42% with *TP53* aberrancy
- 41% post-ibrutinib
- 22% post-venetoclax
- 15% post-PI3Ki



# Venetoclax + CIT

## Outcomes

### Efficacy

50% CR rate by ITT analysis  
11 patients with CLL BM-uMRD  
Median follow-up 17 months  
Median PFS 10.1 months  
Median OS 19.6 months

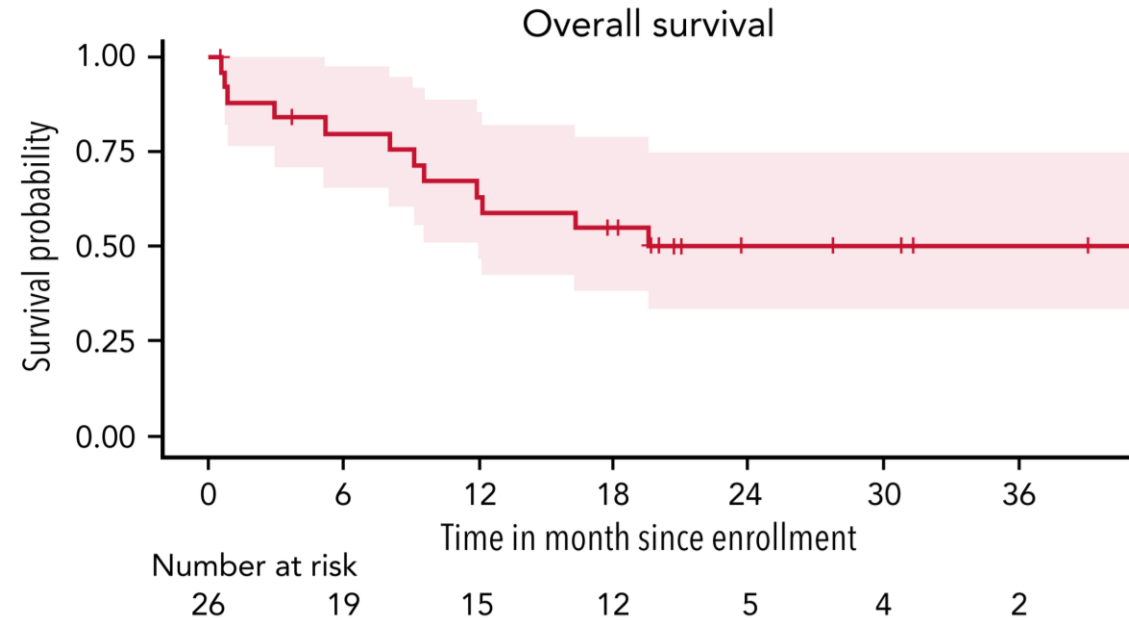
### Safety

Heme tox:

- gr  $\geq 3$  neutropenia (65%)
- thrombocytopenia (50%)
- febrile neutropenia (38%)

Infections: pneumonia, sepsis, and enterocolitis (n=3 each)

No patients experienced TLS with daily venetoclax ramp-up





# CPI - Pembrolizumab

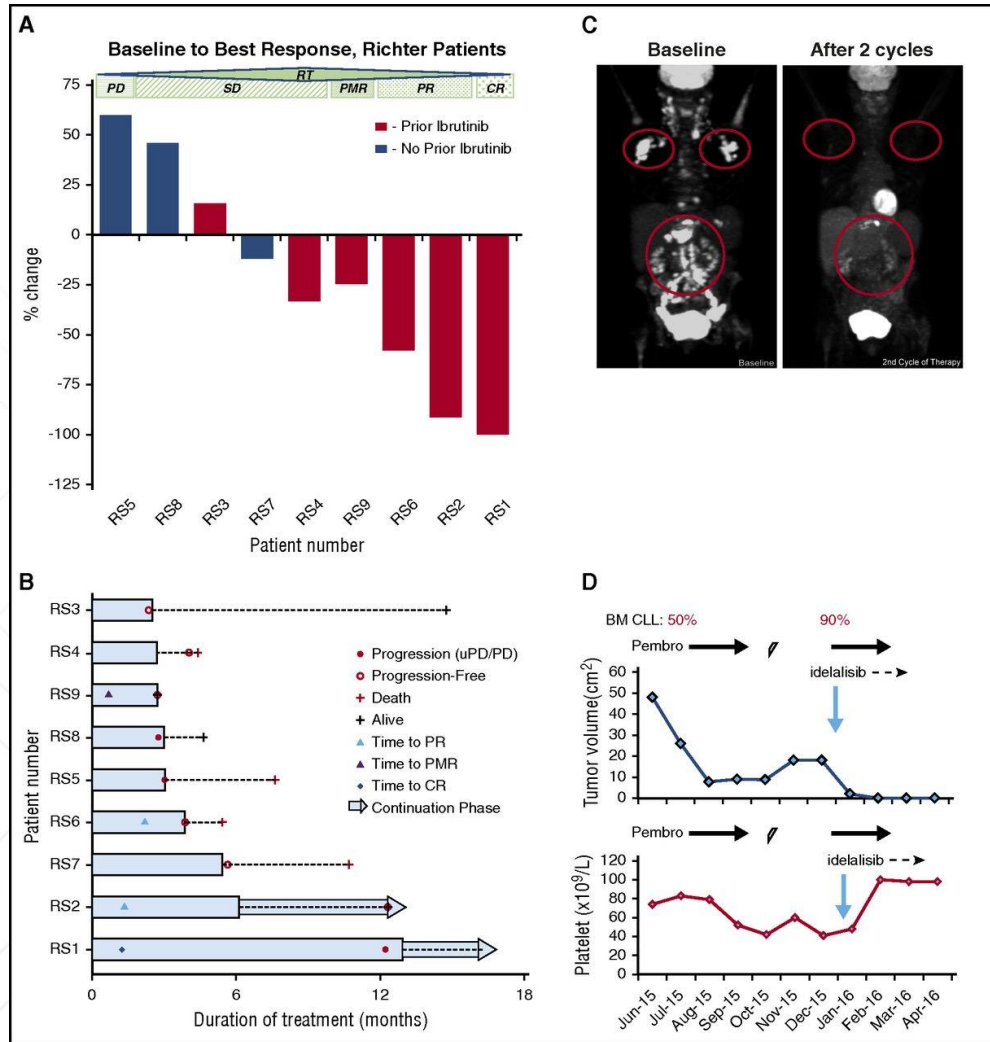
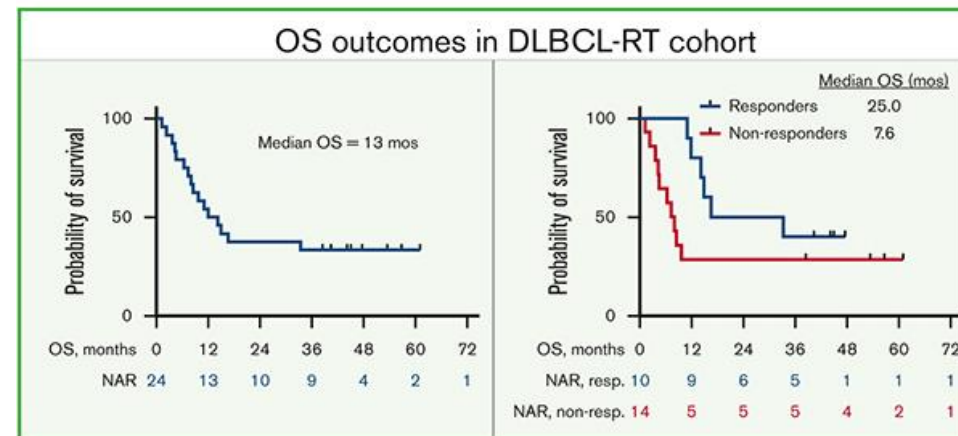


Table I. Best objective tumour response.

	Pembrolizumab <i>n</i> = 23
Objective response rate, <i>n</i> (%) [95% CI]	3 (13.0) [2.8–33.6]
Best objective response, <i>n</i> (%)	
Complete response	1 (4.3)
Partial response	2 (8.7)
Stable disease	1 (4.3)
Progressive disease	11 (47.8)
No assessment <sup>a</sup>	8 (34.8)

# CPI – Nivolumab + ibrutinib

DLBCL-RT (N = 24)		
Characteristics		N (%), median [range]
<b>Baseline parameters</b>	Age (years)	64.5 [47–88]
	Gender (male)	14 (58)
<b>Disease parameters</b>	IGHV unmutated	13/18 (72)
	Del17p	9 (45)
<b>Prior therapy</b>	Prior therapy for CLL	20 (83)
	Prior therapy for RT	10 (42)
	Prior exposure to BTK inhibitor	13 (54)
	Prior Allo-SCT	3 (13)
	Completely treatment naive	1 (4)
<b>Study combination efficacy</b>	<b>ORR</b>	<b>10 (42)</b>
	- CMR	8 (33)
	- PMR	2 (8)
	Post-trial therapy allo-SCT	4 (17)
	<b>Median OS (months)</b>	
- Whole cohort	13	
- Responders	25	
<b>Adverse events</b>	Grade 3-4 immunological toxicity	4 (17)
		4 (17)



CLL (N = 10)		
Characteristics		N (%), median [range]
<b>Baseline parameters</b>	Age (years)	57 [42-70]
	Gender (male)	8 (80)
<b>Disease parameters</b>	IGHV unmutated	4 (40)
	Del17p	4 (40)
<b>Prior therapy</b>	Median lines of therapy	1 (1-3)
<b>Efficacy</b>	CR	3 (30)
<b>Adverse events</b>	Immunological toxicity	1 (10)

\*CLL cohort stopped early due to poor recruitment

DLBCL-RT diffuse large B-cell lymphoma Richter transformation, R/R- re;lapsed refractory, N/D- newly diagnosed

ORR- overall response rate, CMR- complete metabolic response, PMR- partial metabolic response, CR- complete remission

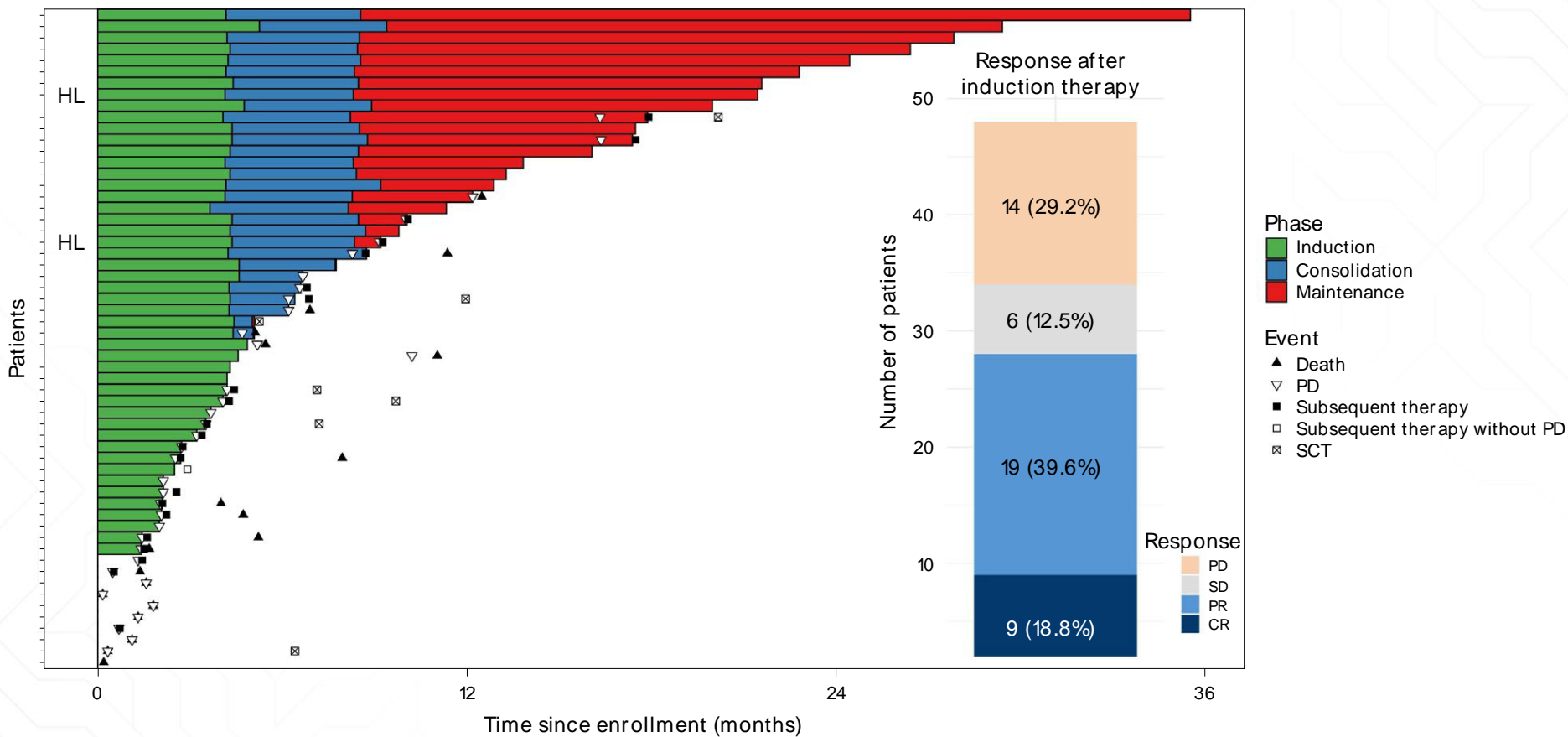


# CPI – Tislelizumab + zanubrutinib

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- Ph 2
  - primary end point – ORR p six cycles
  - N=59, 48 received at least two cycles (analysis population)
    - N=10 previous RT therapy
  - median f/u 13.9 months
  - median age 67 (range 45–82) years.
- ORR 58.3% (95% confidence interval (CI) 43.2–72.4) - 28 of 48
  - CR = 9 (18.8%)
  - PR = 19 (39.6%)
- median DoR not reached
- median PFS 10.0 months (95% CI 3.8–16.3)
- median OS not reached
  - 12-mo OS 74.7% (95% CI 58.4–91.0)

# CPI – Tislelizumab + zanubrutinib



# Pirtobrutinib

## Patient Characteristics

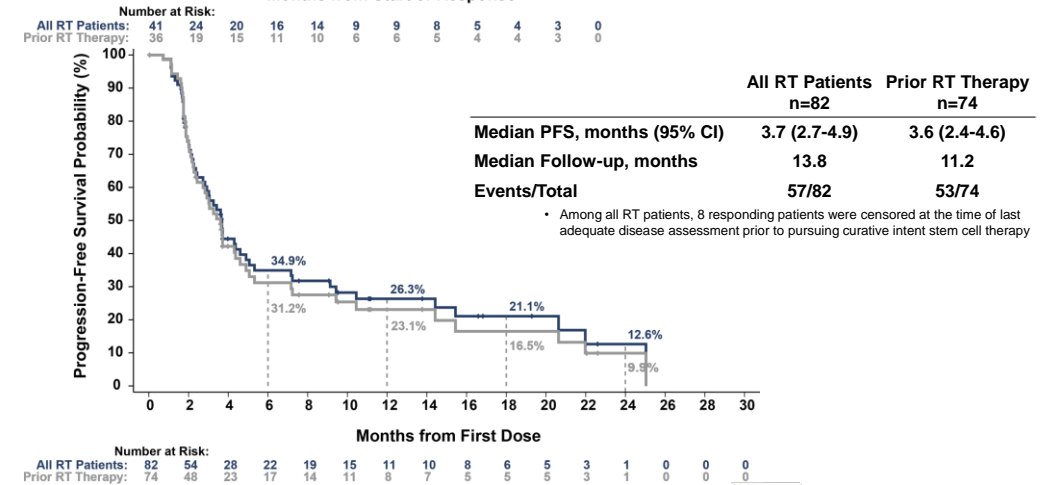
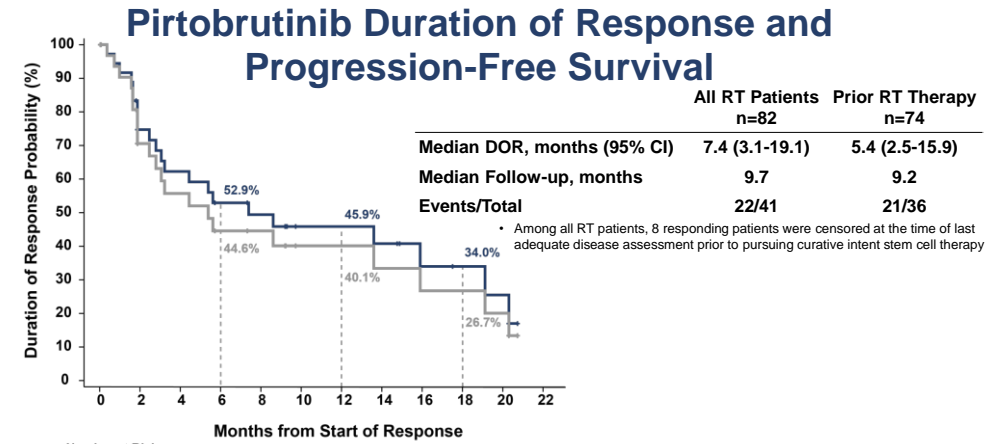
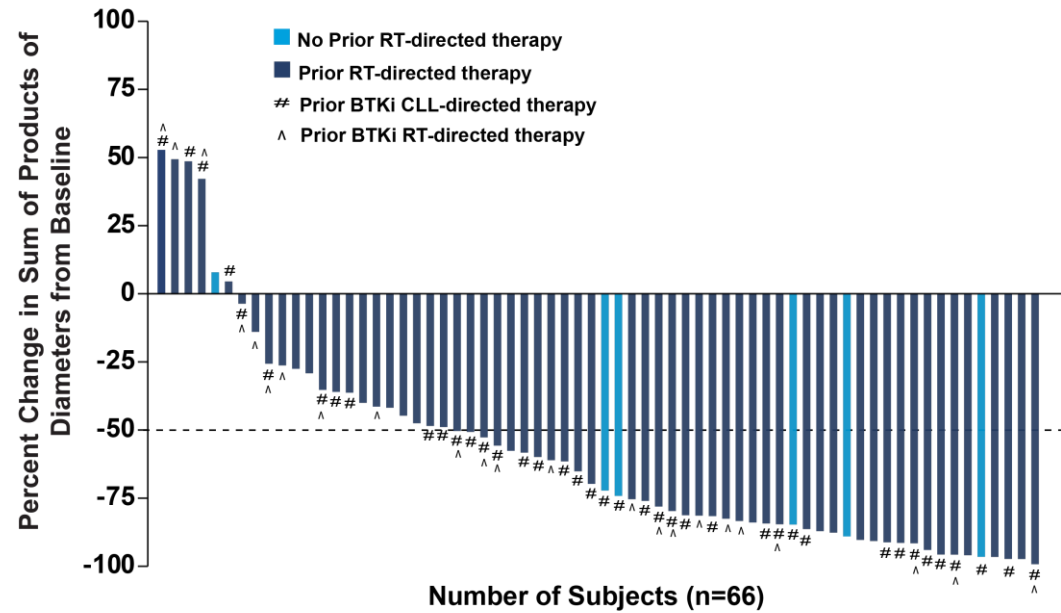
Characteristics	Overall n=82
<b>Median Age</b> , years (range)	67 (26-95)
<b>Male</b> , n (%)	55 (67)
<b>ECOG PS</b> , n (%)	
0	32 (39)
1	38 (46)
2	12 (15)
<b>Ann Arbor Stage</b> , n (%)	
Stage I-II	8 (10)
Stage III-IV	57 (70)
Missing	17 (21)
<b>Tumor Bulk</b> (cm), n (%)	
<5	39 (48)
≥5	36 (44)
No Measurable Lymph Node	7 (9)
<b>Elevated LDH</b> , n (%)	
Yes	66 (81)
No	16 (20)
<b>Median Time</b> , months (IQR)	
From Initial CLL Diagnosis to RT Presentation	61 (17-102)
From Transformation to First Pirtobrutinib Dose	5 (2-13)
<b>Median Number of Prior Lines of</b> , (range)	
CLL Therapy	2 (0-13)
RT Therapy	2 (0-8)
CLL and RT Therapy	4 (0-13)

Prior Therapies	Any	RT-Directed	CLL-Directed
<b>Number of Patients</b> , n/n (%)	81/82 (99)	74/82 (90)	65/82 (79)
<b>Prior Therapies</b> , n (%)			
Anti-CD20 antibody	80 (98)	64 (78)	54 (66)
Chemoimmunotherapy	73 (89)	62 (76)	43 (52)
BCL2 inhibitor	56 (68)	31 (38)	40 (49)
cBTK inhibitor	61 (74)	28 (34)	51 (62)
CAR-T-cell therapy	11 (13)	9 (11)	3 (4)
PI3K inhibitor	12 (15)	8 (10)	4 (5)
Stem cell transplant	10 (12)	5 (6)	6 (7)
Allogeneic	7 (9)	4 (5)	4 (5)
Autologous	3 (4)	1 (1)	2 (2)
Immunomodulator <sup>a</sup>	7 (9)	3 (4)	5 (6)
Other systemic therapy	31 (38)	25 (31)	8 (10)

# Pirtobrutinib

## Pirtobrutinib Efficacy

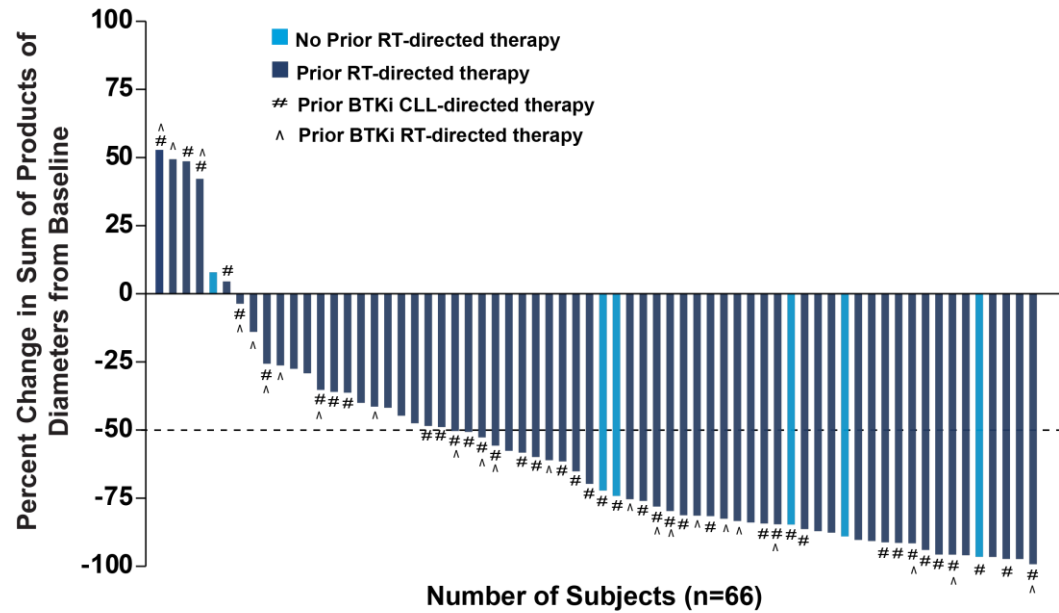
	All n=82	Prior RT Therapy n=74
<b>Overall Response Rate<sup>a</sup>, % (95% CI)</b>	50.0 (38.7-61.3)	48.6 (36.9-60.6)
<b>Best Response, n (%)</b>		
CR	11 (13.4)	9 (12.2)
PR	30 (36.6)	27 (36.5)



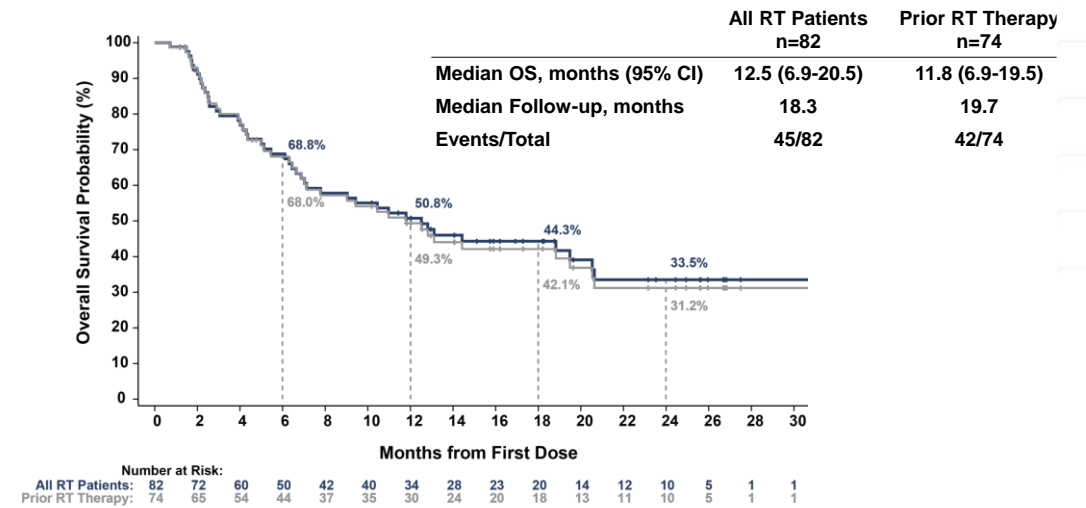
# Pirtobrutinib

## Pirtobrutinib Efficacy

	All n=82	Prior RT Therapy n=74
<b>Overall Response Rate<sup>a</sup>, % (95% CI)</b>	50.0 (38.7-61.3)	48.6 (36.9-60.6)
<b>Best Response, n (%)</b>		
CR	11 (13.4)	9 (12.2)
PR	30 (36.6)	27 (36.5)



## Pirtobrutinib Overall Survival



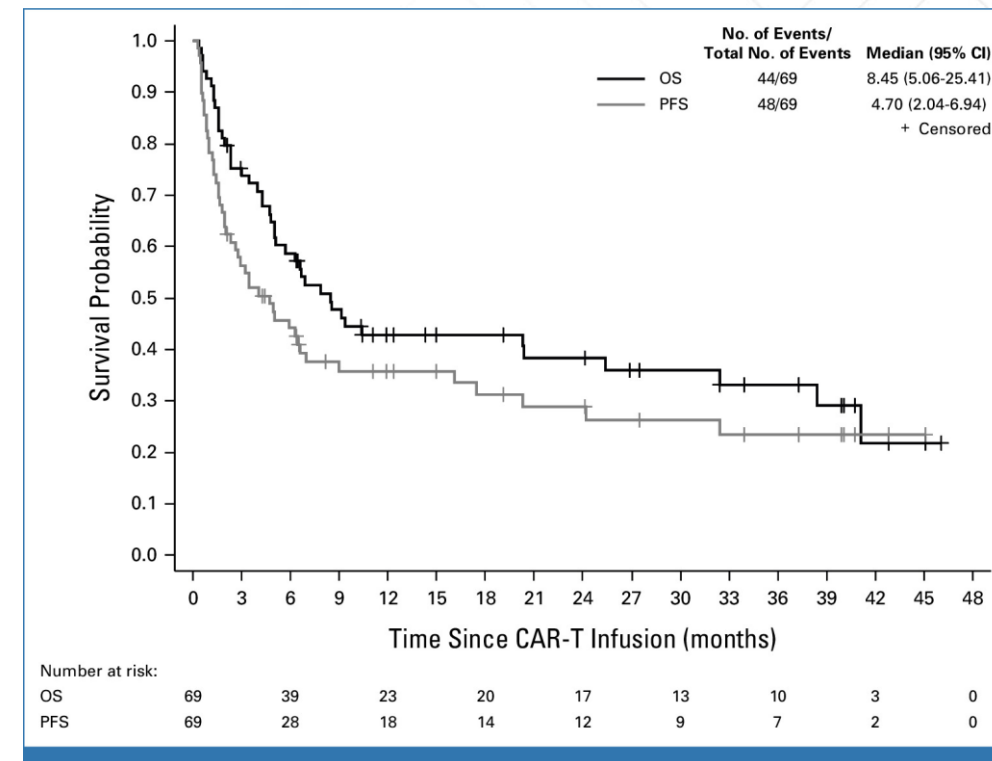
# CAR-T cell therapy

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- N=69
  - median age 64 years (range, 27-80)
  - median 4 tx (range, 1-15)
    - BTK/BCL2i 58 (84%)
- Product
  - axicabtagene ciloleucel - 44 patients (64%)
  - tisagenlecleucel - 17 patients (25%)
  - lisocabtagene maraleucel - 7 patients (10%)
  - brexucabtagene autoleucel - 1 patient (1%)
- 11 pts CRS gr3+ (16%)
- 25 pts ICANS gr3+ (37%)

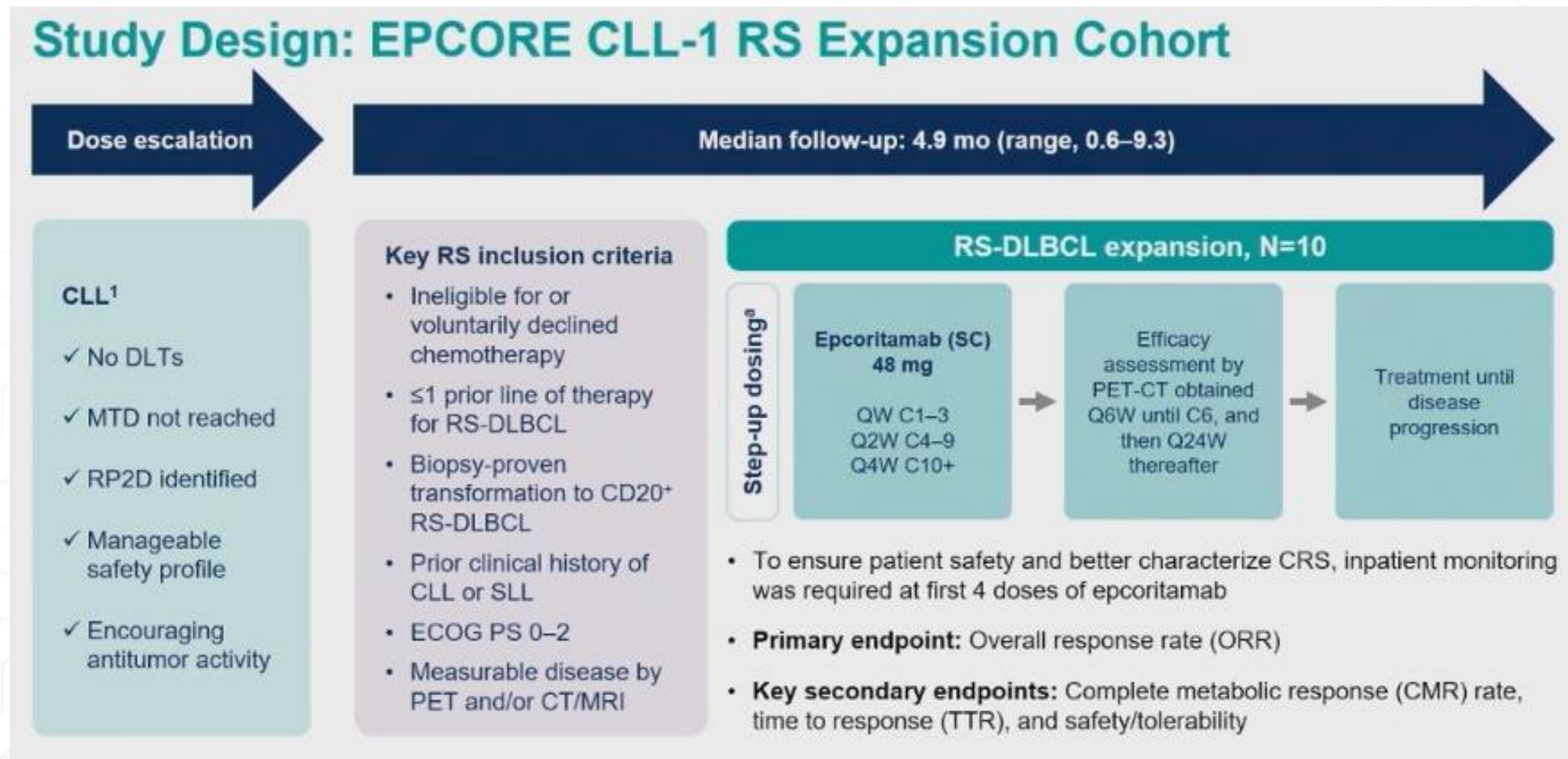
# CAR-T cell therapy

- ORR 63%
  - CR 46%
- median follow-up 24 months
  - median PFS 4.7 months (95% CI, 2.0 to 6.9)
    - 2-year PFS 29% (95% CI, 18 to 41)
  - median OS 8.5 months (95% CI, 5.1 to 25.4)
    - 2-year OS 38% (95% CI, 26 to 50)
  - median DoR for pts in CR 27.6 months (95% CI, 14.5 to NR)





# Bispecific antibodies - epcoritamab





# Bispecific antibodies - epcoritamab

## Treatment History

Characteristic of Prior CLL Therapy	Total N=10	Characteristic of Prior RS-DLBCL Therapy	Total N=10
Median time from initial CLL diagnosis to first dose, y (range)	12 (2.6–24.0)	<b>1 prior line of RS-DLBCL therapy, n (%)</b>	<b>5 (50)</b>
<b>Median number of prior lines of therapy for CLL (range)</b>	<b>3 (0–7)</b>	R-CHOP	3 (30)
Prior CLL/SLL therapy, n (%)	7 (70)	No response	2 (20)
Chemoimmunotherapies	7 (70)	R-DHAP	1 (10)
Targeted agents	6 (60)	No response	1 (10)
BCL2 inhibitor	5 (50)	VR-EPOCH <sup>a</sup>	1 (10)
BTK inhibitor	5 (50)	Median time from disease transformation to first dose, mo (range)	3.4 (0.5–21.4)
CAR T-cell therapy	1 (10)	Median time from end of last line of RS-DLBCL therapy to first dose, mo (range)	2 (0.5–5.4)
Median time from last CLL treatment to first dose, mo (range)	12 (0.2–61.8)	<sup>a</sup> Response to VR-EPOCH unknown. R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; VR-EPOCH, venetoclax plus dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.	
Data cutoff: September 16, 2022.			

# Bispecific antibodies - epcoritamab

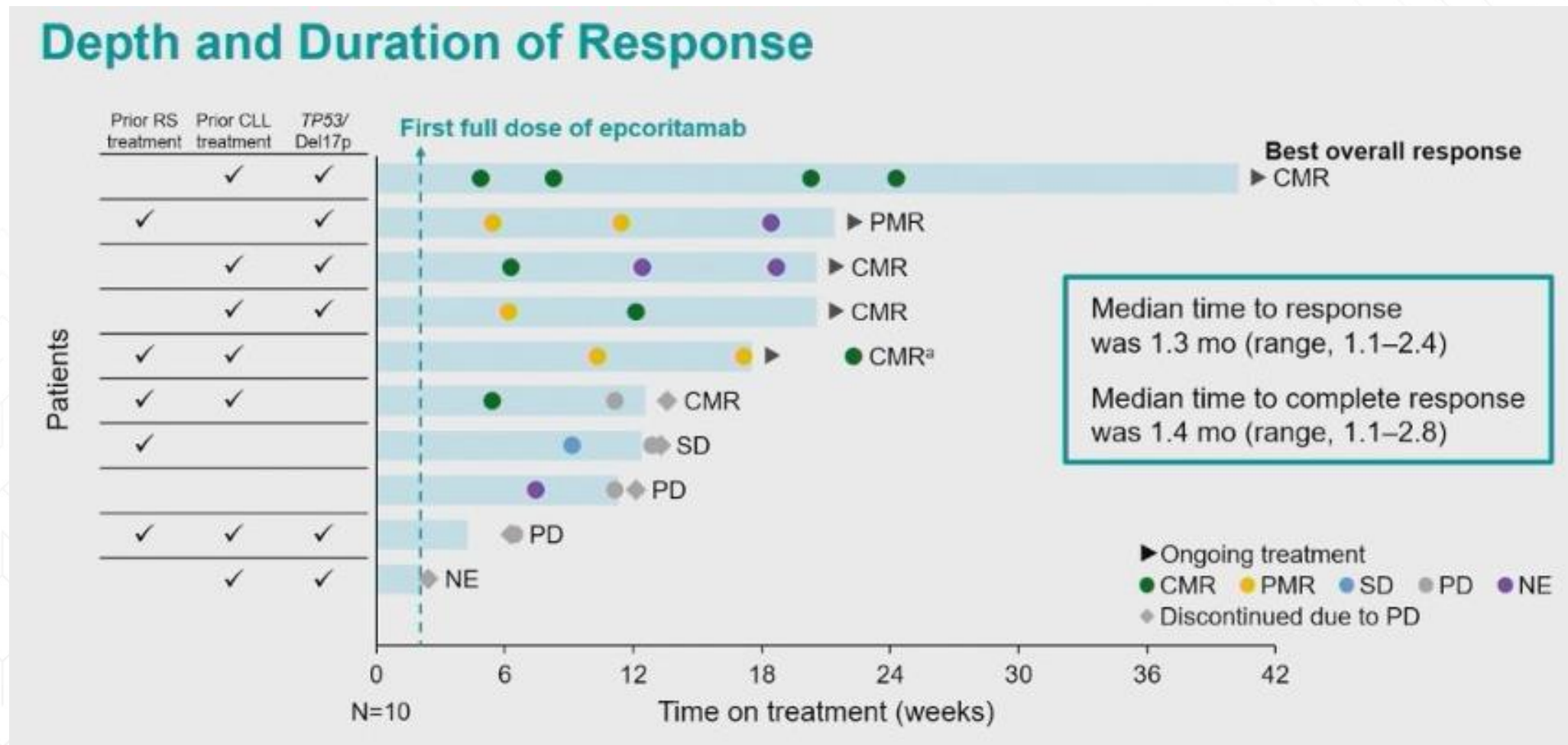
## Best Overall Response

Response, n (%) <sup>a</sup>	Total Efficacy Evaluable N=10
<b>Overall response<sup>b</sup></b>	<b>6 (60)</b>
Complete metabolic response (CMR)	5 (50)
Partial metabolic response (PMR)	1 (10)
Stable disease	1 (10)
Progressive disease	2 (20)
Not evaluable	1 (10) <sup>c</sup>

Data cutoff: September 8, 2022. Median follow-up: 4.9 mo (range, 0.6–9.3).

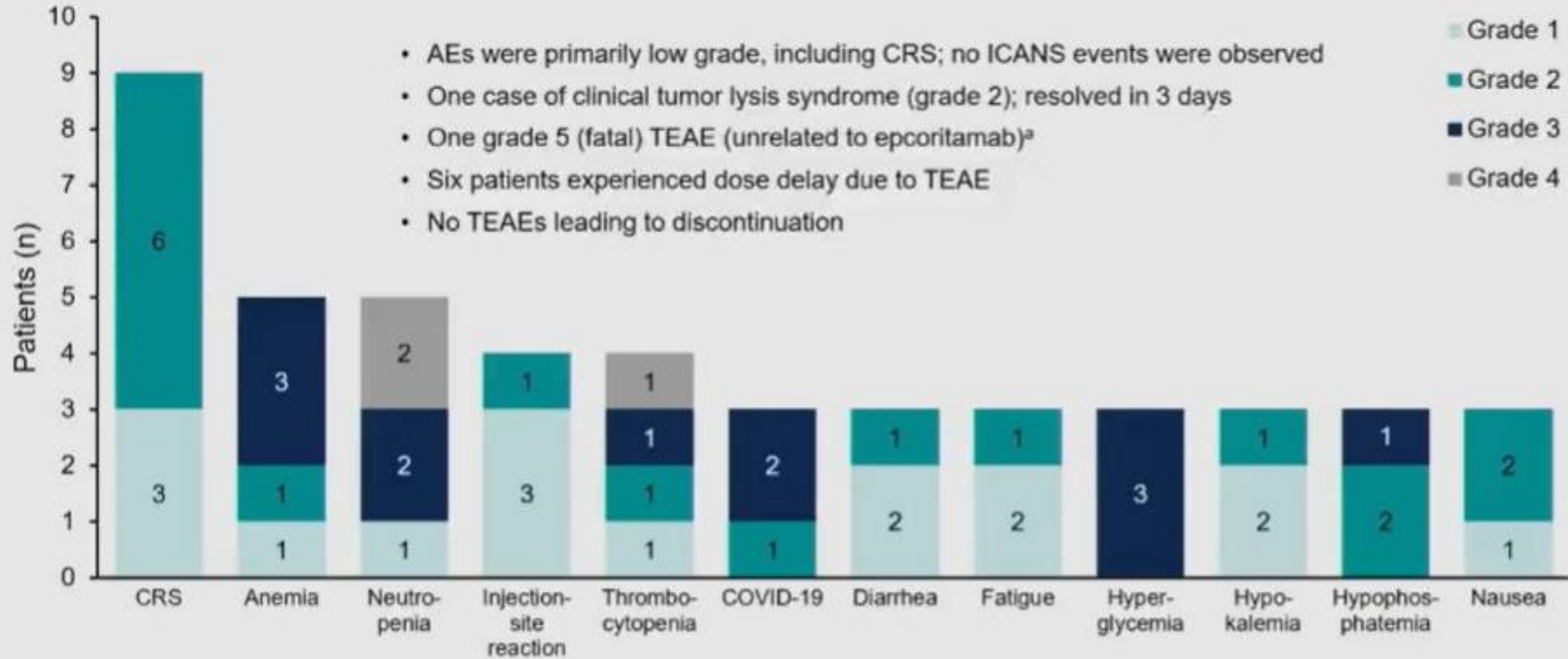
<sup>a</sup>Based on modified response-evaluable population, defined as patients with  $\geq 1$  target lesion at baseline and  $\geq 1$  postbaseline response evaluation and/or patients who died within 60 d of first dose. <sup>b</sup>Response assessment according to Lugano 2014 criteria. <sup>c</sup>Patient stopped treatment on C1D15 due to progression and did not receive any scans.

# Bispecific antibodies - epcoritamab



# Bispecific antibodies - epcoritamab

## Treatment-Emergent AEs ( $\geq 30\%$ )





# Summary

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- Extremely challenging diagnosis
- Understand relevant predictive factors
  - Treatment history – tx naïve, previous BTKi
  - TP53 status
  - Clonal relationship
  - Allo transplant eligibility
- Early use of CPI, venetoclax, BTKi c/nc, bispecific antibodies, CAR-T

# Thank you

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