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# Third line therapy in CLL: what are the best options?

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USA



# Non-Covalent BTKi Overcome BTK C481 Resistance

LOXO-305 is a non-covalent BTK inhibitor that is potent against both WT and C481-mutant BTK

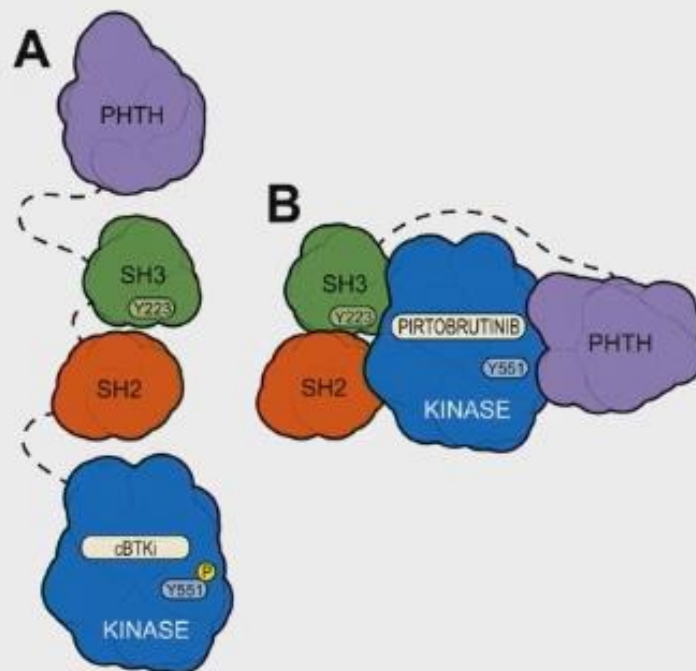
LOXO-305

BTK inhibition, regardless of BTK mutation

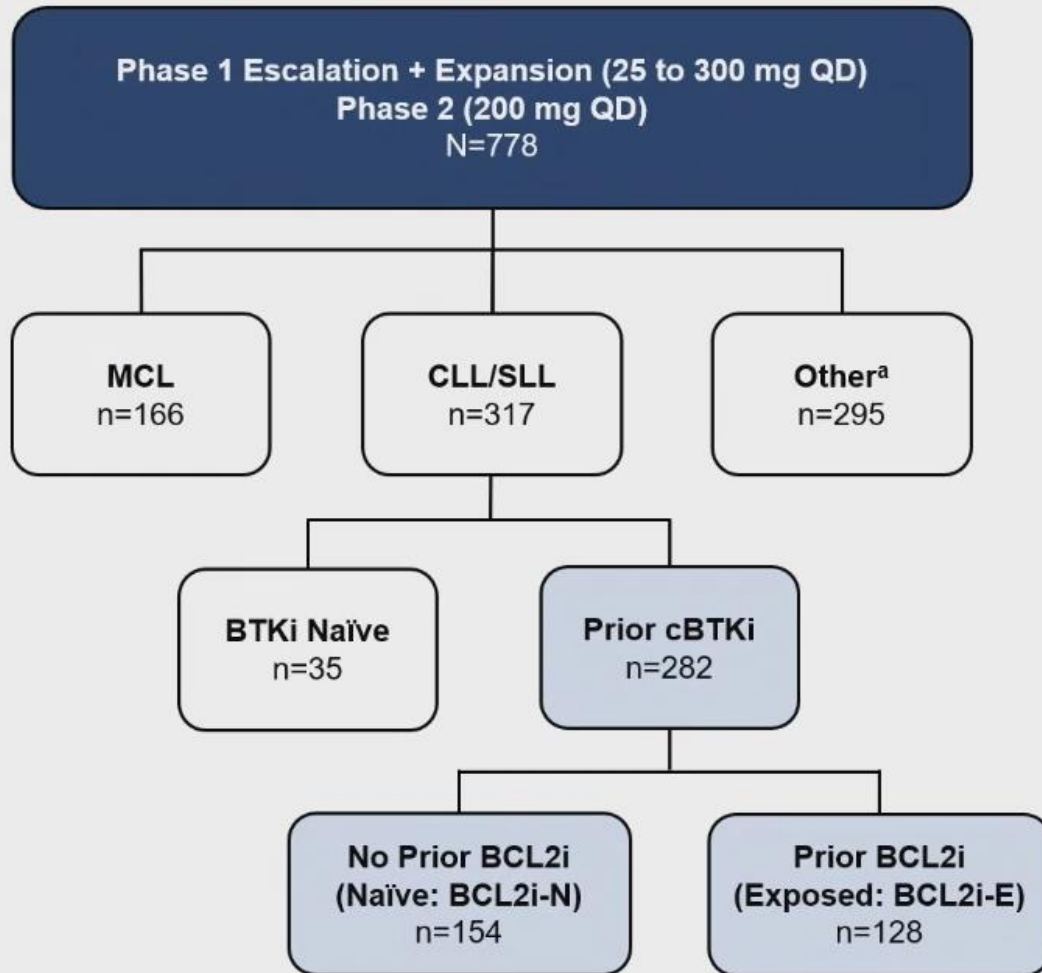
C481

Does not require C481 to bind to the kinase domain

Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation<sup>7</sup>



# BRUIN: Phase 1/2 Study Design



## Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

## Eligibility

- Age ≥18
- ECOG PS 0-2
- Active disease and in need of treatment
- Previously treated

## Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to iwCLL 2018 criteria, DoR, PFS, and OS)

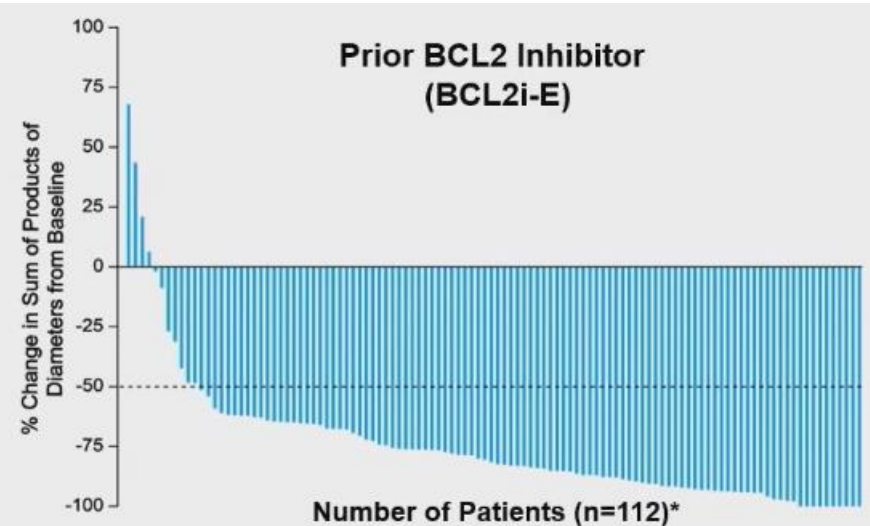
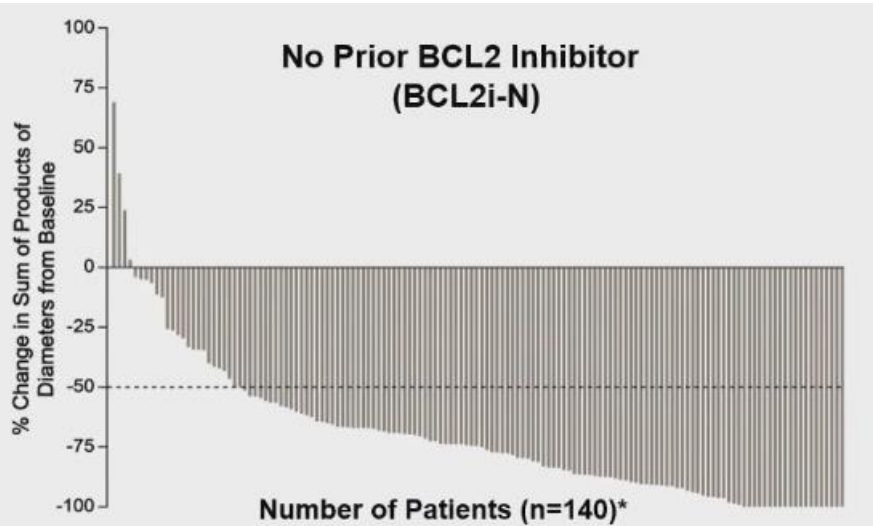
# Baseline Characteristics

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
<b>Rai staging, n (%)</b>			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
<b>Bulky Lymphadenopathy ≥5 cm, n (%)</b>	88 (31)	42 (27)	46 (36)
<b>ECOG PS, n (%)</b>			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
<b>Median number of prior lines of systemic therapy, (range)</b>	4 (1-11)	3 (1-9)	5 (1-11)
<b>Prior therapy, n (%)</b>			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
<b>Median time from diagnosis to first dose, years (IQR)</b>	11 (8-15)	11 (7-15)	12 (8-15)
<b>Reason for any prior BTKi discontinuation<sup>a</sup>, n (%)</b>			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics <sup>b</sup>	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
<b>Mutation status, n/n available (%)</b>			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
<b>High Risk Molecular Features, n/n available (%)</b>			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex Karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

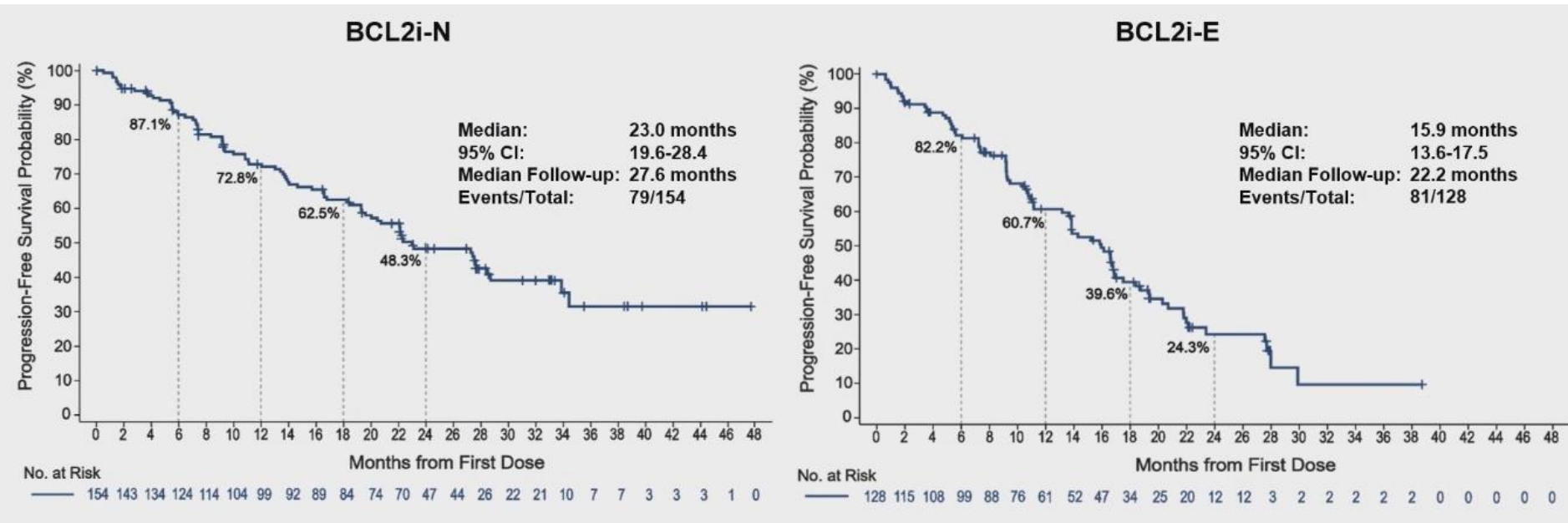
# Pirtobrutinib Effective after cBTKi w/wo Prior BCL2i



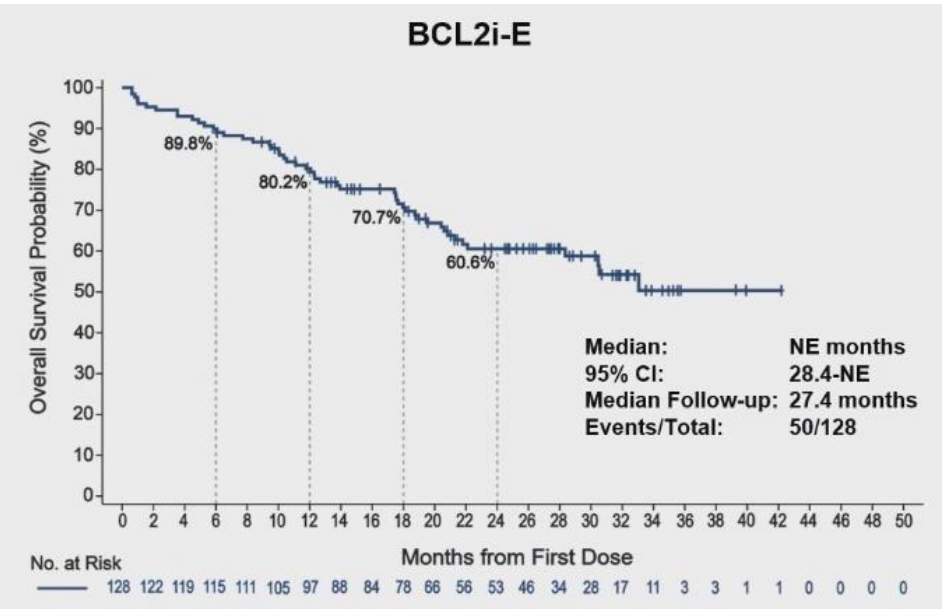
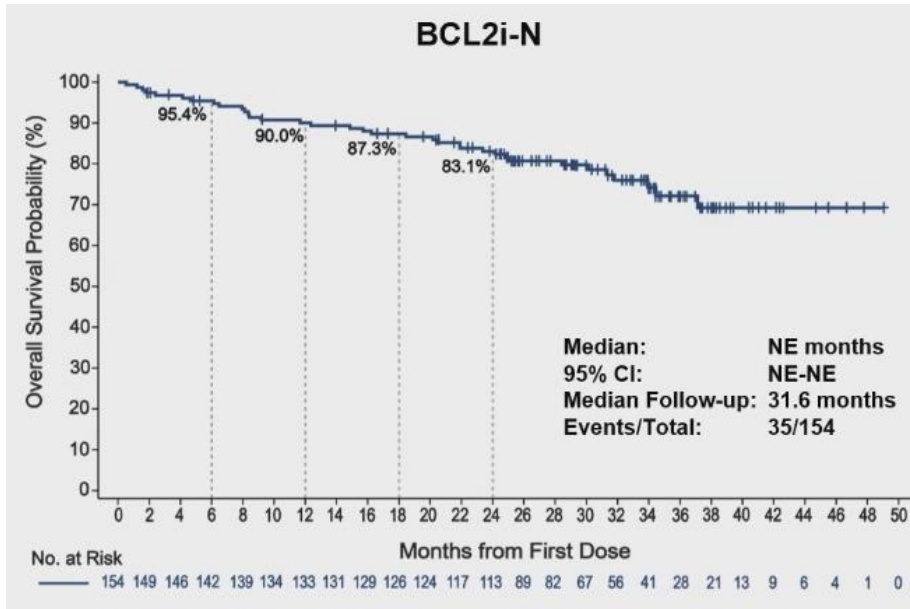
BCL2i-N	(n=154) <sup>b</sup>
ORR <sup>a</sup> incl. PR-L, % (95% CI)	83.1 (76.2-88.7)
<b>Best Response, n (%)</b>	
CR	5 (3.2)
nPR	2 (1.3)
PR	108 (70.1)
PR-L	13 (8.4)

BCL2i-E	(n=128) <sup>c</sup>
ORR <sup>a</sup> incl. PR-L, % (95% CI)	79.7 (71.7-86.3)
<b>Best Response, n (%)</b>	
CR	0 (0)
nPR	0 (0)
PR	88 (68.8)
PR-L	14 (10.9)

# PFS with Prior BTKi w/wo Prior BCL2i



# OS with Prior BTKi w/wo Prior BCL2i





# Conclusions

- With median follow-up of 30 months, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in heavily pretreated patients with CLL/SLL who received prior covalent BTK inhibitor
  - ORR including PR-L was ~80% regardless of prior BCL2 inhibitor exposure
  - Median PFS was 19.4 months overall, with 23.0 months for BCL2i-N patients and 15.9 months for BCL2i-E patients
- Pirtobrutinib was well-tolerated with low-rates of discontinuation due to drug-related toxicity among both BCL2i-N and BCL2i-E patients
- These results suggest that continuation of BTK pathway inhibition may be an important sequencing approach to consider in the treatment of CLL/SLL
- On December 1, 2023, the FDA granted accelerated approval to pirtobrutinib for adults with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor



Search

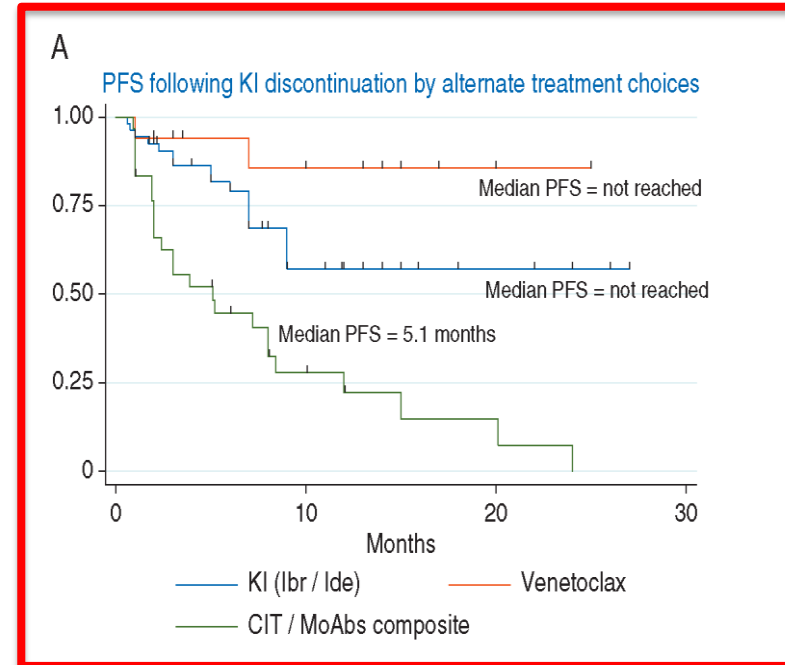
Menu

**FDA grants accelerated approval to  
pirtobrutinib for chronic lymphocytic  
leukemia and small lymphocytic lymphoma**

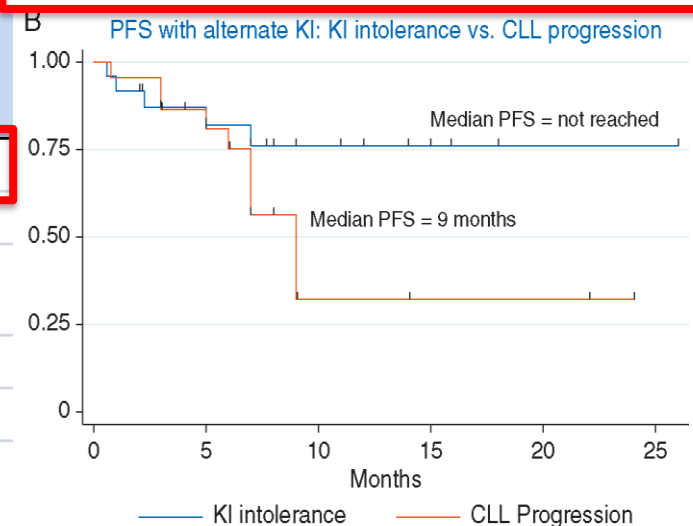
# Response to Subsequent Therapy Following Initial Kinase Inhibitor Therapy

Reasons for discontinuation first KI

	Ibrutinib (n = 258 discontinuation events)	Idelalisib (n = 58 discontinuation events)
Toxicity	51.2% (n = 132)	44.8% (n = 26)
Progression	20.5% (n = 53)	27.6% (n = 16)
Other/death not secondary to progression	11% (n = 28)	6.9% (n = 4)
MD/patient preference	6.2% (n = 16)	17.2% (n = 10)
Richter's transformation	5.0% (n = 13)	3.5% (n = 2)
Stem cell transplant/CAR T cells	3.9% (n = 10)	0%



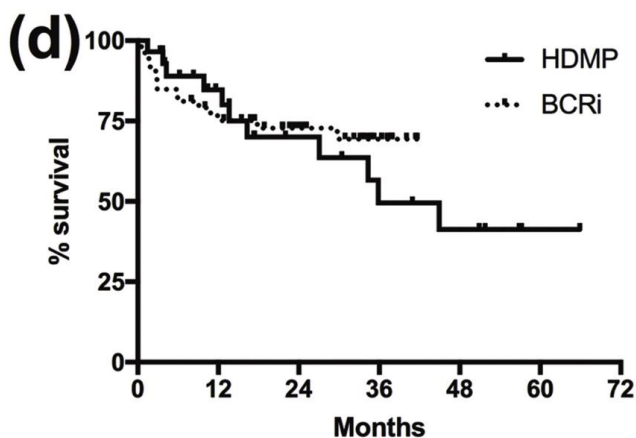
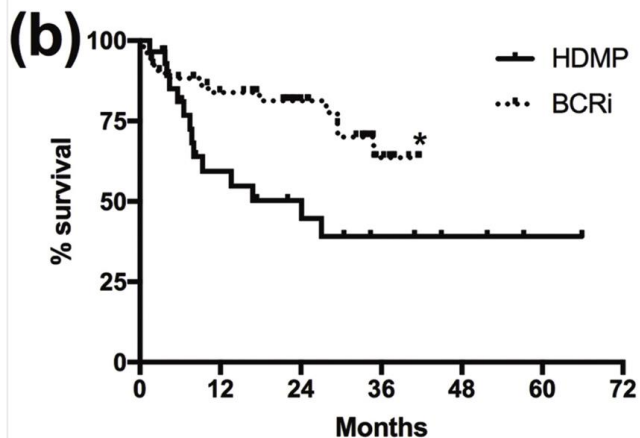
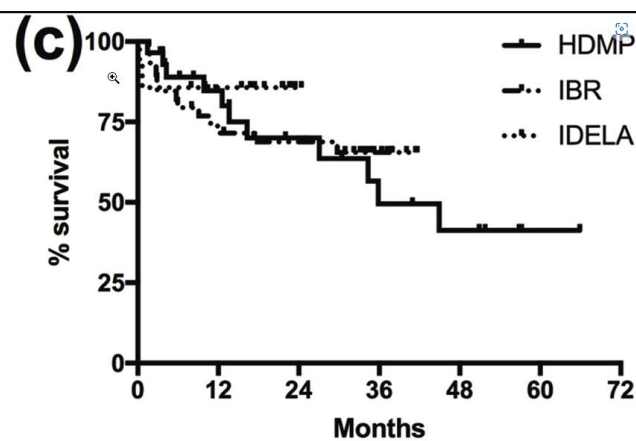
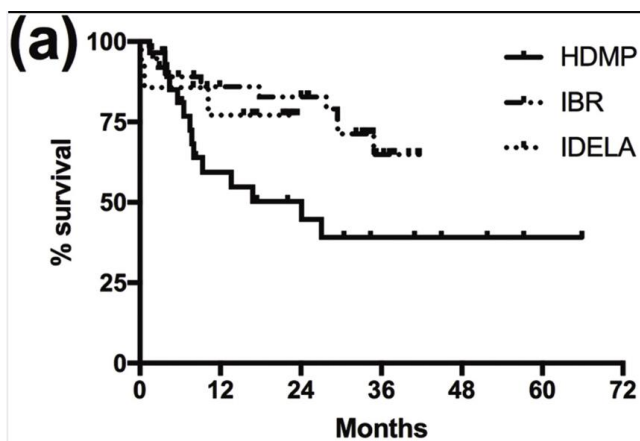
	Ibrutinib → Idelalisib	Idelalisib → Ibrutinib	Kinase inhibitor → venetoclax
ORR (%)	46	75	74
CR (%)	0	5	32
PR/PR with lymphocytosis (%)	46	70	42
Stable disease (%)	39	15	16
Progressive disease (%)	15	10	10



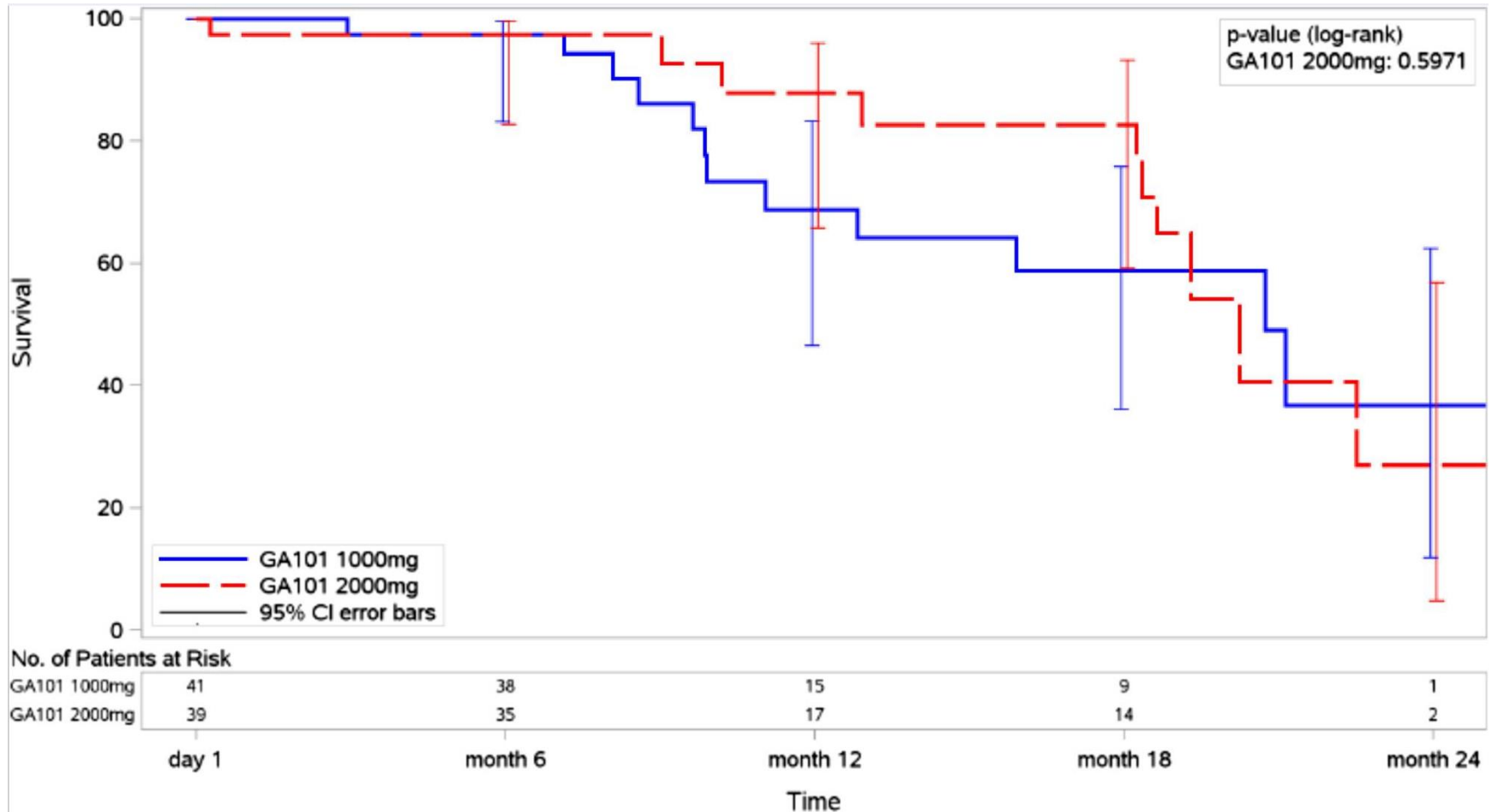
# High-dose steroids (+/- CD20) vs. novel agents

PFS

OS

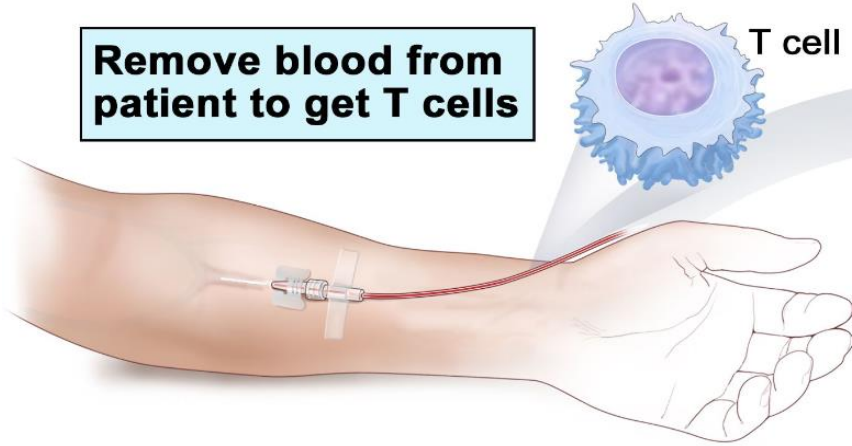


# CD20 monotherapy in CLL: obinituzumab



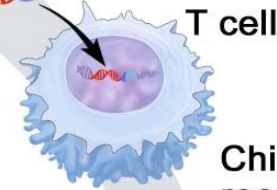
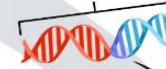
# CAR T-cell Therapy

**Remove blood from patient to get T cells**



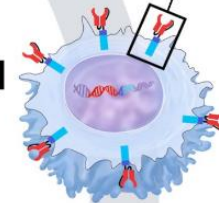
**Make CAR T cells in the lab**

Insert gene for CAR

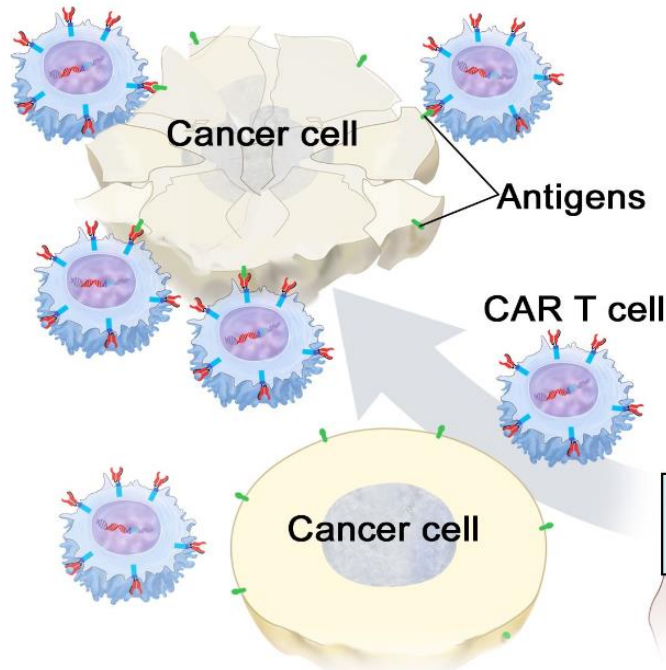


Chimeric antigen receptor (CAR)

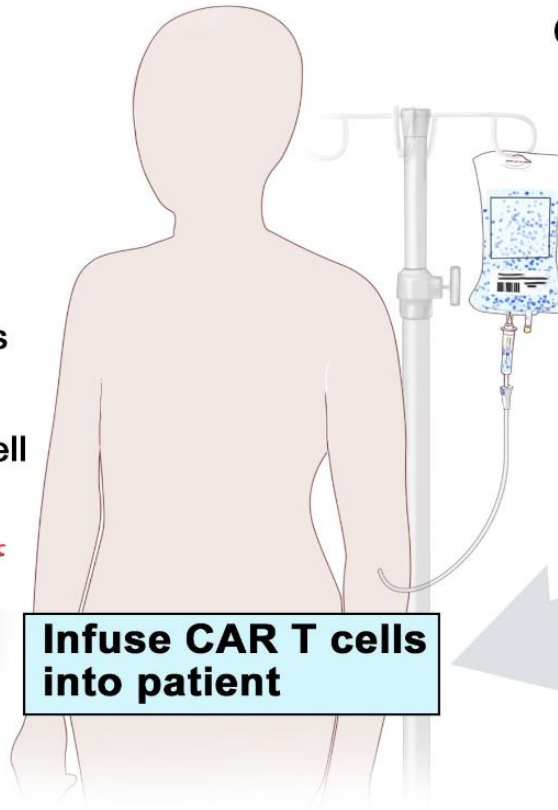
**CAR T cell**



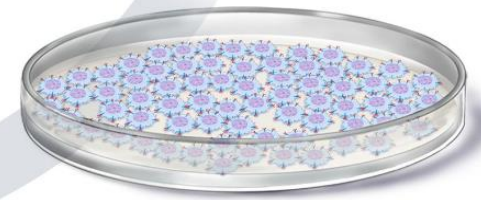
**CAR T cells bind to cancer cells and kill them**



**Infuse CAR T cells into patient**



**Grow millions of CAR T cells**



# CAR T cell therapy in RR CLL

## TRANSCEND CLL 004 Lisocabtagene Maraleucel (liso-cel)

### DOR by best response

### PFS by best response

A

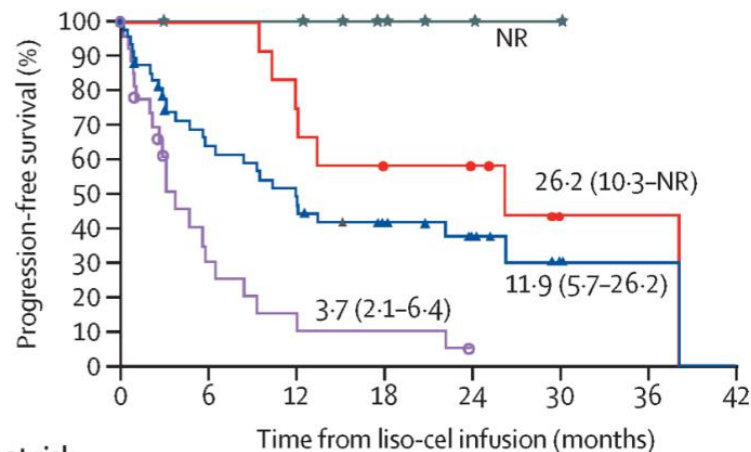
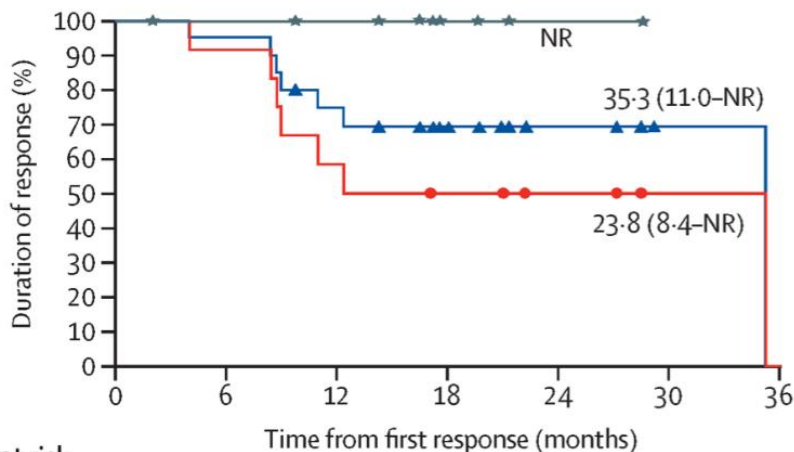
B

★ CR or CRi   ● PR or nPR   ▲ Responder

★ CR or CRi   ● PR or nPR  
○ Non-responder   ▲ Total

Median follow-up 19.7 months (95% CI 16.5-27.2)

Median follow-up 20.8 months (95% CI 17.6-25.2)



Number at risk

	0	6	12	18	24	30	36
CR or CRi	9	8	7	3	1	0	0
PR or nPR	12	11	7	5	3	1	0
Responder	21	19	14	8	4	1	0

Number at risk

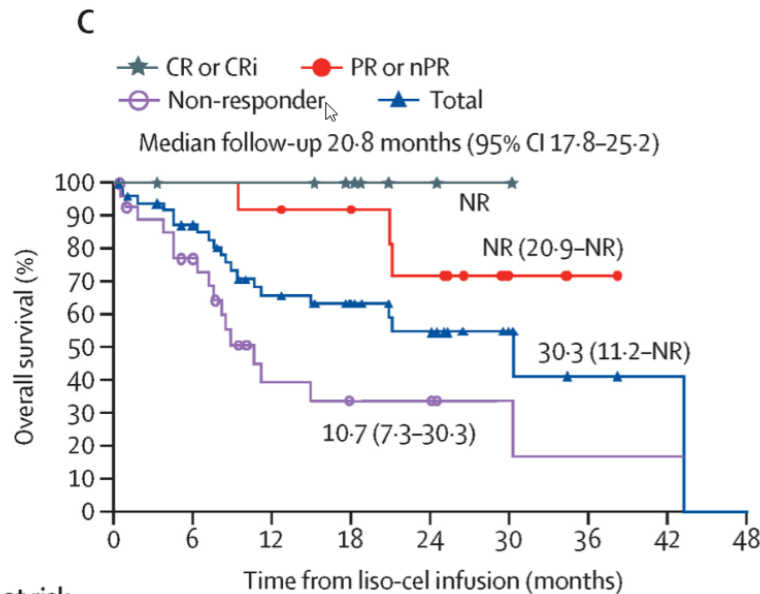
	0	6	12	18	24	30	36	42
CR or CRi	9	8	8	5	2	1	0	0
PR or nPR	12	12	9	6	5	1	1	0
Non-responder	28	6	2	2	0	0	0	0
Total	49	26	19	13	7	2	1	0

# CAR T cell therapy in RR CLL

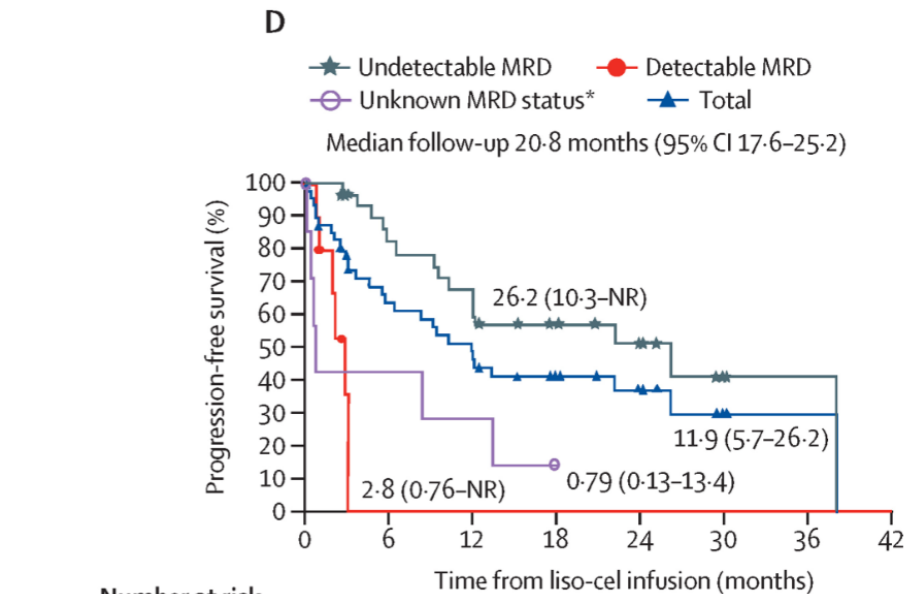
## TRANSCEND CLL 004 Lisocabtagene Maraleucel (liso-cel)

### OS by best response

### PFS by MRD



Number at risk	0	6	12	18	24	30	36	42	48
CR or CRi	9	8	8	6	2	1	0	0	0
PR or nPR	12	12	11	9	7	2	1	0	0
Non-responder	28	18	7	4	4	2	1	1	0
Total	49	38	26	19	13	5	2	1	0



Number at risk	0	6	12	18	24	30	36	42
Undetectable MRD	31	23	17	13	7	2	1	0
Detectable MRD	10	0	0	0	0	0	0	0
Unknown MRD status*	8	3	2	0	0	0	0	0
Total	49	26	19	13	7	2	1	0

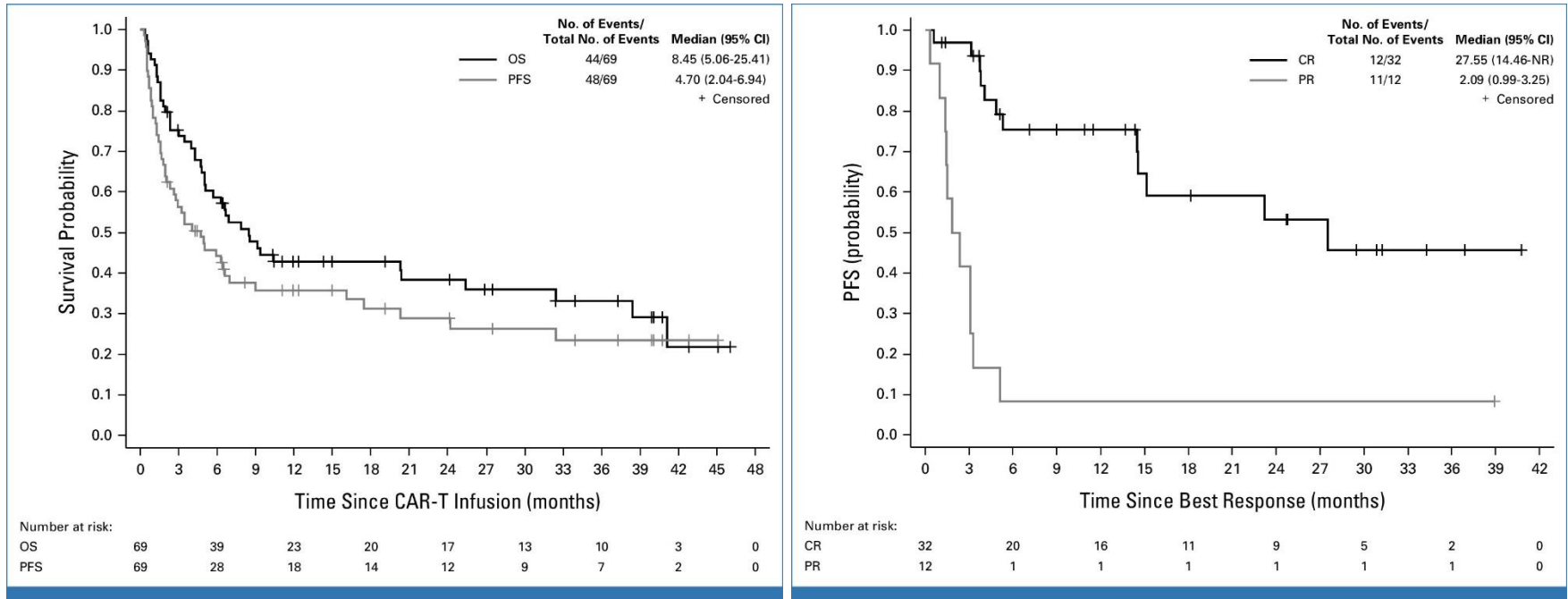
# Lisocabtagene Maraleucel (liso-cel) Toxicity

- **Cytokine release syndrome (CRS)** 85% (grade 3, 9%; no grade 4/5)
- **Neurological events (NE)** 45% (grade 3, 18%; grade 4, 1%; no grade 5)
- **69% received tocilizumab and/or corticosteroids for CRS/NEs**

Patients with cytokine release syndrome	
Any grade	99 (85%)
Grade 1	43 (37%)
Grade 2	46 (39%)
Grade 3	10 (9%)
Grade 4	0
Grade 5	0
Time to cytokine release syndrome onset, days*	4 (1-7)
Time to cytokine release syndrome resolution, days*	6 (4-11)
Patients with neurological events†	
Any grade	53 (45%)
Grade 1	13 (11%)
Grade 2	18 (15%)
Grade 3	21 (18%)
Grade 4	1 (1%)
Grade 5	0
Time to neurological event onset, days*	7 (4-11)
Time to neurological event resolution, days*	7 (4-16)
Tocilizumab and corticosteroid use for cytokine release syndrome	
Doses of tocilizumab (n=76)	1 (1-2)
Tocilizumab only	41 (35%)
Corticosteroids only	2 (2%)
Both tocilizumab and corticosteroids	35 (30%)
Tocilizumab or corticosteroids or both	78 (67%)
Tocilizumab and corticosteroid use for neurological event	
Doses of tocilizumab (n=8)	1 (1-1)
Tocilizumab only	0
Corticosteroids only	31 (26%)
Both tocilizumab and corticosteroids	8 (7%)
Tocilizumab or corticosteroids or both	39 (33%)
Other adverse events of special interest	
Prolonged cytopenia‡	63 (54%)
Grade ≥3 infections§	20 (17%)
Hypogammaglobulinaemia¶	18 (15%)
Tumour lysis syndrome	13 (11%)
Second primary malignancy	11 (9%)
Macrophage activation syndrome**	4 (3%)



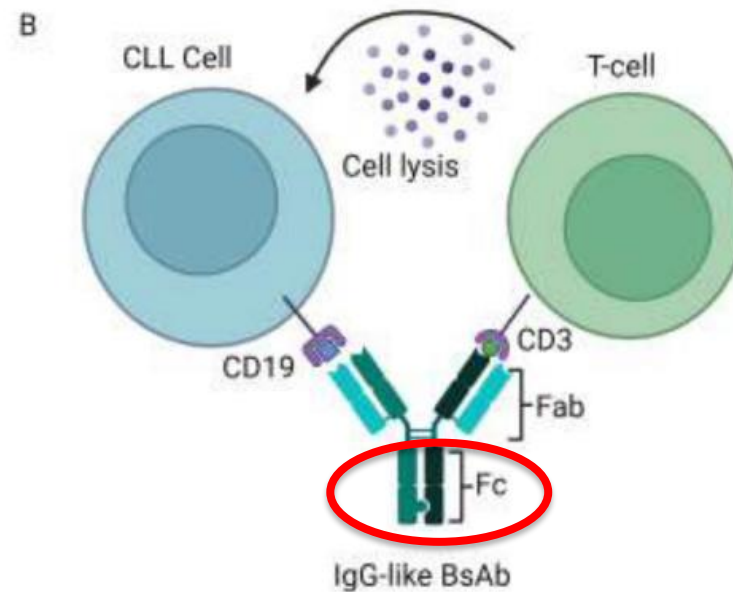
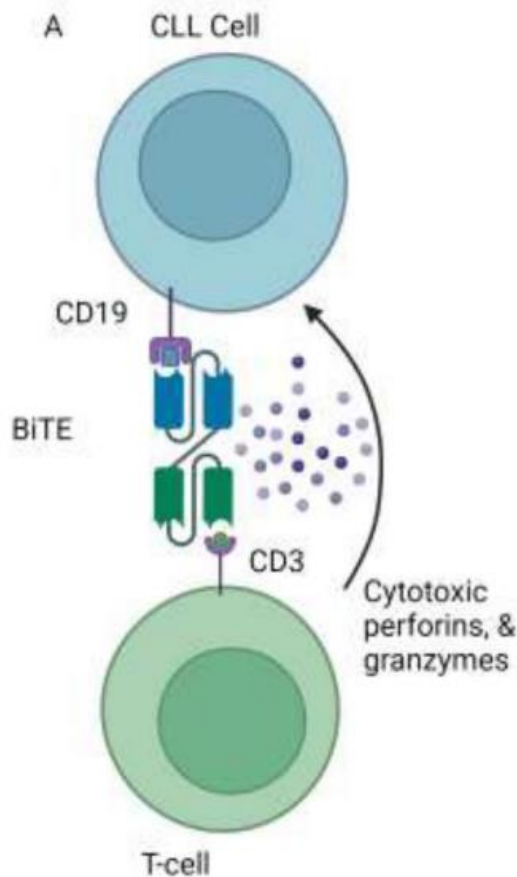
# OS and PFS in CLL Richter transformation with CAR T cell therapy (n=69)



- Median PFS was 4.7 months
- Median OS was 8.5 months
- 1-year and 2-year PFS rates were 35.7% and 28.9%
- 1-year and 2-year OS rates were 42.9% and 38.3%

## BsAbs lacking an Fc portion (ie. BiTEs, i.e. blinatumomab)

## IgG-like bsAbs (i.e. epcoritamab)



**Fc domain offers increased stability, allowing for intermittent administration**

**BsAbs without an Fc domain exhibit rapid clearance and necessitate continuous infusion**

# Current bispecific CLL clinical trials

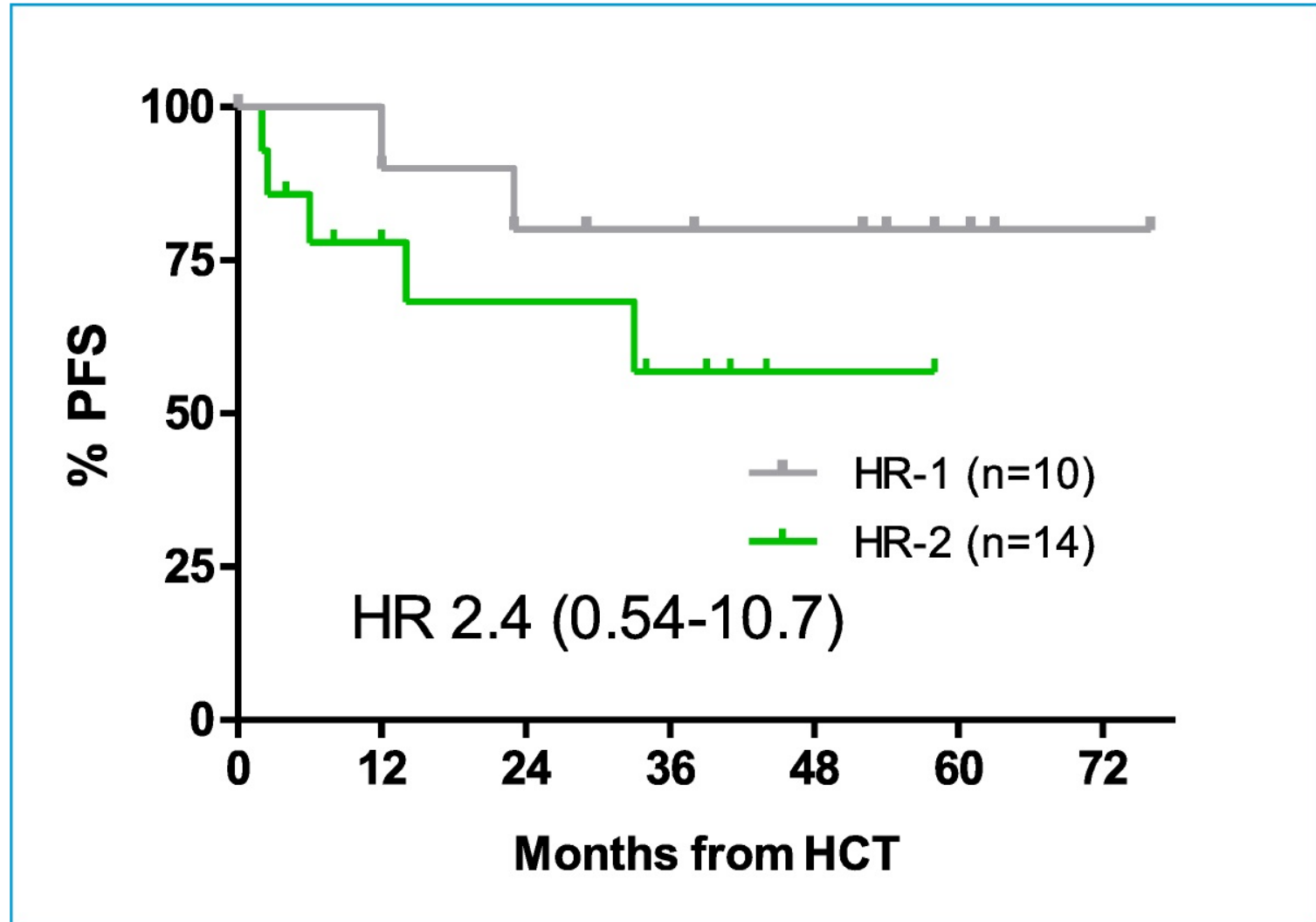
Phase (Study name)	Country (State if in USA)	Bispecific product/ Target	Population	Comment	Clinicaltrials.gov ID#
1/2	Australia, Belgium Denmark, France, Germany, Netherlands, Spain, USA (many)	Epcoritamab CD20/CD3	Age ≥18 r/r CD20+ CLL at least 2 prior lines, or RT	Monotherapy, or in combination with venetoclax, lenalidomide, or R-CHOP.	NCT04623541
1/2	Australia	GB261 CD20/CD3	Age ≥18 CD20+ r/r B-NHL or CLL/SLL		NCT03960840
1	UK	NVG-111 ROR1/CD3	Age ≥18 R/r ROR1+ malignancies, CLL/SLL, MCL, FL, DLBCL (excludes RT)		NCT04763083
1	USA (AK, NJ, TN, TX)	TG-1801 CD47/CD19	Age ≥18 R/r B-NHL including RT, CLL		NCT04806035
2	USA (CA)	Mosunetuzumab CD20/CD3	Age ≥18 R/r high -grade B-cell lymphomas including RT	In combination with Loncastuximab Tesrine Not for CLL/SLL without transformation	NCT05672251

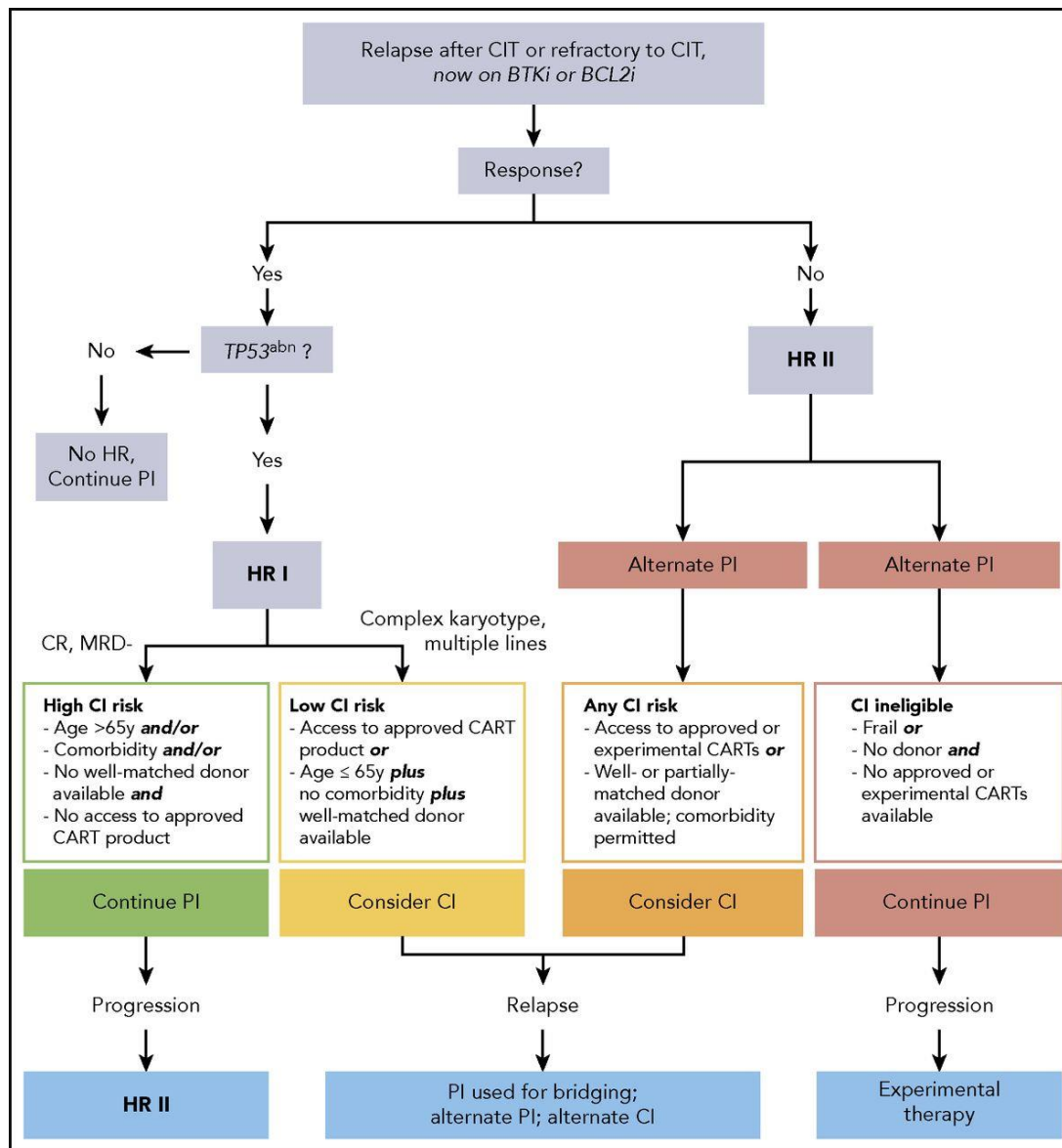
Abbreviations: B-ALL = B-cell acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; Co-exp = co-expression; IL = interleukin; IL-2BR = Interleukin-2 $\beta$  receptor; MCL = mantle cell lymphoma; MM = multiple myeloma; NHL = Non-Hodgkin's lymphoma; r/r = relapsed/refractory; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone chemoimmunotherapy regimen; RT = Richter's transformation; SLL = small lymphocytic lymphoma; UK = United Kingdom; USA = United States of America (States indicated by their 2-letter postal abbreviations).

# CLL risk stratification for HSC in the era of novel agents

Refractoriness to	TP53 abnormality present (del17p/TP53 <sup>mut</sup> )	High risk Category
CIT only	yes	<b>I – CIT-resistant</b> (BTKi- and BCL2i-sensitive)
CIT + BTKi <b>or</b> CIT + BCL2i <b>or</b> BTKi + BCL2i (+/- CIT)	yes or no	<b>II – CIT- and PI-resistant</b> (BTKi- and/or BCL2i-refractory)

# Outcome of HCT based on risk category

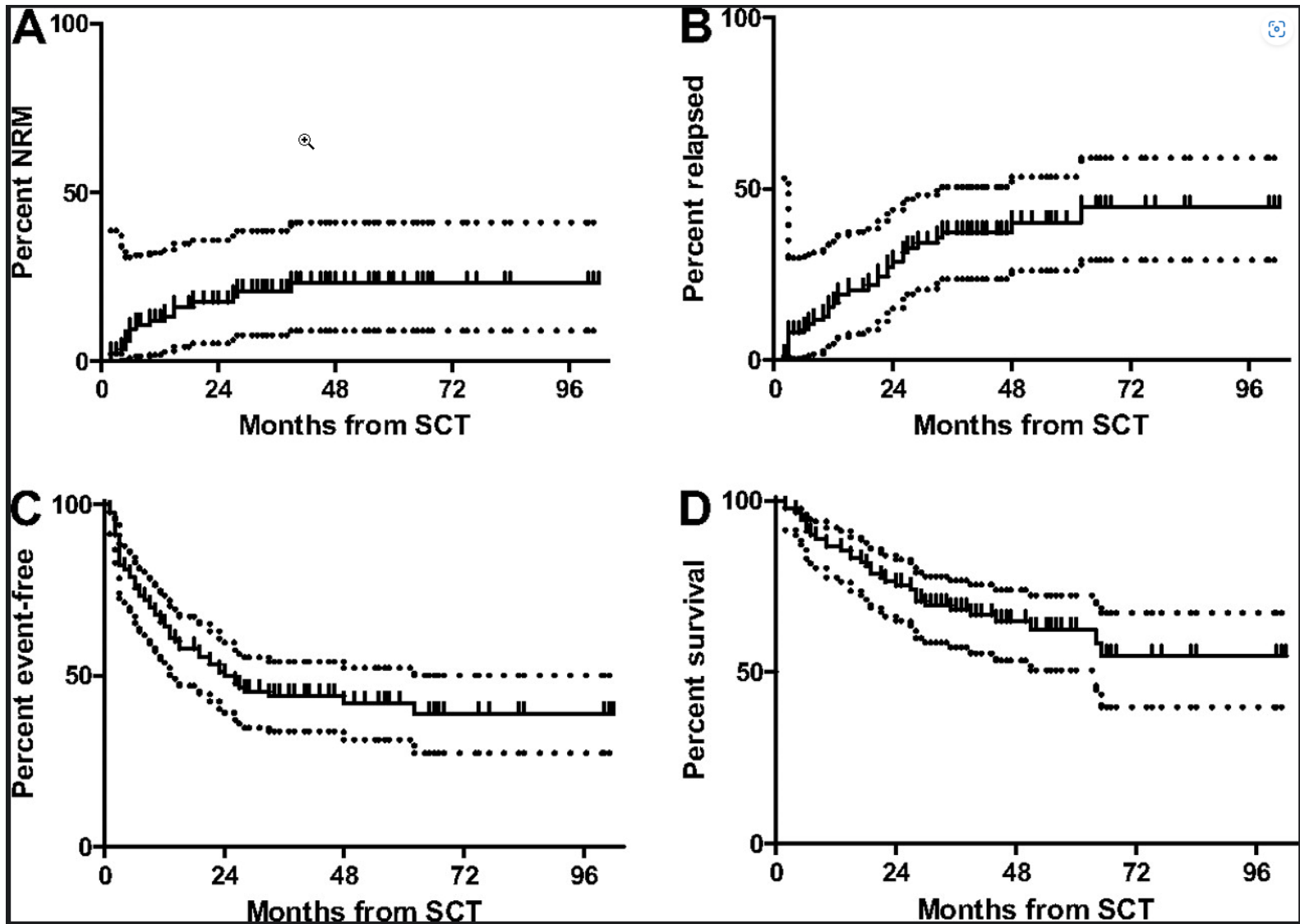




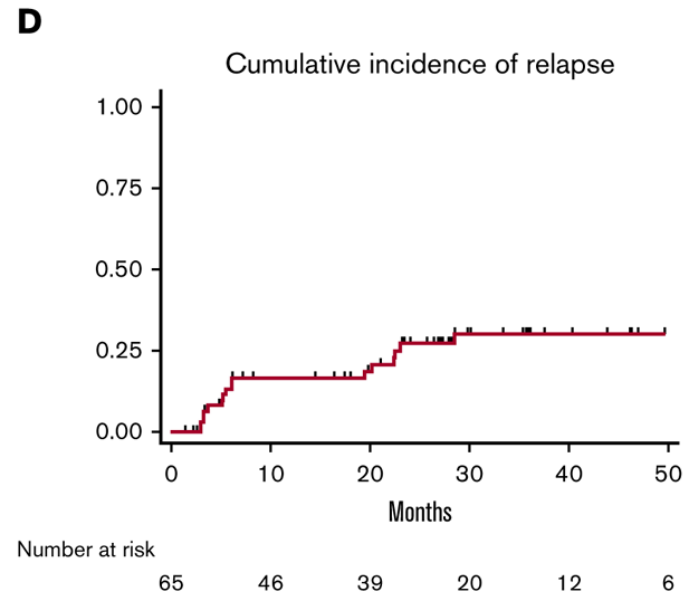
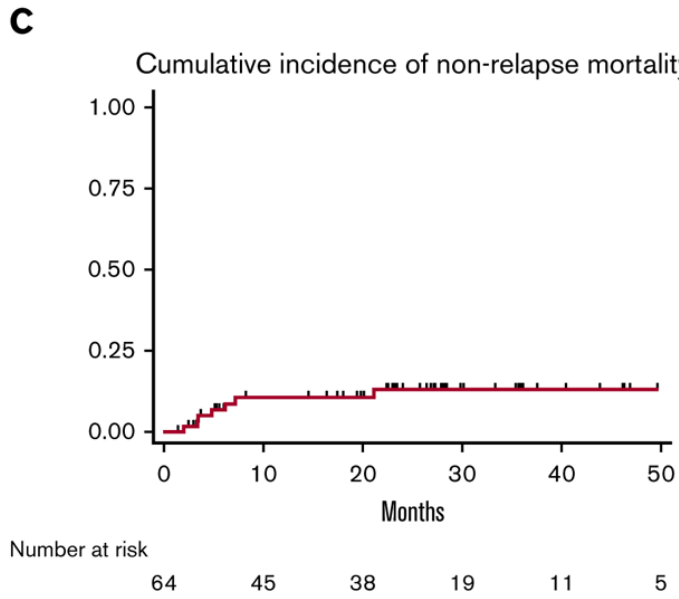
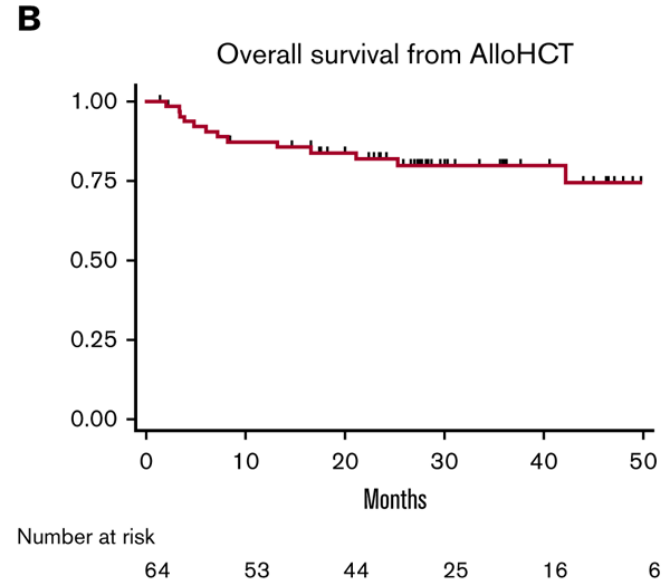
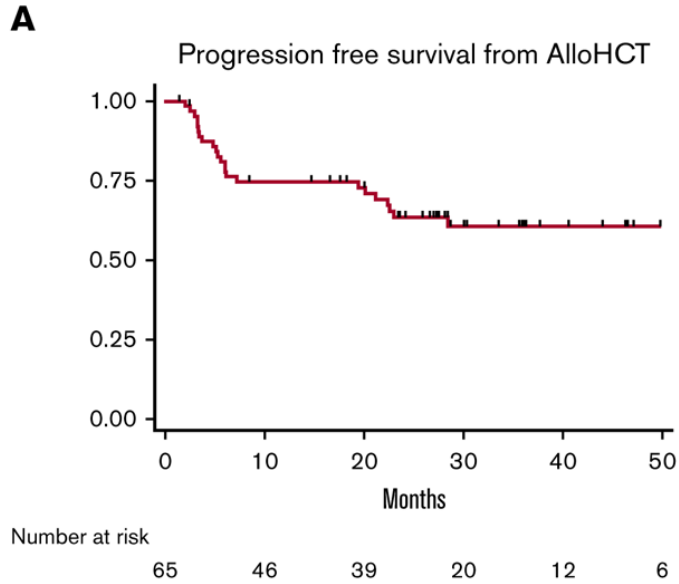
### Abbreviations:

- HR I/II: high risk category
- PI: pathway inhibitor
- CI: Cellular immunotherapy

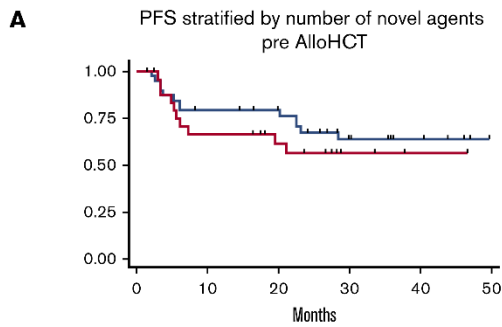
# Outcome of 90 allografted patients after SCT



# AlloHSC in CLL



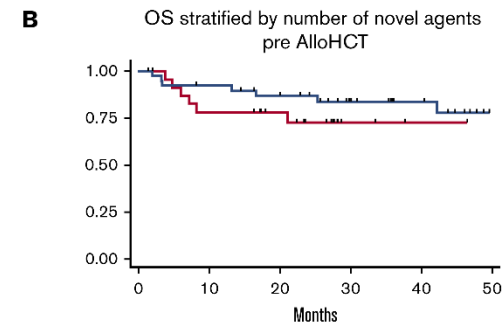




Number at risk

1 novel agent	40	30	27	17	11	6
2+ novel agents	25	16	12	3	1	0

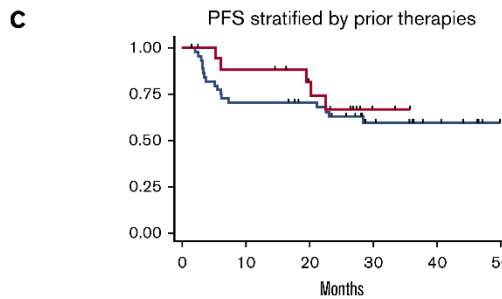
— 1 novel agent — 2+ novel agents



Number at risk

1 novel agent	40	35	30	22	15	6
2+ novel agents	24	18	14	3	1	0

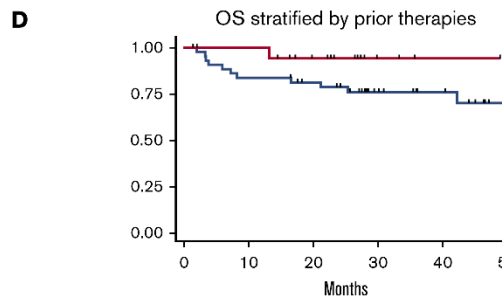
— 1 novel agent — 2+ novel agents



Number at risk

chemo / novel agent hx	45	31	28	17	11	5
novel agent only hx	18	15	11	3	1	1

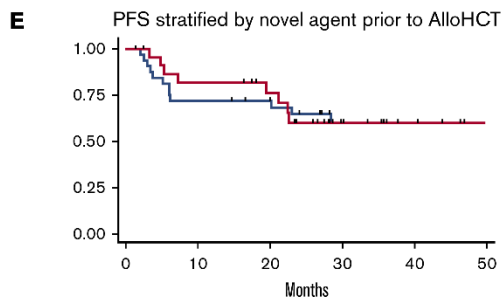
— prior chemo / novel agents — novel agents only



Number at risk

chemo / novel agent hx	44	36	32	21	14	5
novel agent only hx	18	17	12	4	2	1

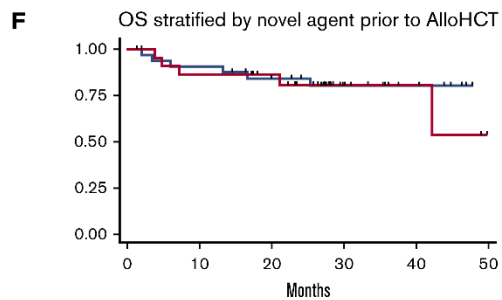
— prior chemo / novel agents — novel agent only



Number at risk

Ibrutinib	33	23	20	12	8	4
Venetoclax	23	18	14	3	1	0

— Ibrutinib — Venetoclax



Number at risk

Ibrutinib	33	29	24	15	10	4
Venetoclax	23	19	15	5	3	0

— Ibrutinib — Venetoclax

- Number of novel agents prior to alloHCT do not impact survival
- HSC comorbidity index predicts PFS
- PFS is not impacted by high-risk disease characteristics



**Thank you!**

**Jan Burger, MD PhD**

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