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Novel Agents in CLL

ASH 2021 Updates

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Abstracts to Be Reviewed

- **#391: Pirtobrutinib, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/SLL: Updated Results from the Phase 1/2 BRUIN Study**
- **#392: Preliminary Efficacy and Safety of MK-1026, a Non-Covalent Inhibitor of Wild-Type and C481S Mutated Bruton Tyrosine Kinase, in B-Cell Malignancies: A Phase 2 Dose Expansion Study**
- **#3730: A Phase 1 Study to Evaluate the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Lisaftoclax (APG-2575), a Novel BCL-2 Inhibitor (BCL-2i), in Patients (pts) with Certain Relapsed or Refractory (R/R) Hematologic Malignancies (HMs)**
- **#2627: Subcutaneous Epcoritamab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Preliminary Results from the Epcore CLL-1 Trial**

Introduction

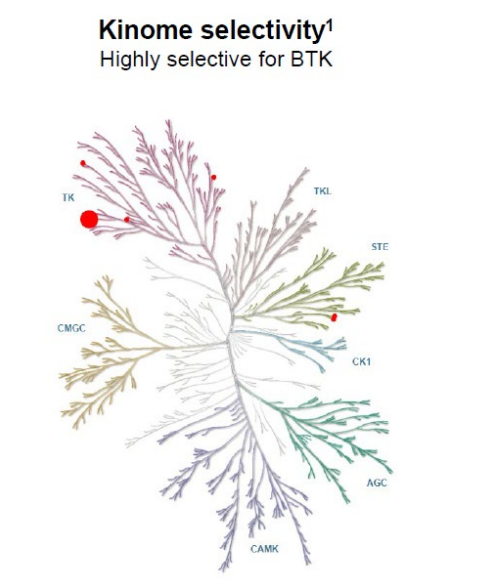
- Bruton tyrosine kinase inhibitors (BTKi, like ibrutinib, acalabrutinib, zanubrutinib) and BCL-2 Inhibitor venetoclax are all FDA-approved agents and are currently used in the routine management of CLL
- All have become standard approaches in both frontline and relapsed refractory settings in CLL among other B-cell histologies, thus no longer novel
- This presentation will focus on recent updates from ASH 2021, highlighting molecules and biologics with novel mechanisms of action, all of which are remain under clinical investigation.

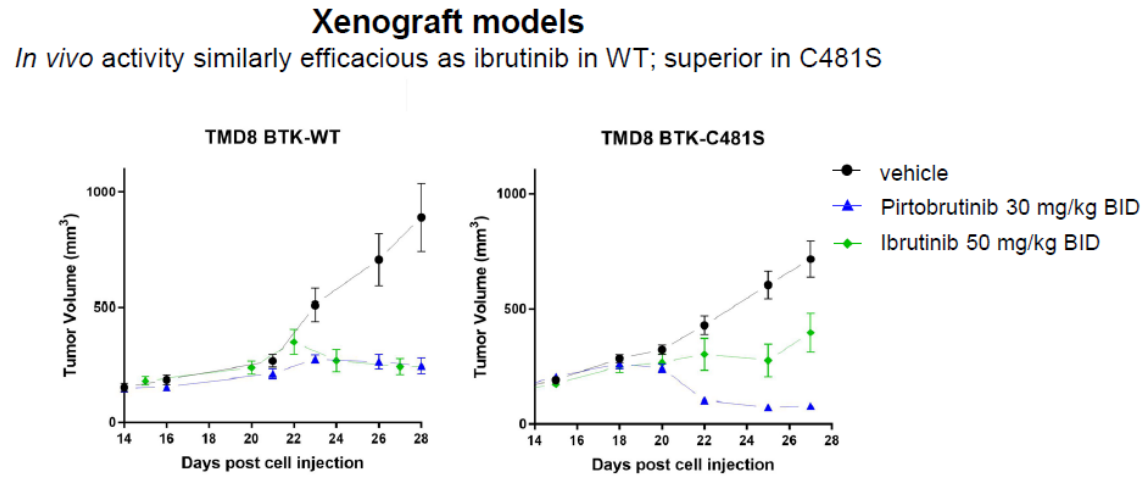
Abstract 391: Mato et al, ASH 2021

Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathan B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

Pirtobrutinib Is a Potent and Selective Reversible BTKi





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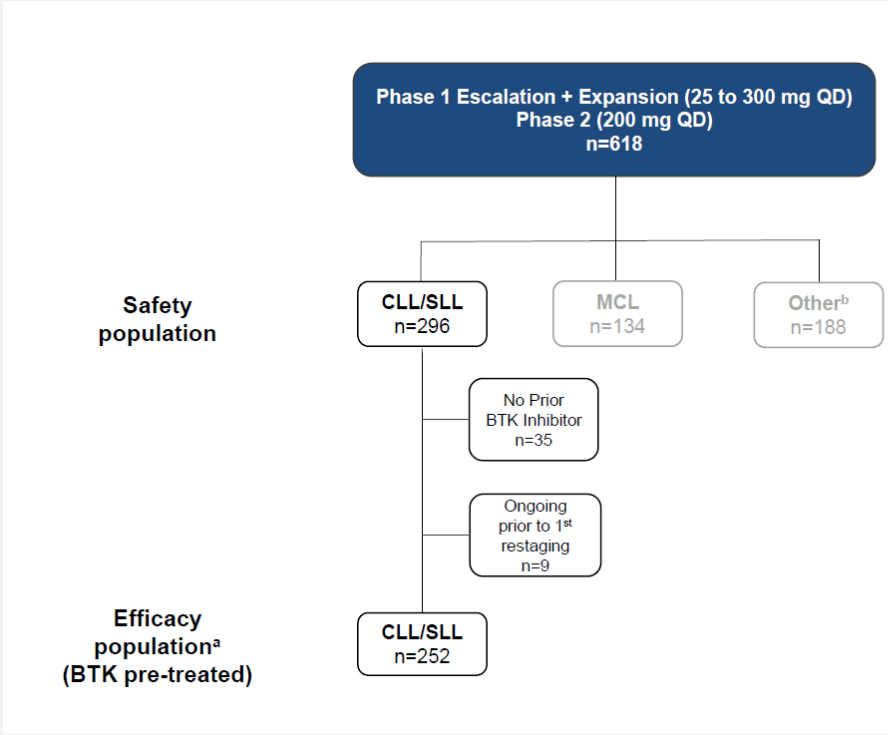
Bruin: Phase 1 / 2 Study Design



Phase 1 3+3 design

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

Eligibility

- Age ≥18
- ECOG 0-2
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

Key endpoints

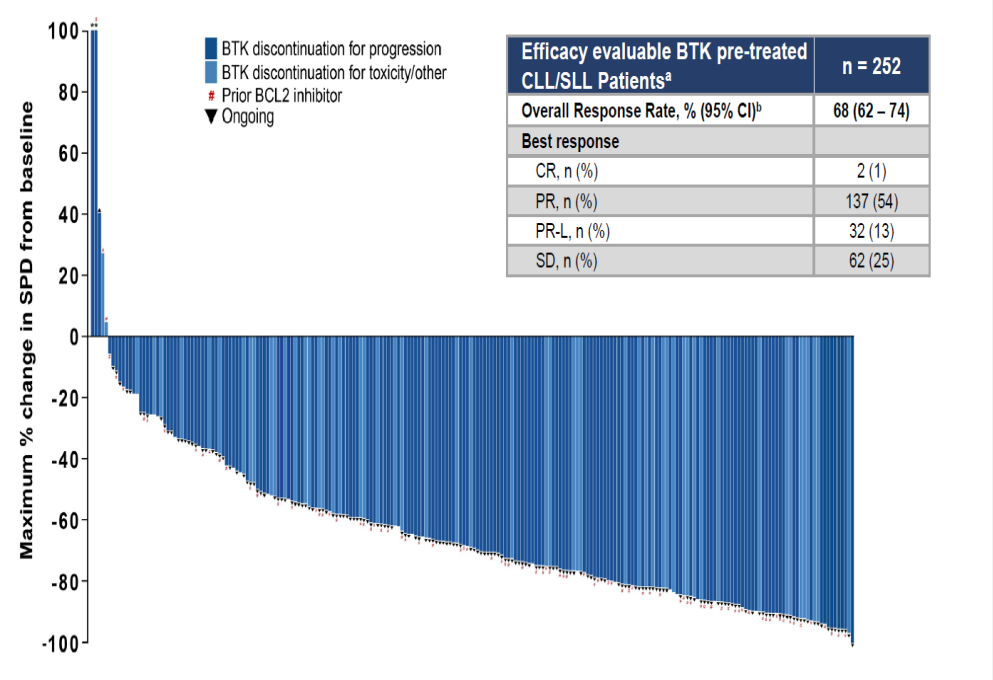
- Safety/tolerability
- Determine MTD & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DoR based on disease criteria (iwCLL, IWWM, Lugano)

Baseline Characteristics

Characteristics	N = 261
Median age, years (range)	69 (36-88)
Female, n (%)	84 (32)
Male, n (%)	177 (68)
ECOG PS[a], n (%)	
0	138 (53)
1	104 (40)
2	19 (7)
Median number of prior lines of systemic therapy (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	261 (100)
Anti-CD20 antibody	230 (88)
Chemotherapy	207 (79)
BCL2 inhibitor	108 (41)
PI3K inhibitor	51 (20)
CAR-T	15 (6)
Stem cell transplant	6 (2)
Allogeneic stem cell transplant	5 (2)
Autologous stem cell transplant	1 (<1)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)

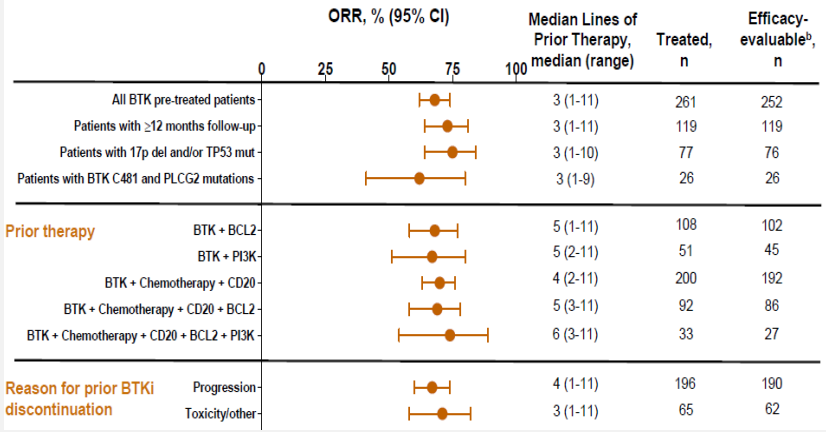
Baseline Molecular Characteristics[a]	
Mutation status, n (%)	
BTK C481-mutant	89 (43)
BTK C481-wildtype	118 (57)
PLCG2-mutant	33 (16)
High Risk Molecular Features, n (%)	
17p deletion	51 (28)
TP53 mutation	64 (37)
17p deletion or TP53 mutation	77 (36)
Both 17p deletion and TP53 mutation	38 (27)
IGHV unmutated	168 (84)
11q deletion	45 (25)

Pirtobrutinib Efficacy



Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Pirtobrutinib Efficacy Regardless of Other Prior Therapy[a]



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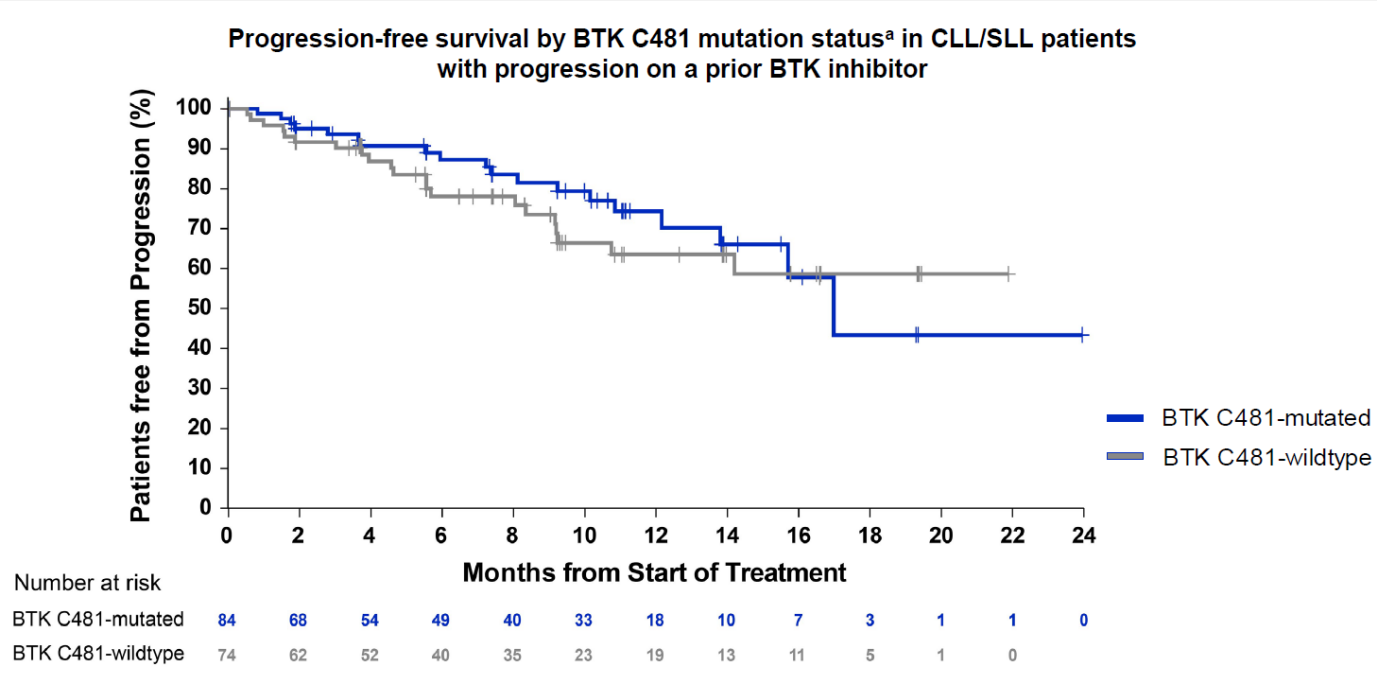
Outcome and BTK C481 Mutation Status



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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

Pirtobrutinib Future Development: CLL

- **BRUIN CLL-313: A Phase 3 Open-Label, Randomized Study of Pirtobrutinib Versus Bendamustine Plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**
- **BRUIN CLL-321: A Phase 3 Open-Label, Randomized Study of Pirtobrutinib Versus Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**
- **BRUIN CLL-322: A Phase 3 Open-Label, Randomized Study of Fixed Duration Pirtobrutinib Plus Venetoclax and Rituximab Versus Venetoclax and Rituximab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

Abstract 392: Woyach et al, ASH 2021

Preliminary Efficacy and Safety of MK-1026, a Non-Covalent Inhibitor of Wild-type and C481S Mutated Bruton Tyrosine Kinase, in B-cell Malignancies: Malignancies: A Phase 2 Dose Expansion Study

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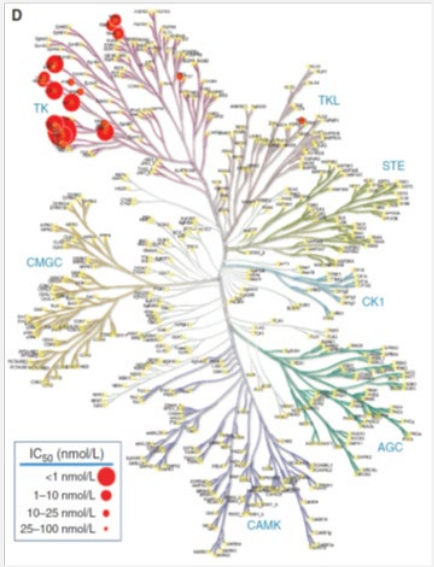
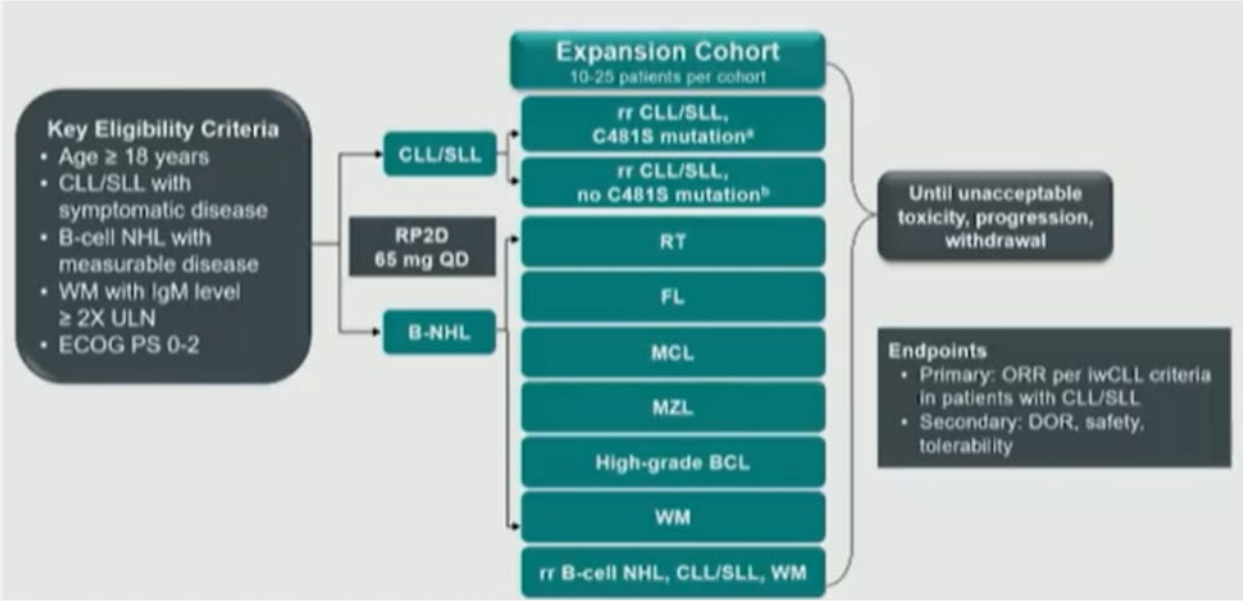
Nemtabrutinib (MK-1026/ARG-531): Selectivity and Study Design

MK-1026[2]
Kinome Selectivity





Reiff SD, et al. *Cancer Discovery.* 2018.

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Baseline Characteristics

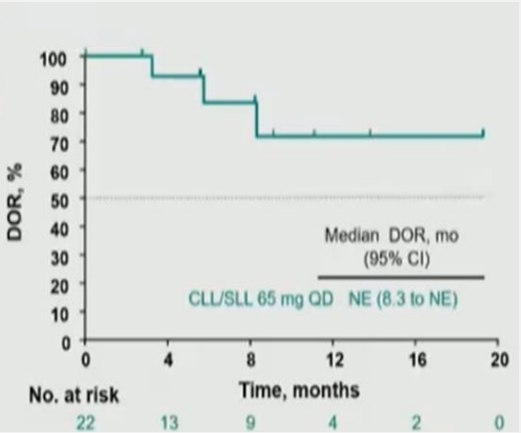
Characteristic, n (%)	CLL/SLL 65 mg QD N = 51
Prior lines, median (range)	4 (1-18)
Prior BTK inhibitor therapy	43 (84.3)
ECOG PS 0	14 (27.5)
1	32 (62.7)
2	5 (9.8)
IGHV Unmutated	30 (58.8)
Mutated	2 (3.9)
Unknown	19 (37.3)
Del (17p) Present	12 (23.5)
Absent	33 (64.7)
Missing	6 (11.8)
BTK C481S Present	32 (62.7)
Absent	12 (23.5)
Unknown/Missing	7 (13.7)

Nemtabrutinib: Efficacy

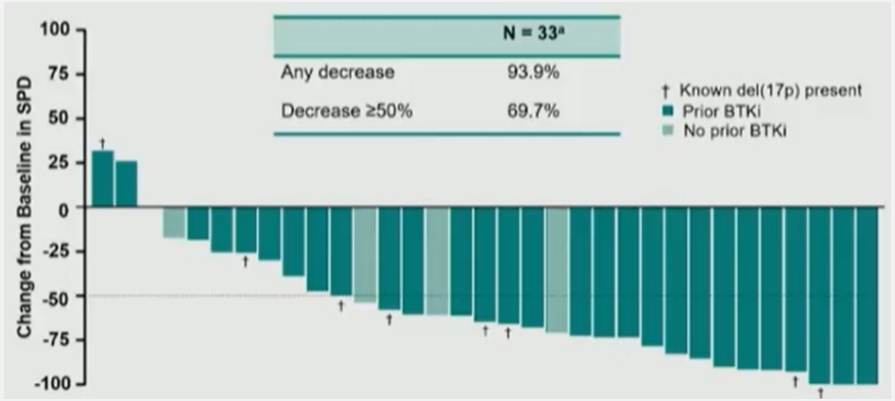
Response Rate

n (%) [95% CI]	CLL/SLL 65 mg QD N = 38[a]
ORR	22 (57.9%) [40.8-73.6]
CR	1 (2.6%) [0.0-13.8]
PR	12 (31.6%) [17.5-48.6]
PR-L	9 (23.7%) [11.4-40.2]
SD	15 (39.5%) [24.0-5.6]

Duration of Response



Change in Baseline SPD



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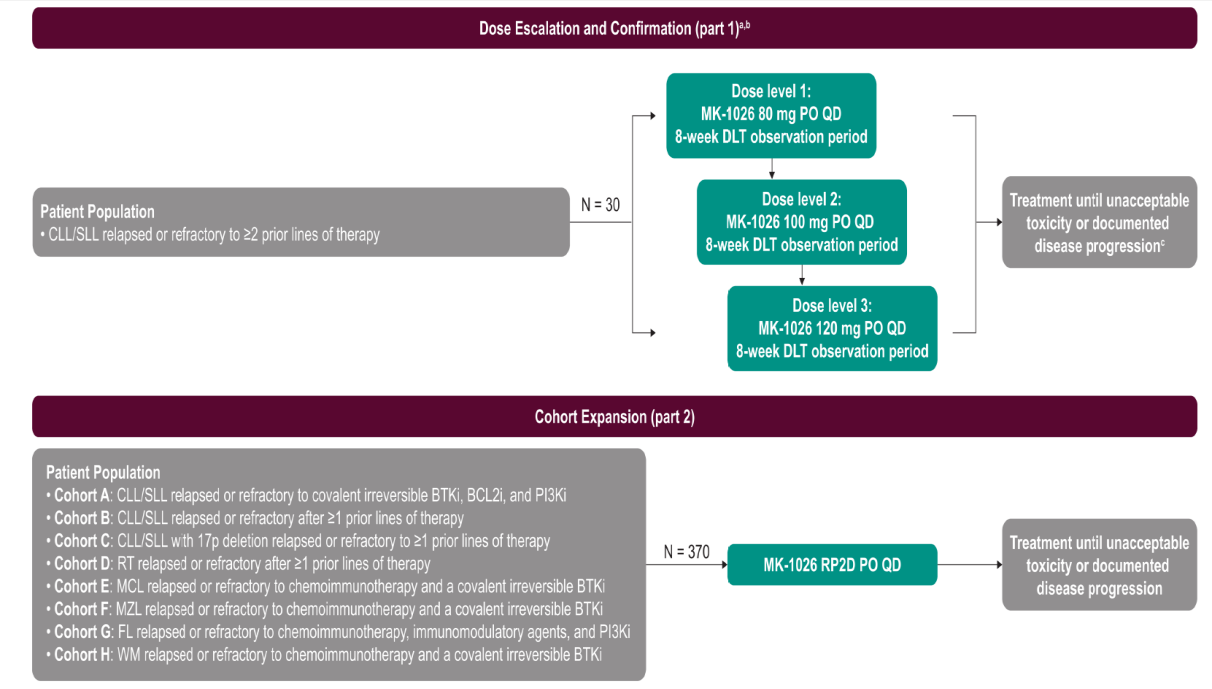
Nemtabrutinib: Safety

Events, n (%)		All Patients N = 118
All TEAEs		114 (96.6)
Grade ≥3 TEAEs[a]		80 (68.0)
MK-1026-related TEAE		78 (66.1)
Grade ≥3 related TEAEs[b]		31 (26.3)
Related TEAEs leading to discontinuation		9 (7.6)
TEAEs ≥20%	**All**	**Grade ≥3**
Fatigue	33.1%	3.4%
Constipation	31.4%	0.8%
Dysgeusia	28.0%	0
Cough	24.6%	0
Nausea	24.6%	0.8%
Pyrexia	24.6%	0
Dizziness	22.9%	0
Hypertension	22.9%	9.3%
Peripheral edema	22.0%	0
Diarrhea	21.2%	0.8%
Arthralgia	20.3%	0

Nemtabrutinib: Future Development



Chaudhry A, et al. ASH 2021. Abstract 3737.

Abstract 3730: Sun et al, ASH 2021

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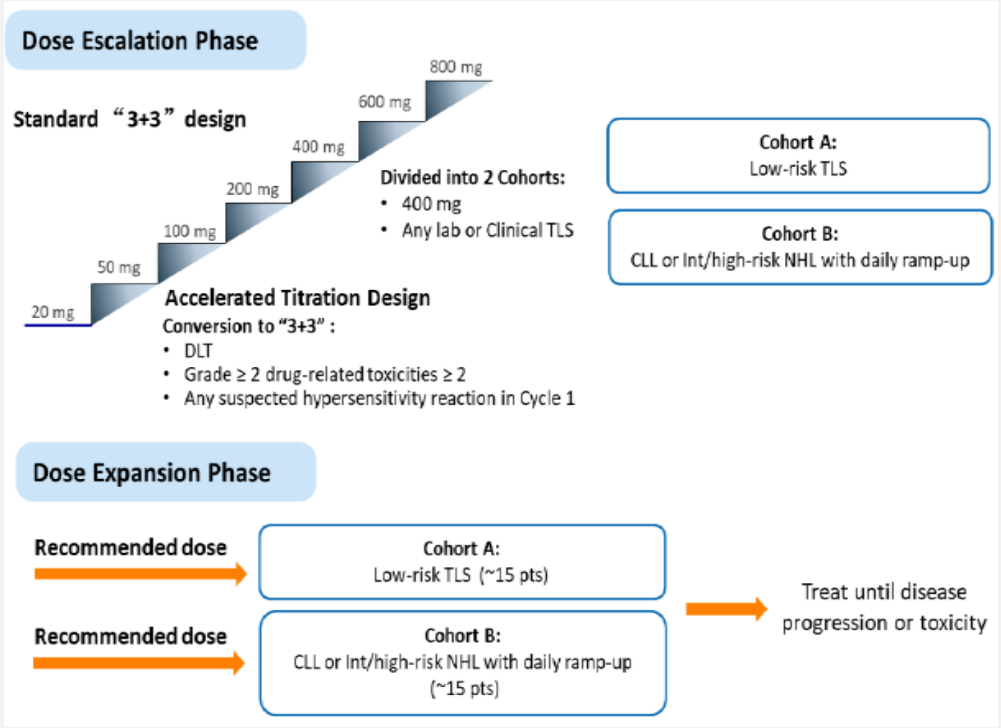
Lisaftoclax: FIH Chinese Multicenter Study Design



Ailawadhi et al, ASCO 2021
presented FIH global study
35 patients enrolled 12 with CLL
Daily ramp-up
MTD not met and no TLS up to 1200 mg
ORR in 14 CLL pts 85% all PRs

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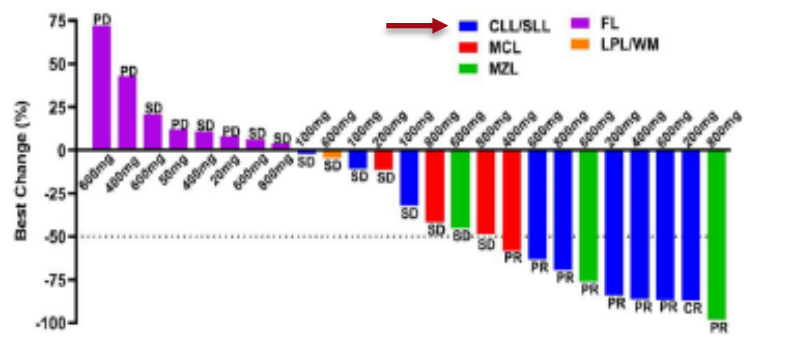
Lisaftoclax: Efficacy

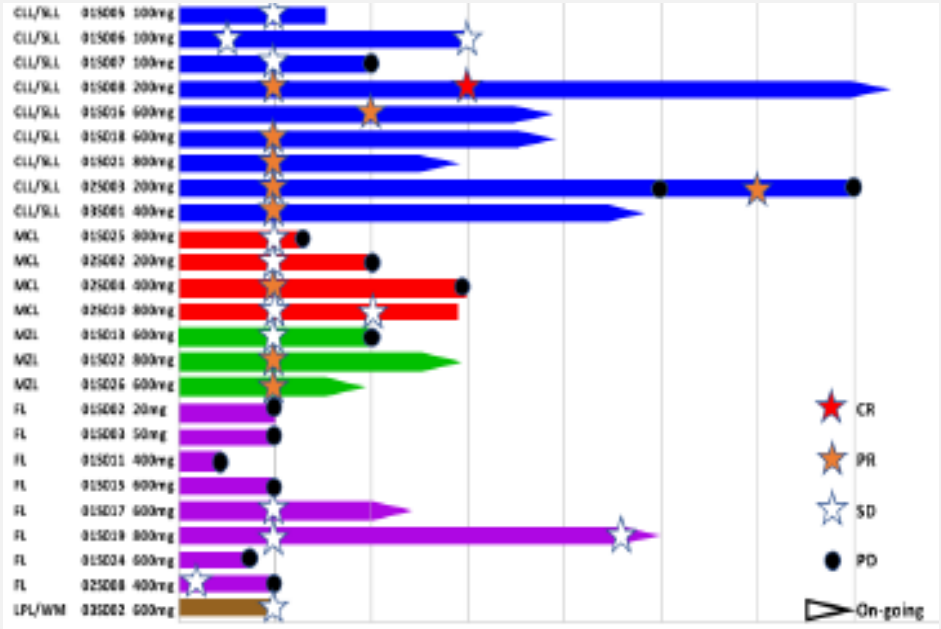
↓ Response Rate

	CLL/SLL	MCL	MZL	FL	LPL/WM	Total
Patient with the assessment of Efficacy	9	4	3	8	1	25
Overall Response, n(%)	6 (66.7)	1 (25.0)	2 (66.7)	0	0	9 (36.0)
CR	1 (11.1)	0	0	0	0	1 (4.0)
PR	5 (55.6)	1 (25.0)	2 (66.7)	0	0	8 (32.0)
SD	3 (33.3)	3 (75.0)	1 (33.3)	4 (50.0)	1 (100.0)	12 (48.0)
PD	0	0	0	4 (50.0)	0	4 (16.0)

Waterfall Plot of LN Response



Swimmer's Plot



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Lisaftoclax: Safety

TEAE per Dose Level

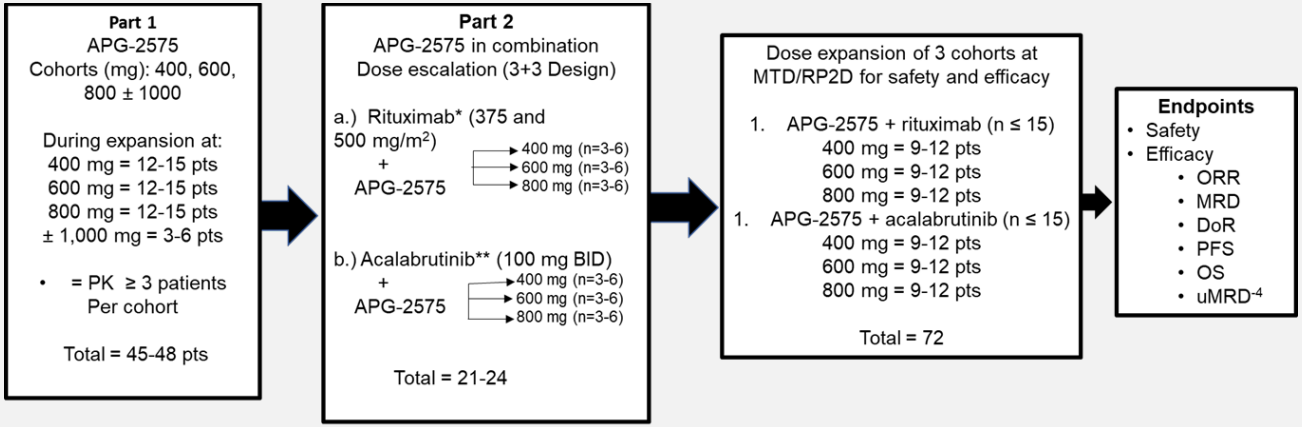
	20 mg	50 mg	100 mg	200 mg	400 mg	600 mg	800 mg	Total
Population	2	1	3	3	6	9	7	31
Any TRAE，n (%)	2 (100%)	1 (100%)	3 (100%)	3 (100%)	4 (66.7%)	7 (77.8%)	8 (100%)	28 (87.5%
System Organ Class/Preferred term，n (%)								
Platelet count decreased	1 (50.0%)	0	2 (66.7%)	1 (33.3%)	2 (33.3%)	2 (22.2%)	3 (37.5%)	11 (34.4%
Anemia	1 (50.0%)	1 (100%)	2 (66.7%)	0	0	2 (22.2%)	3 (37.5%)	9 (28.1%)
Neutrophil count decreased	0	0	2 (66.7%)	2 (66.7%)	1 (16.7%)	1 (11.1%)	1 (12.5%)	7 (21.9%)
White blood cell count decreased	0	0	1 (33.3%)	1 (33.3%)	1 (16.7%)	0	4 (50.0%)	7 (21.9%)
Hyperuricemia	0	0	1 (33.3%)	0	0	2 (22.2%)	2 (25.0%)	5 (15.6%)
Diarrhea	0	0	0	1 (33.3%)	1 (16.7%)	2 (22.2%)	1 (12.5%)	5 (15.6%)
Hyperphosphatemia	0	0	0	0	0	2 (22.2%)	2 (25.0%)	4 (12.5%)
Hypertriglyceridemia	0	0	1 (33.3%)	1 (33.3%)	0	1 (11.1%)	1 (12.5%)	4 (12.5%)

TEAE ≥ Grade 3 All Dose Levels

	≥Grade 3, n (%)	SAE, n (%)
Population	31	31
Any TRAE, n (%)	7 (21.9)	1 (3.2)
System Organ Class/Preferred term, n (%)		
Platelet count decreased	4 (12.5)	1 (3.2)
Neutrophil count decreased	3 (9.4)	0
White blood cell count decreased	1 (3.1)	0
Anemia	2 (6.3)	1 (3.2)

Lisaftoclax: Future Development

Study Design



Ramp-Up Schema

Target Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
400 mg	20 mg	→ 50	→ 100	→ 200	400[a]		
600 mg	20 mg	→ 50	→ 100	→ 200	→ 400	600[b]	
800 mg	20 mg	→ 50	→ 100	→ 200	→ 400	→ 600	800[c]

Dose Cohort (a) 400 mg, Cycle 1 Day 1; (b) 600 mg, Cycle 1 Day 1; (c) 800 mg, Cycle 1 Day 1

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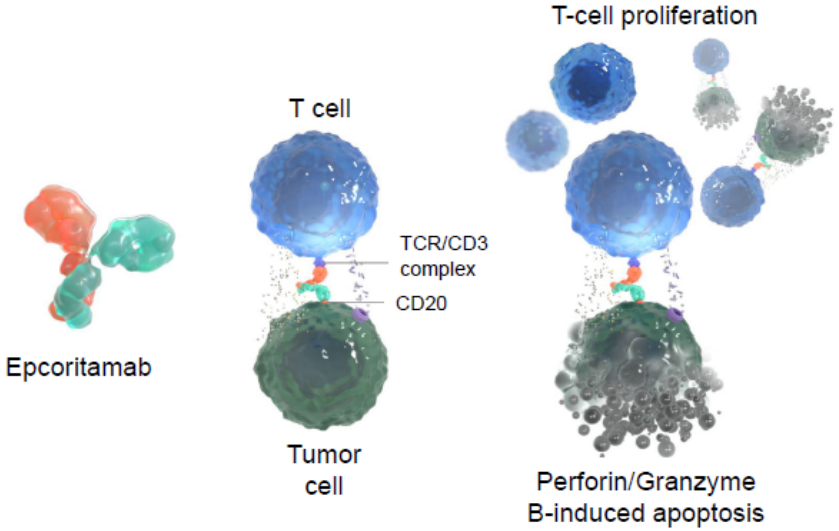
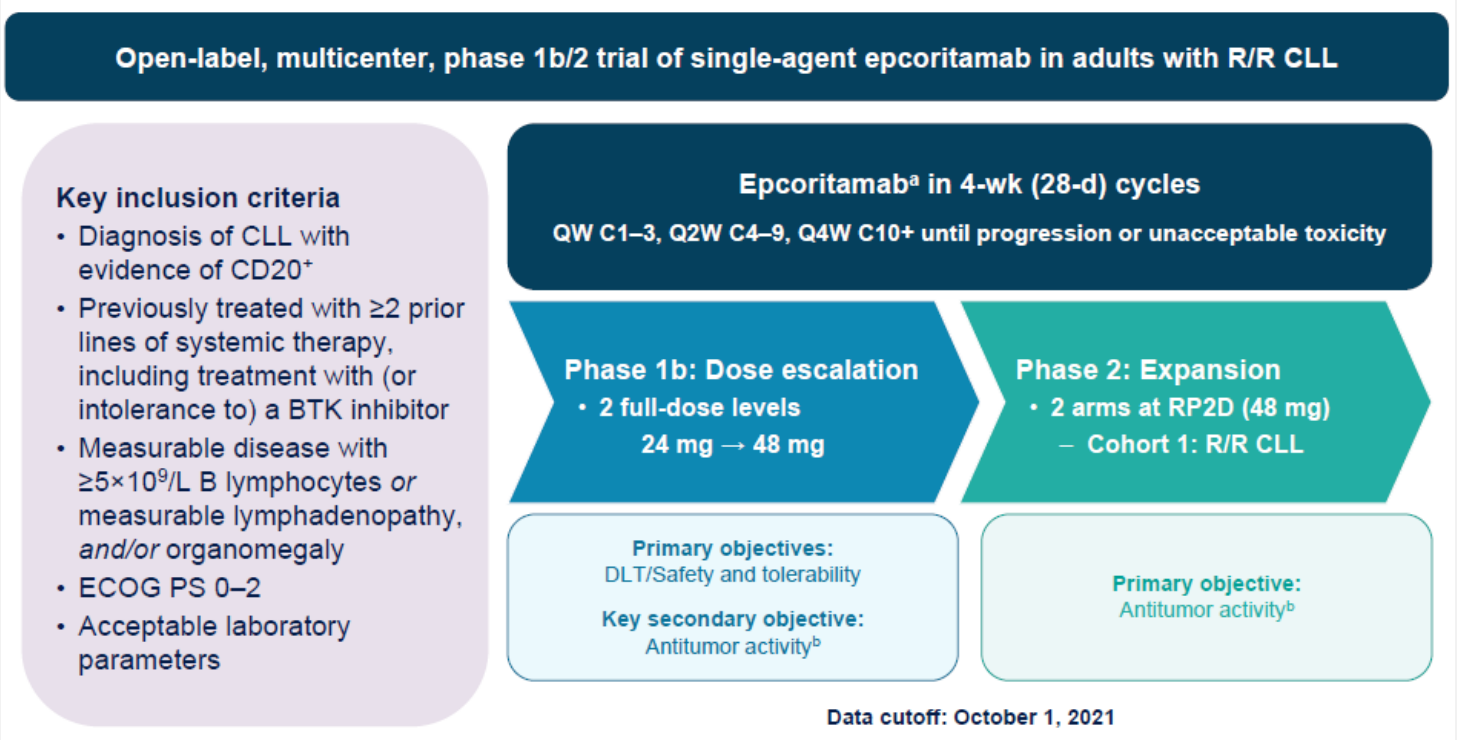
Abstract 2627: Kater et al, ASH 2021

Epcoritamab

- Epicoritamab is a fully humanized bispecific antibody that induces potent activation and cytotoxic activity of $CD4^+$ and $CD8^+$ T cells, which targets and eliminates CD20-expressing cells



EPCORE CLL-1: Study Design



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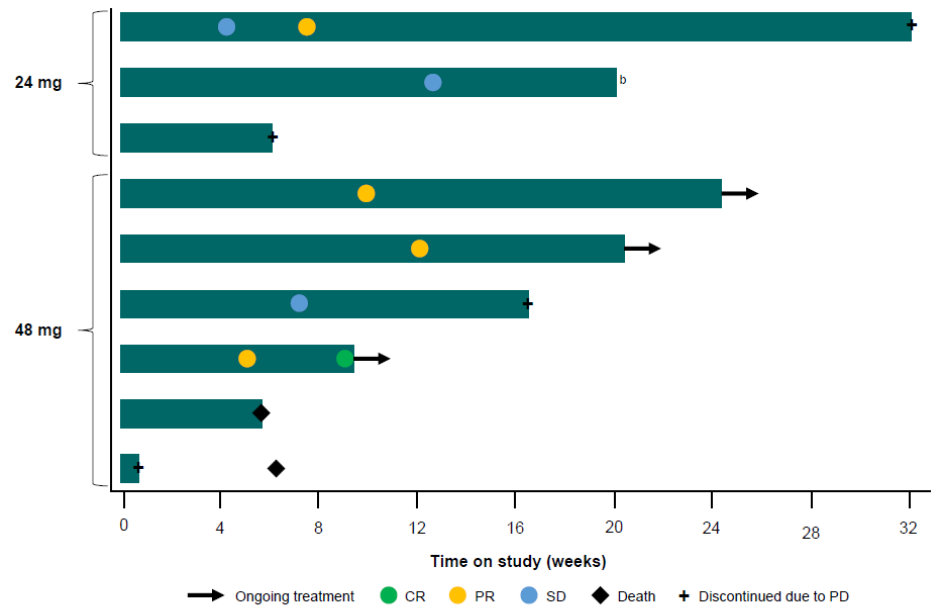
Epcoritamab: Baseline Characteristics

Characteristic		Total N=11
Median age (range), y		63 (50–77)
Male, n (%)		10 (91)
Median time from initial diagnosis (range), mo		157 (57–234)
ECOG PS, n (%)	0	6 (55)
	1	5 (45)
CLL stage,[a] (%)	Rai intermediate risk	2 (18)
	Rai high risk	3 (27)
	Binet A	1 (9)
	Binet B	1 (9)
	Binet C	4 (36)
Median lines of prior therapy (range)		6 (2–9)
Prior treatment, n (%)	BTK inhibitor	11 (100)
	Ibrutinib	9 (82)
	Venetoclax	7 (64)
	CAR-T therapy	2 (18)
Mutation status, n (%)	*TP53*	7 (64)[b]
	IGHV	2 (18)[c]
	SF3B1	2 (18)[d]
	NOTCH1	2 (18)[e]
	BIRC3	1 (9)[f]
Chromosomal alteration, n (%)	del(11q)	5 (45)[g]
	del(13q)	8 (73)
	del(17p)	7 (64)[h]
	Trisomy 12	3 (27)[i]

Data cutoff: October 1, 2021. [a]CLL stage assessed at screening. Method of staging varied by geographic region. [b]*TP53* data were missing for 1 patient. [c]*IGHV* data were missing for 3 patients. [d]*SF3B1* data were missing for 8 patients. [e]*NOTCH1* data were missing for 8 patients. [f]*BIRC3* data were missing for 9 patients. [g]del(11q) data were missing for 1 patient. [h]del(17p) data were missing for 1 patient. [i]Trisomy 12 data were missing for 2 patients.

Epcoritamab: Efficacy

Swimmer's Plot



Data cutoff: October 1, 2021. [a]The response-evaluable population includes patients who had evaluable disease at baseline and ≥1 postbaseline response evaluation or died within 60 d of first dose. [b]Patient discontinued due to physician decision.

Responses were observed in 4 patients, including 1 CR and 3 PRs

Responders had high-risk disease; 3 of 4 responders had *TP53* aberrations

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Epcoritamab: Safety

TEAE ≥15%, n (%)	Total N=11			
	Grade 1–2	Grade 3	Grade 4	Any grade
CRS	8 (73)	0	0	8 (73)
Fatigue	4 (36)	0	0	4 (36)
Injection-site reaction	4 (36)	0	0	4 (36)
Nausea	2 (18)	1 (9)	0	3 (27)
Abdominal pain	1 (9)	1 (9)	0	2 (18)
ALT increased	1 (9)	1 (9)	0	2 (18)
Constipation	2 (18)	0	0	2 (18)
Cough	2 (18)	0	0	2 (18)
Diarrhea	2 (18)	0	0	2 (18)
Dyspnea	2 (18)	0	0	2 (18)
Erythema	2 (18)	0	0	2 (18)
Hypotension	2 (18)	0	0	2 (18)
Hyponatremia	2 (18)	0	0	2 (18)
Hypophosphatemia	2 (18)	0	0	2 (18)
Peripheral edema	2 (18)	0	0	2 (18)
Pyrexia	2 (18)	0	0	2 (18)
Hematologic TEAEs				
Thrombocytopenia	0	1 (9)	4 (36)	5 (45)
Anemia	0	3 (27)	0	3 (27)
Neutropenia	0	1 (9)	2 (18)	3 (27)

Data cutoff: October 1, 2021.

- No DLTs occurred at 24 or 48 mg
- The most common TEAEs were CRS (73%), thrombocytopenia (45%), fatigue (36%), and injection-site reaction (36%)

	Total N=11
CRS,[a] n (%)	8 (73)
Grade 1	2 (18)
Grade 2	6 (55)
CRS leading to dose delay	3 (27)
Median time to onset, d (range)	9 (2–23)

Data cutoff: October 1, 2021. [a]CRS graded by Lee et al[9] criteria.

- CRS events occurred early in treatment and resolved
- No patient discontinued epcoritamab due to CRS
- No cases of ICANS or tumor lysis syndrome were observed

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Conclusions

- Reversible BTKi appear well tolerated and demonstrate significant activity in R/R CLL in both wt and mutated BTK settings
- BCL2 inhibitor lisaftoclax demonstrates encouraging activity with a manageable safety profile and ease of use with daily ramp-up without TLS
- Bispecific epcoritamab demonstrates encouraging activity in a heavily pretreated high-risk R/R CLL population with an acceptable safety profile
- There is ongoing future development, with combination therapy currently being explored
- There are additional targets to address resistance currently in clinical development (including, but not limited to PKC-ß, PROTAC BTK degraders, MCL1/CDK9 inhibitors, anti-BAFF mAb)


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