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Novel Strategies Combining BTK and BCL-2 Inhibitors for CLL

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Chronic Lymphocytic Leukemia

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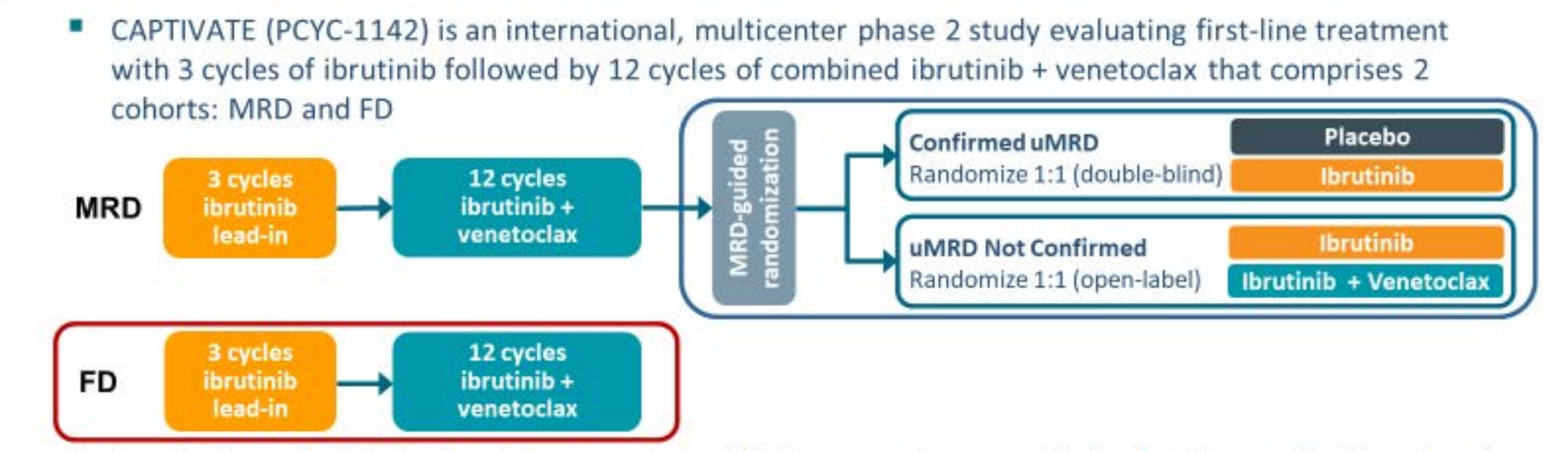
Educational Objectives:

- Understand Efficacy Outcomes of Ibrutinib Venetoclax Combinations:
  - Large Phase II Updates in TN (CAPTIVATE) and RR (TAP-CLARITY) CLL
  - Phase III GLOW Study: Fixed Duration Ibr/Ven vs ChlorG in TN CLL>65
- Review outcomes of alternative BTKi Ven Combinations +/- AntiCD20
- Take a look towards future read outs
  - Ongoing BTK/Ven Based Combinations Studies

CAPTIVATE: Phase II Study in TN CLL



Primary Endpoints and Interim Findings of Both Cohorts Have Been Previously Reported

MRD Cohort: Wierda ASH 2020; Wierda et al J Clin Oncol 2021 Oct PMID: 34618601

FD Cohort: Ghia ASCO 2021, Allan EHA 2021

CAPTIVATE: Study Schema

Key Inclusion Criteria

- Previously **Untreated** CLL/SLL
- **Active Disease** requiring treatment per iwCLL criteria
- Age **<70** years
- ECOG PS **0-1**

Endpoints

- MRD Cohort: **1 year DFS** in patients with **Confirmed uMRD**
  - ✓ Confirmed uMRD: defined as having uMRD (<10–4 by 8-color flow cytometry) serially over at least 3 cycles, and undetectable MRD in both PB and BM
- FD Cohort: **CR/CRi** rate per INV in patients **without del17p**
- Key 2º Endpoints CAPTIVATE: uMRD Rates, ORR, DoR (FD), PFS, OS (MRD), TLS Risk Reduction, Safety

CAPTIVATE: Key Baseline Characteristics

Characteristic	MRD Cohort	FD Cohort
Total Number of Subjects:	164	159
Median Age (range)	58 (28-69)	60 (33-71)
High Risk Features: (%) Unmutated IGHV Del17p/*TP53* Mutation Complex Karyotype	 60 20 19	 56 17 19

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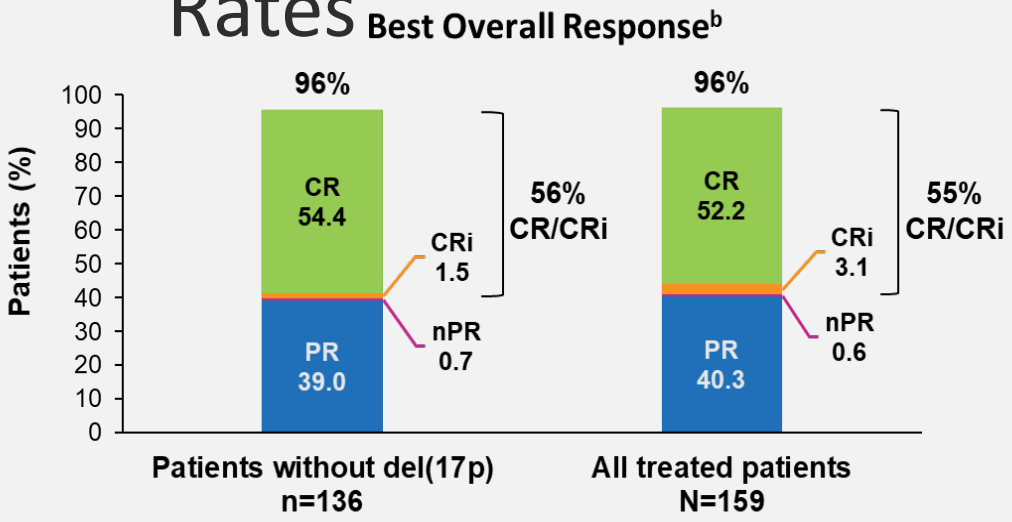
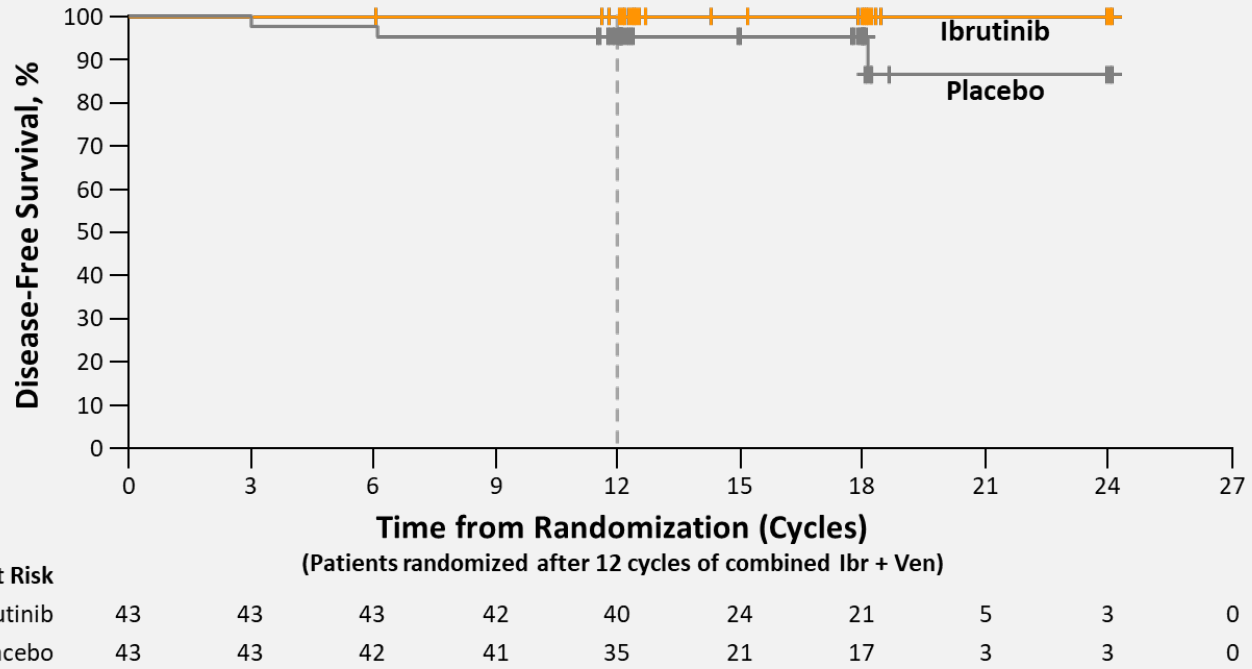
CAPTIVATE: Primary Endpoints

FD Cohort: Response Rates



MRD Cohort: 1 yr DFS



*2 yr DFS Update ASH 2021: Ghia et al, Abstract #68 Saturday 9:45 am.

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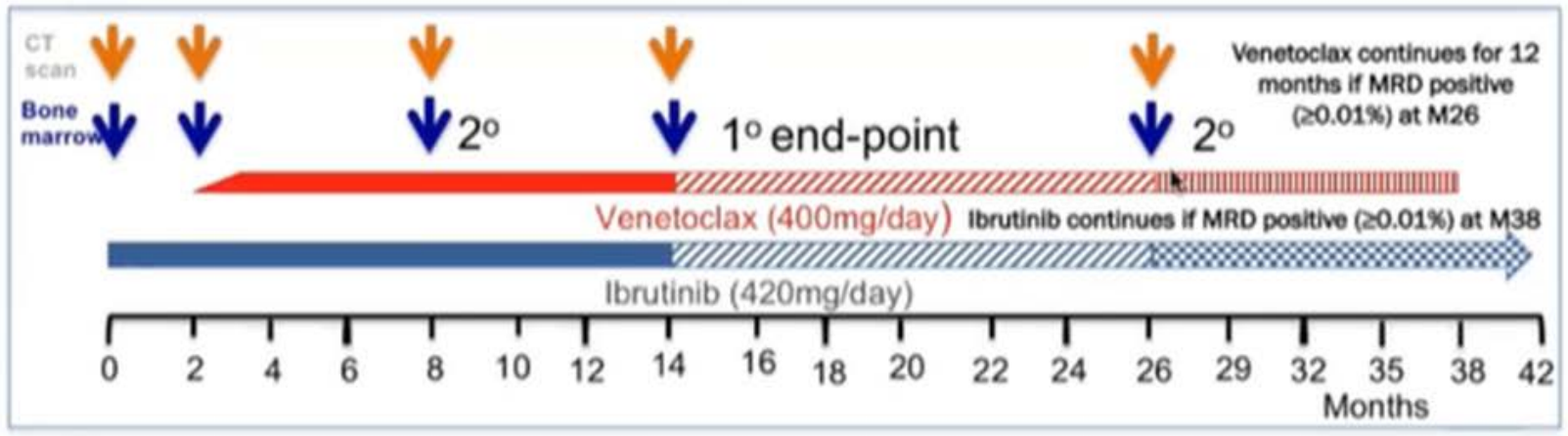
CAPTIVATE: Key Secondary Endpoints

Endpoint	MRD	FD
uMRD: ITT (%) PB BM	 75% 68%	 77% 60%
CR with DoR>12 months	n/a	89%
PFS	>95% (31 m)	95 (28 m)
TLS Reduction: (%) High ->Med or Low	90%	94%

CAPTIVATE: Safety

Measure	MRD	FD
Completion of all 12 combo cycles:	90%	92%
Tumor Lysis: Laboratory Clinical	 1% 0	 0 0
Dose Reductions: Ibrutinib Venetoclax	 15% 10%	 10% 14%
Drug Discontinuations Due to AE: Ibrutinib Venetoclax	 6% 4%	 5% 2%
Most Common Grade 3 / 4 AEs Neutropenia HTN Thrombocytopenia Diarrhea	35% 7% 5% 5%	33% 6% NR 3%
AESI Atrial Fibrillation Hemorrhage Fatal AE	 2% 1% 0	 4% 2% 1%

TAP-CLARITY: Phase II Study in RR CLL



Duration of VEN therapy: 3 consecutive MRD4 (<0.01% CLL) in PB confirmed in BM:
MRD <0.01% at M8 → stop I+V at M14; MRD <0.01% at M14 → stop I+V at M26
MRD negative (<0.01%) at M26 → stop I+V at M26, if MRD positive (≥0.01%) continue IBR

- R/R CLL
- uMRD Treatment Duration Strategy
- Primary Endpoint: uMRD rate after 12 cycles of combination therapy
- Amended to allow a 3rd year of Ibr/Ven for MRD+ subjects
- 2 cycle Ibr lead-in

Hillmen et al JCO 2019 Munir ASH 2020 (Update)

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TAP-CLARITY: Baseline Characteristics

Characteristic	Patients (n = 54)
Gender (Male/Female)	37 (69%) / 17 (31%)
Age (Median [Range])	64 (31 – 83)
Current Binet Stage (A / B / C / NK)	12 (22%) / 18 (33%) / 22 (41%) / 2 (4%)
Lymph nodes ("bulky" ≥ 5cm)	4 (8%)
ECOG (0/1/2/NK)	32 (59%) / 18 (33%) / 3 (6%) / 1 (2%)
V_H (mutated/unmutated/VH3-21/failed)	10 (19%) / 40 (74%) / 3 (6%) / 1 (2%)
17p del	10/50 (20%)
11q del (not 17p del)	13/51 (25%)
Prior therapies (median [range])	1 (1 to 6)
• previous FCR or BR	44/54 (82%)
→ relapse within 3 years of BR or FCR	22/44 (50%)
• previous idelalisib	11/54 (20%)

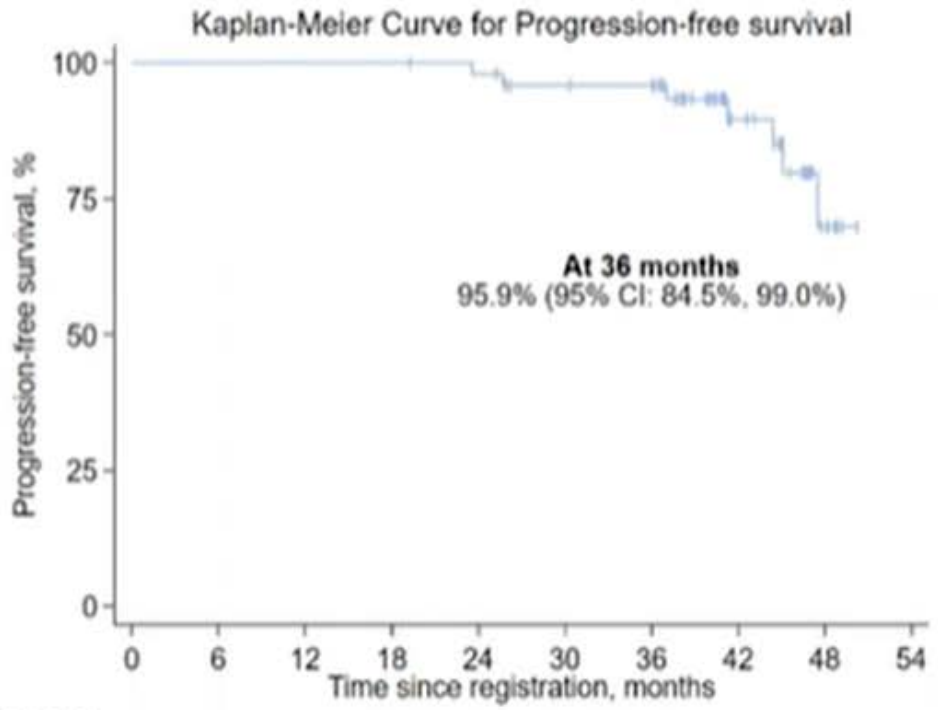
TAP-CLARITY: Primary Endpoint

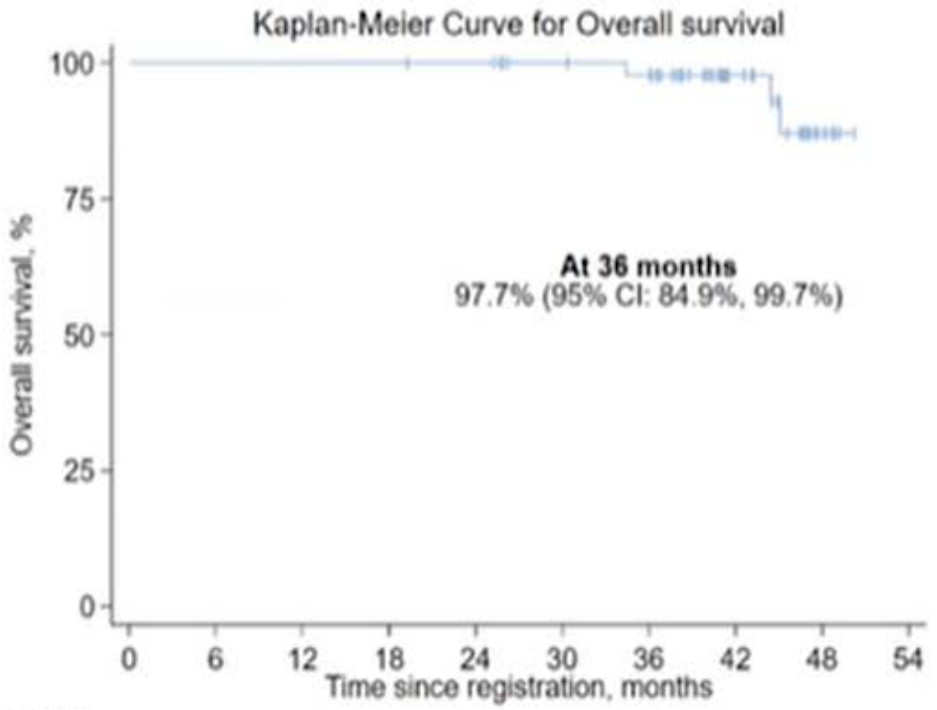
All at Month 14	PB MRD negative	BM MRD negative	Trephine normal
All patients	**29/50 (58%)**	**20/50 (40%)**	**39/48 (81%)**
FCR/BR rel <36 months	14/20 (70%)	9/20 (45%)	18/19 (95%)
Prior idelalisib	6/9 (67%)	5/9 (56%)	7/9 (78%)

50/50 patients have reached at least Month 14 and have had a bone marrow MRD PB or BM <0.01% CLL cells (10^{-4}) by flow cytometry

TAP-CLARITY: PFS/OS

Median PFS and OS not reached. Estimated PFS and OS shown at month 36





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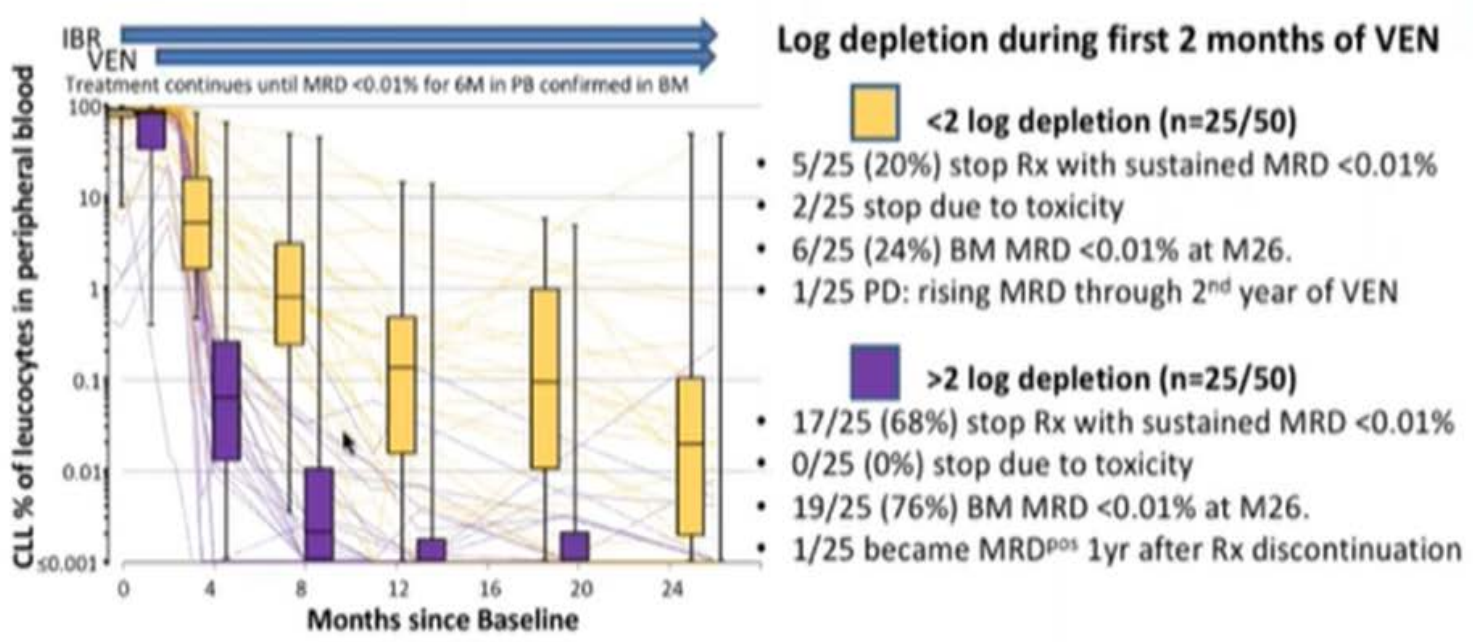
TAP-CLARITY: MRD Kinetics and Response



Jain et al JAMA Oncology
Similar Findings
MRD <1% by 3 cycles of combined treatment vs not
uMRD rates 75% vs 25% respectively

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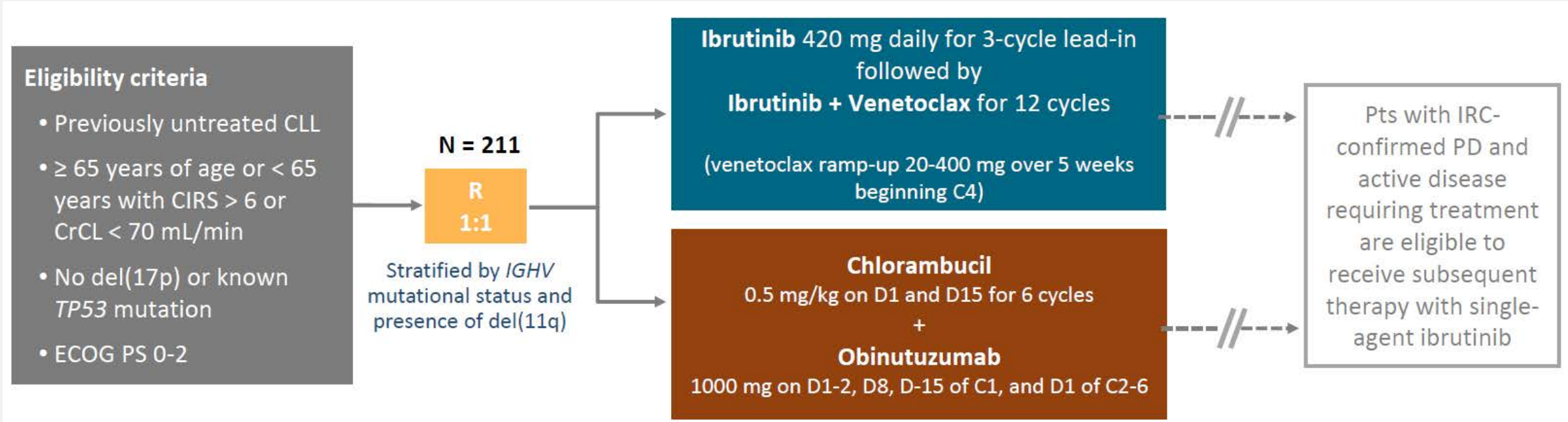
GLOW: Phase III Trial Ibr/Ven Fixed Duration vs Chlorambucil Obinutuzumab

Review of Study Schema, Efficacy, Safety

GLOW: Study Schema



Primary end point: Progression-free survival by independent review committee (IRC)

- 71 PFS events to detect an effect size with an HR = 0.5 (80% power at a 2-sided significance level of 0.05)

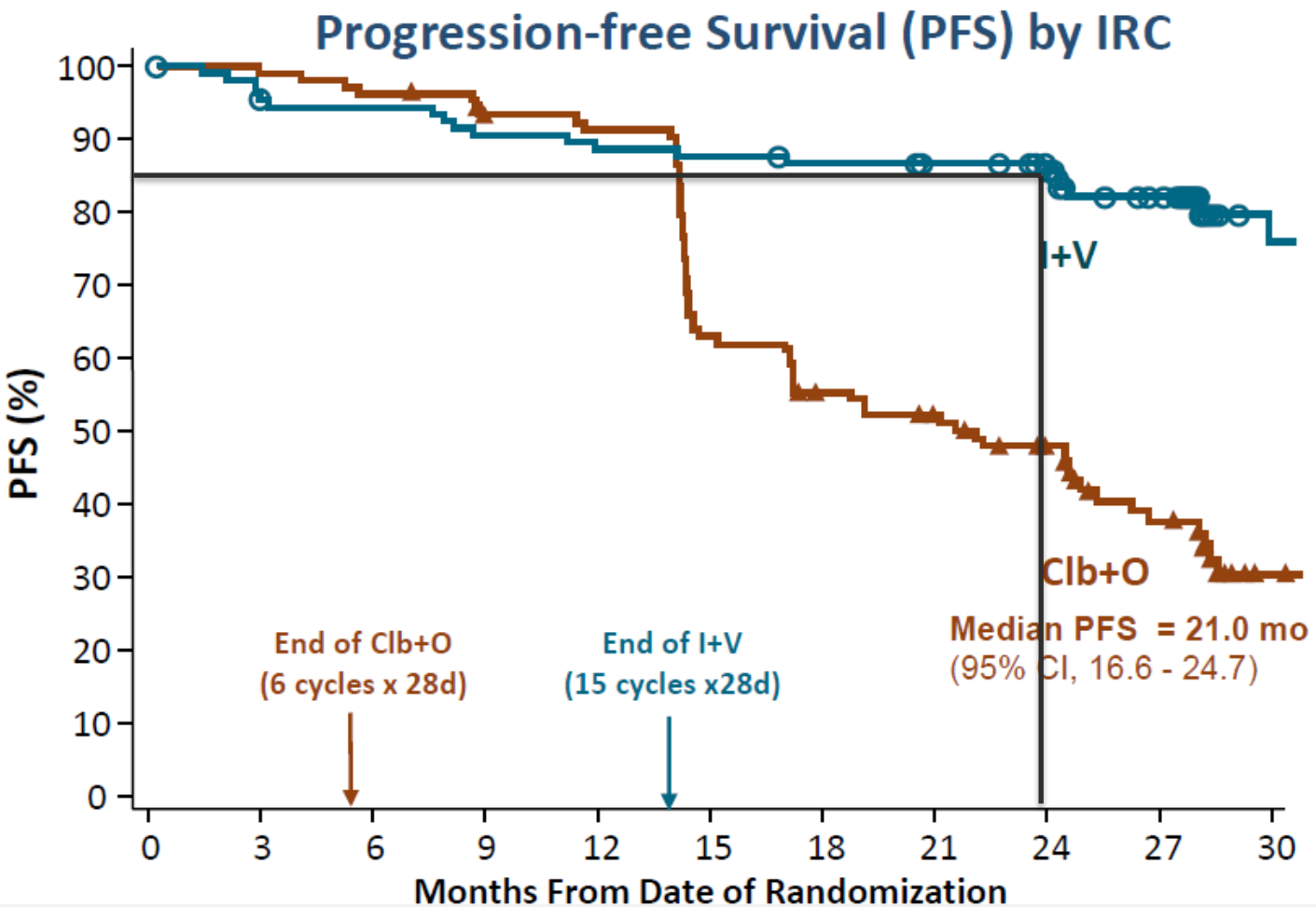
Key secondary end points: Undetectable MRD in BM, CR rate (IRC), ORR (IRC), OS; safety was also evaluated

Kater et al EHA 2021

GLOW: Baseline Characteristics

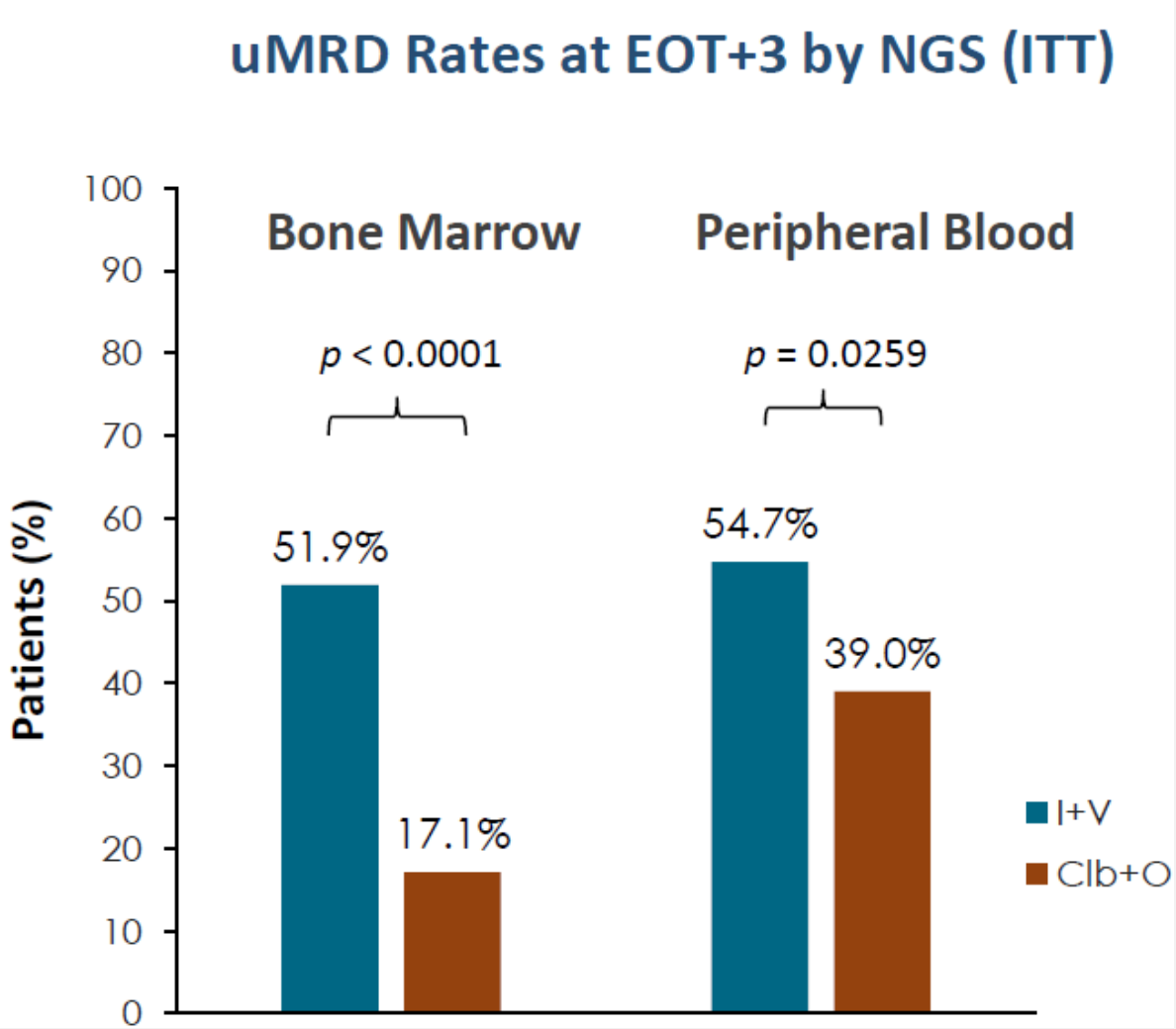
Characteristic	I+V (N = 106)	Clb+O (N = 105)
Age, median (range), years	71.0 (47, 93)	71.0 (57, 88)
≥ 75 years, %	33.0	35.2
Male, %	55.7	60.0
ECOG PS 1-2, %	67.0	62.9
CIRS score, median (IQR)	9 (6-12)	8 (5-10)
> 6, %	**69.8**	**58.1**
CrCl, median (range) mL/min	66.5 (34.0, 168.1)	63.2 (32.3, 180.9)
Rai Stage III-IV, %	57.3	52.5
Bulky Disease ≥5cm, %	39.0	36.2
Elevated LDH, %	**33.0**	**48.6**
Mutated *IGHV*[a], %	25.5	25.7
Unmutated *IGHV*[a], %	51.9	51.4
Del(11q), %	18.9	17.1
TP53 mutation, %	6.6	1.9

GLOW: Primary Endpoint



- I+V HR for PFS .216 (0.131-0.357; p<0.0001)
- Regardless of subgroup PFS HR I+V vs Chlor+O
- ORR/CR:
  - I+V 86.8%/38.7%
  - Chlor+O 84.8%/11.4%
- 90% of Responders in I+V maintained response 24 months later compared to 41% in comparator arm
- TTNT >95% I+V vs ~78% ChlorG at 24 months

GLOW: Secondary Endpoint uMRD



- MRD endpoint by NGS $1x10^{-4}$
- I+V Concordance is 92.9% between PB and BM
- PB uMRD I+V: 55% EOT+3 49% EOT+12 (84.5% maintain)
- Updated Data ORAL ABSTRACT #70 Munir et al Saturday 12/11/21 10:15am

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GLOW: Secondary Endpoint Safety

Grade 3 or Higher AEs in ≥5% of Patients

	I+V (N = 106)	Clb+O (N = 105)
Median exposure, mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

[a]Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O

[b]Includes multiple preferred terms

- 78.3% of patients completed 12 months of combined treatment
- 1.9% of patients discontinued ibrutinib due to a fib
- 4 patients discontinued due to death
- 7 deaths occurred during treatment
  - 2 cardiac, 2 sudden death

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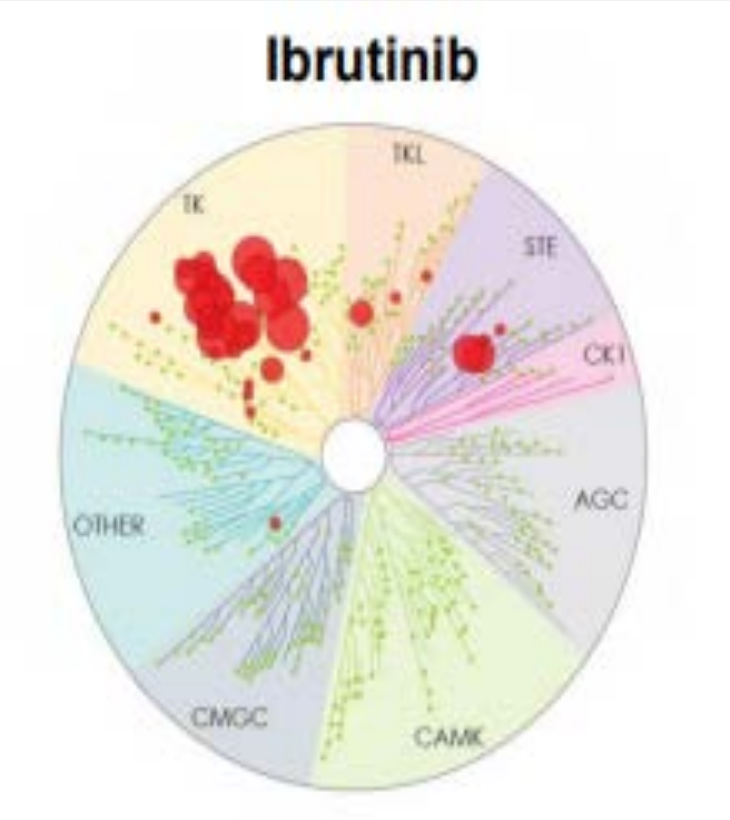
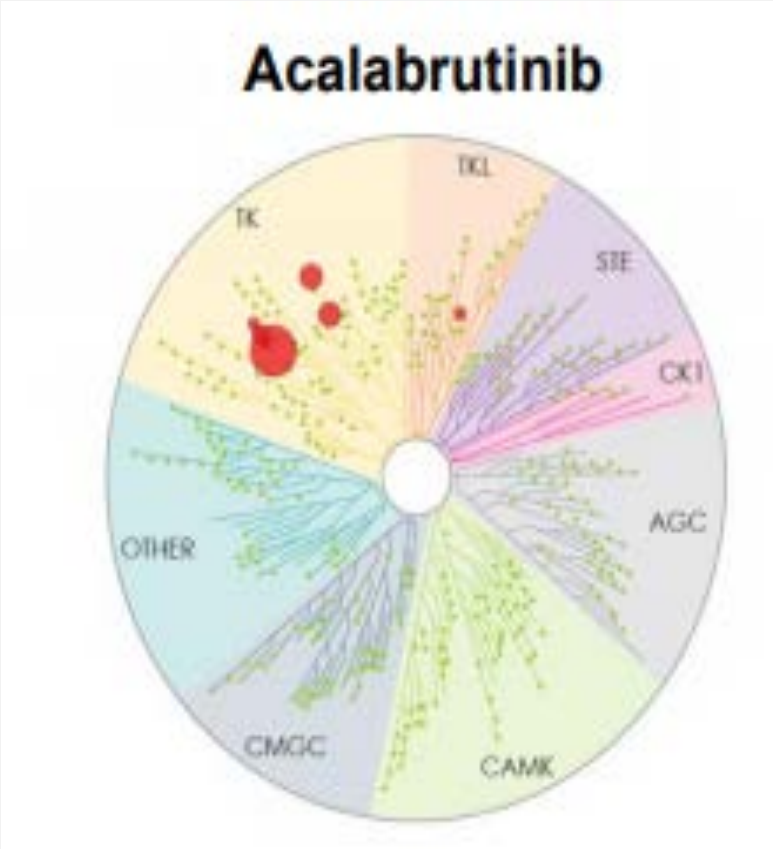
Alternative BTKi/Ven Combinations:

A Look at Reported Outcomes and Study Updates

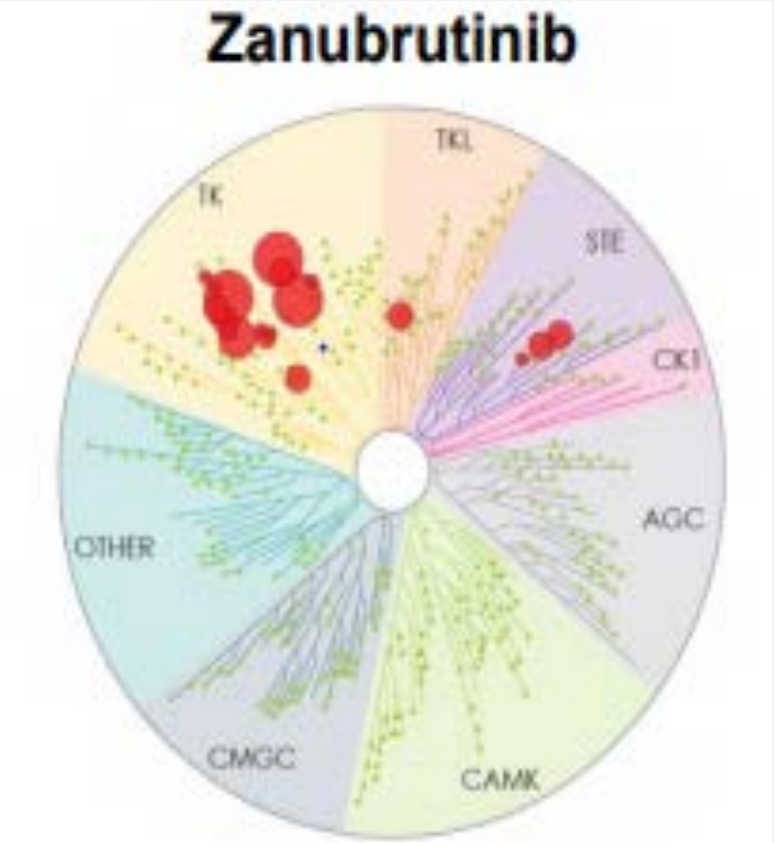
Current FDA Approved BTKi Landscape



Indications: CLL, MCL, WM, MZL, GVHD



Indications: CLL, MCL



Indications: MCL, WM, MZL

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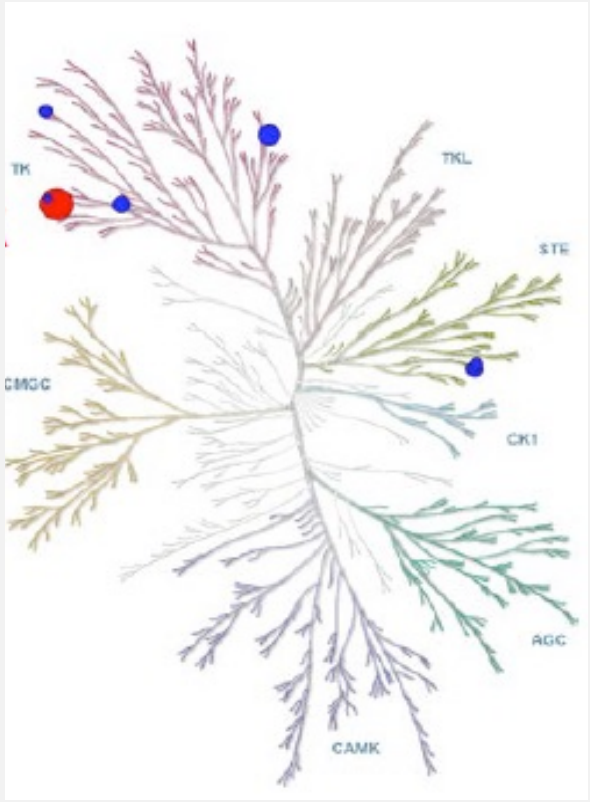
Adapted from Kapstein et al ASH 2018 abstract 1871

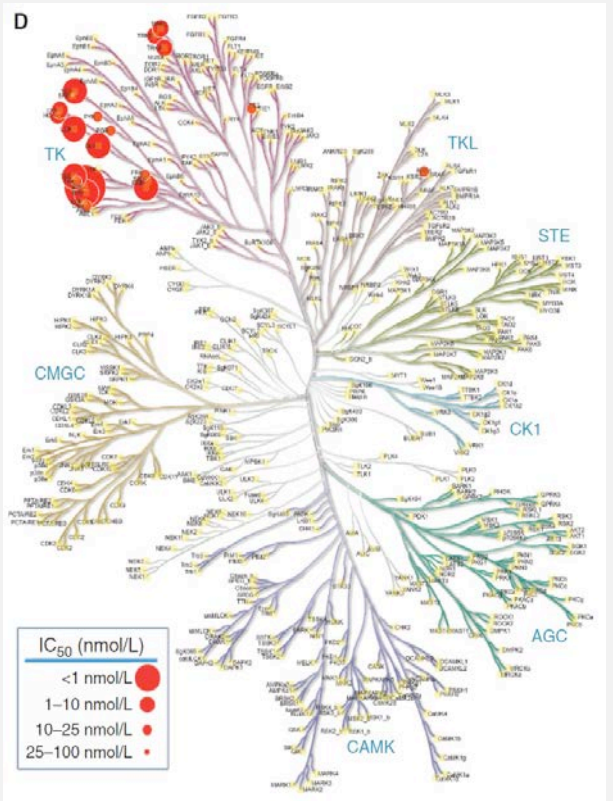
Current Reversible BTKi in Clinical Development

Kinase	IC_{50} [ATP] = K_M (nM)
BTK C481S	1.42
BTK	3.15
ERBB4	13.3
BRK	54.3
MEK2	82.7
MEK1	147
YES1	157
TXK	209
BMX	1155
TEC	1234
BLK	4100
EGFR	>1000
ITK	>5000
SRC	>5000
JAK1	>30000
JAK2	ND
JAK3	ND

Pirtobrutinib[1] Kinome Selectivity



MK-1026[2] Kinome Selectivity



Kinase	Biochemical inhibition IC_{50} (nmol/L)
BRK	2.5
LCK*	3.9
YES*	4.2
BMX**	5.2
TEC**	5.8
BLK*	9.7
TRKB***	12
TRKA***	13
HCK*	18
LYNa*	19
TRKC***	19
FGR*	26
TIE2	29
FYN*	32
RAF1	35
TXK**	36
CSK	45
FRK*	48
MEK1	599
ITK	>10,000

*Src family kinases
**TEK family kinases
***TRK family kinases

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1. Brandhuber et al SOHO 2018
2. Reiff et al Cancer Discovery 2018

Summary of Frontline CLL Combination Studies

Author	Drugs in Combo Arms	Total Cycles	N	Median Age	ORR/CR	uMRD PB	PFS/OS
Jain PMID: 34110383	Ibr/Ven	15-24	88	65	82/69	66 (BM)	93/97
Davids PMID: 34534514	Acalabrutinib, Venetoclax, Obinutuzumab	16 or 24	37	63	100/46	89	100/100
Soumerai PMID: 34826411	Zanubrutinib, Venetoclax, Obinutuzumab	8-24	39	62	100/57	85	97.5/100

ASH 2021 Important Abstracts:

- #67 Zanu/Ven in TN Del17p Arm D Sequoia (early safety)
- #68 Ibr/Ven CAPTIVATE 2 yr DFS MRD Cohort
- #71 CLL13 Coprimary Endpoint of uMRD PB, GVe, GIVe, RVe, vs CIT
- #641 Filo, IV vs FCR (prelim)
- #3720 Jain I+V LongTerm uMRD results
- #3753 Soumerai BOVen Early MRD Kinetics as Biomarker for failure

A Look Towards Future Readouts: Frontline CLL Phase 3 Combination Studies

NCT #	Study Group	Phase	Trial Arms	N	Primary Endpoint
NCT04608318	GCLLSG (CLL17)	3	• Ibr mono • VenG • Ibr/Ven FD	897	PFS
NCT03737981	Alliance (A041702)	3	• IbrG • Ibr/Ven/G	454	PFS
NCT03701282	ECOG (E9161)	3	• Ibr/Ven/G • Ibr/G	720	PFS
NCT05057494	AstraZeneca (MAJIC)	3	• Acala/Ven • VenG	750	PFS
NCT03836261	AstraZeneca (ACE-CL-311)	3	• Acala/Ven • Acala/Ven/G • FCR	780	PFS

Conclusions

- Large Phase II and Phase III studies have confirmed the efficacy and safety of BTKi/Venetoclax based combinations in frontline and relapsed setting
- New Benchmarks for uMRD and PFS have been established and continue to mature
- Relatively low toxicity profile which is acceptable and management in both younger and older unfit populations
- Need for anti-CD20 in combination approaches remains unanswered
- Current Phase III studies are assessing combination vs current standard Treat to Progression and FD targeted agent approaches


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