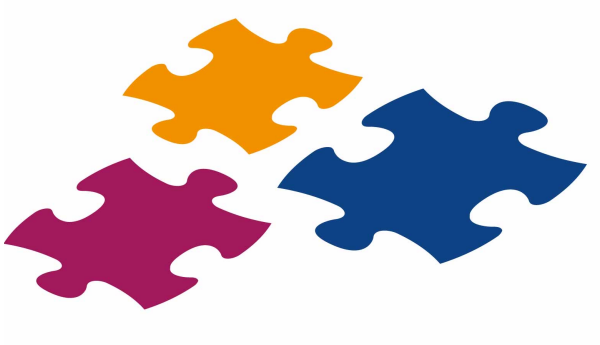


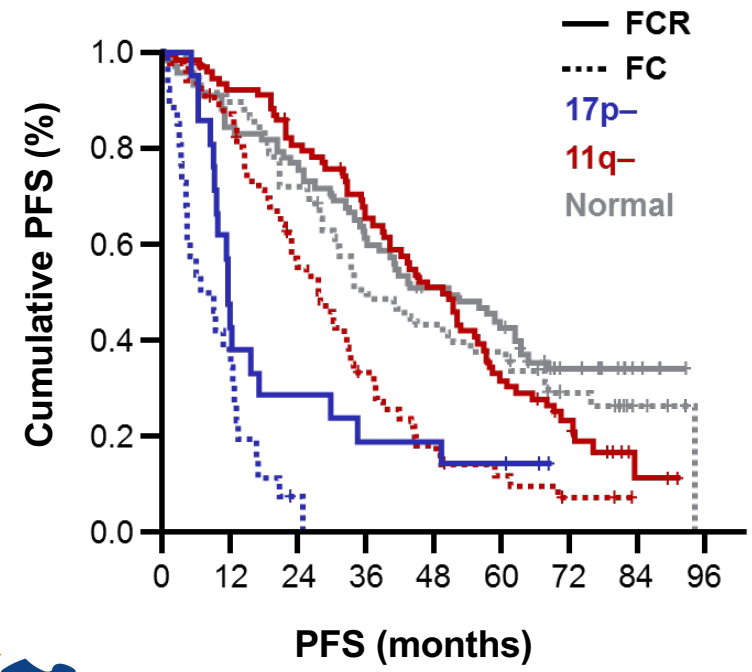
NUOVI BTKi PER LA LEUCEMIA LINFATICA CRONICA: MECCANISMI D'AZIONE E PROSPETTIVE TERAPEUTICHE

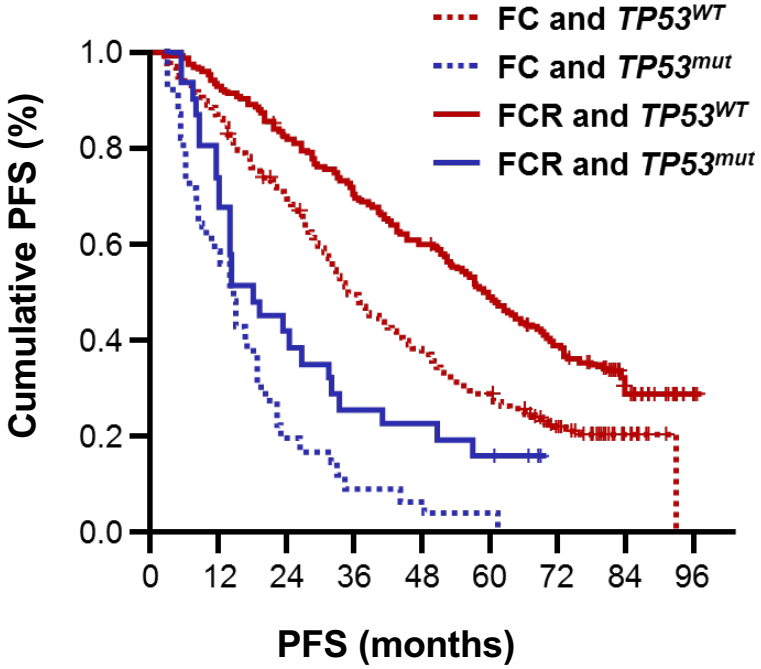
Chiara Salvetti
U.O. Clinica Ematologica
I.R.C.C.S. Ospedale Policlinico San Martino, Genova

Patients with TP53 aberrations do poorly on standard chemotherapy

CLL8: FCR vs. FC as first-line treatment for CLL (N=817)

Follow up: 70 months

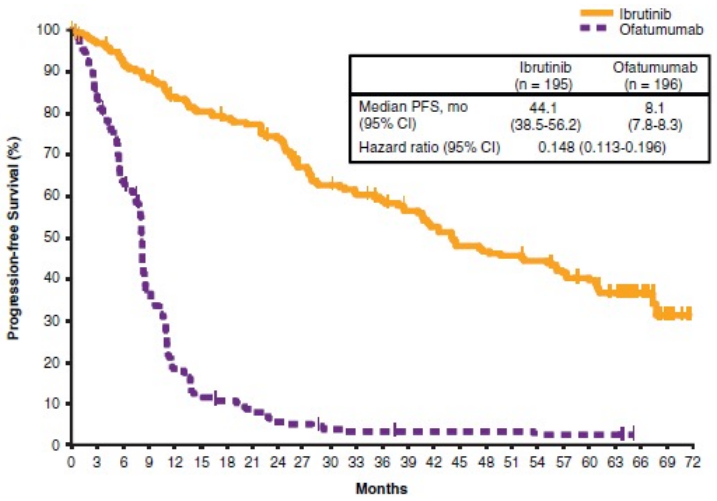




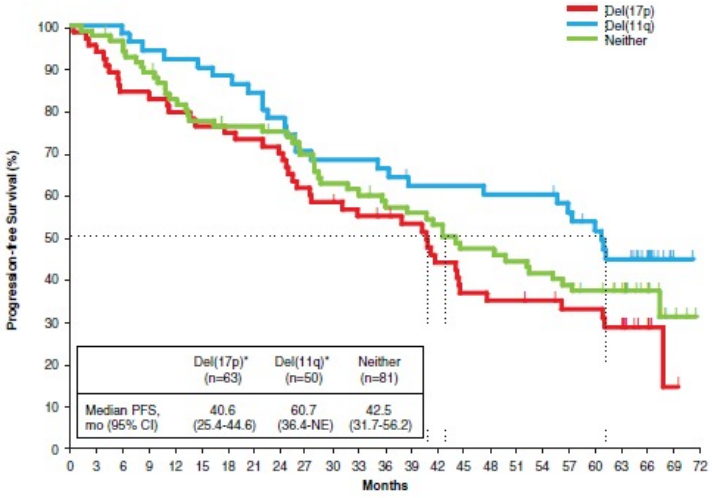
Stilgenbauer S, et al. Blood 2014

Ibrutinib monotherapy in R/R CLL: up to 6 years of follow-up from the RESONATE study

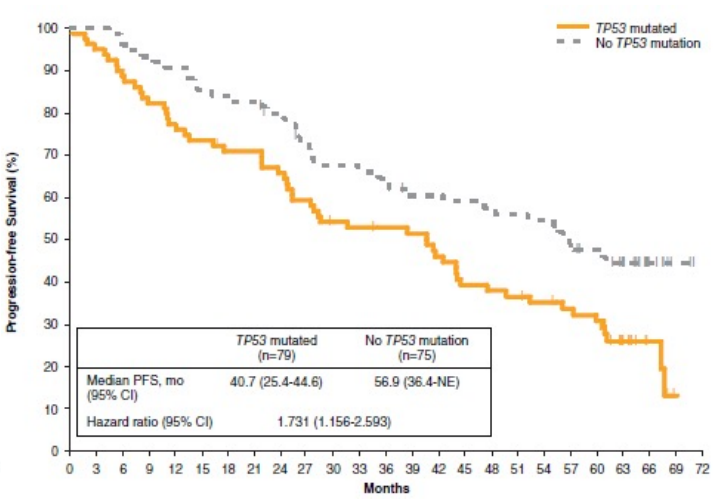
Phase III RESONATE study – ibrutinib vs ofatumumab in R/R CLL (n=391)



ITT population
Median PFS: 44.1 months



Median PFS
Del17: 40.6 months
Del11: 60.7 months
No del17/no del11: 42.7 months



Median PFS
TP53 mut: 40.7 months
No TP53 mut: 56.9 months

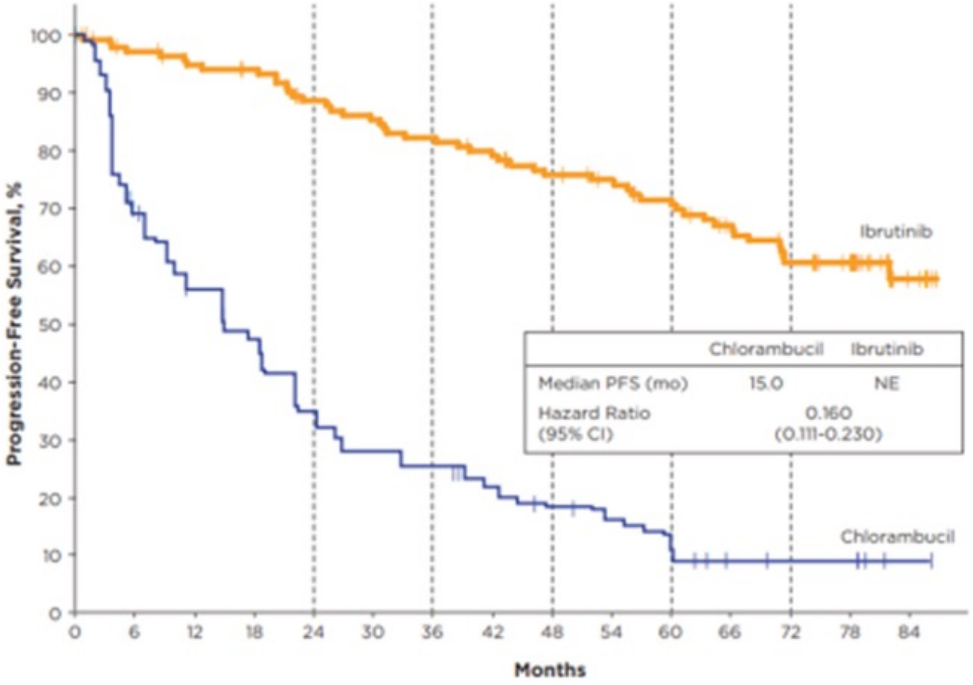
Munir T et al. Am J Hematol 2019

Ibrutinib monotherapy in TN CLL: up to 7 years of follow-up from the RESONATE-2 study

Phase III RESONATE-2 study – ibrutinib vs chlorambucil

Previously untreated CLL (n=269)

Age ≥65, ineligible to fludarabine containing regimen, NO del(17p)

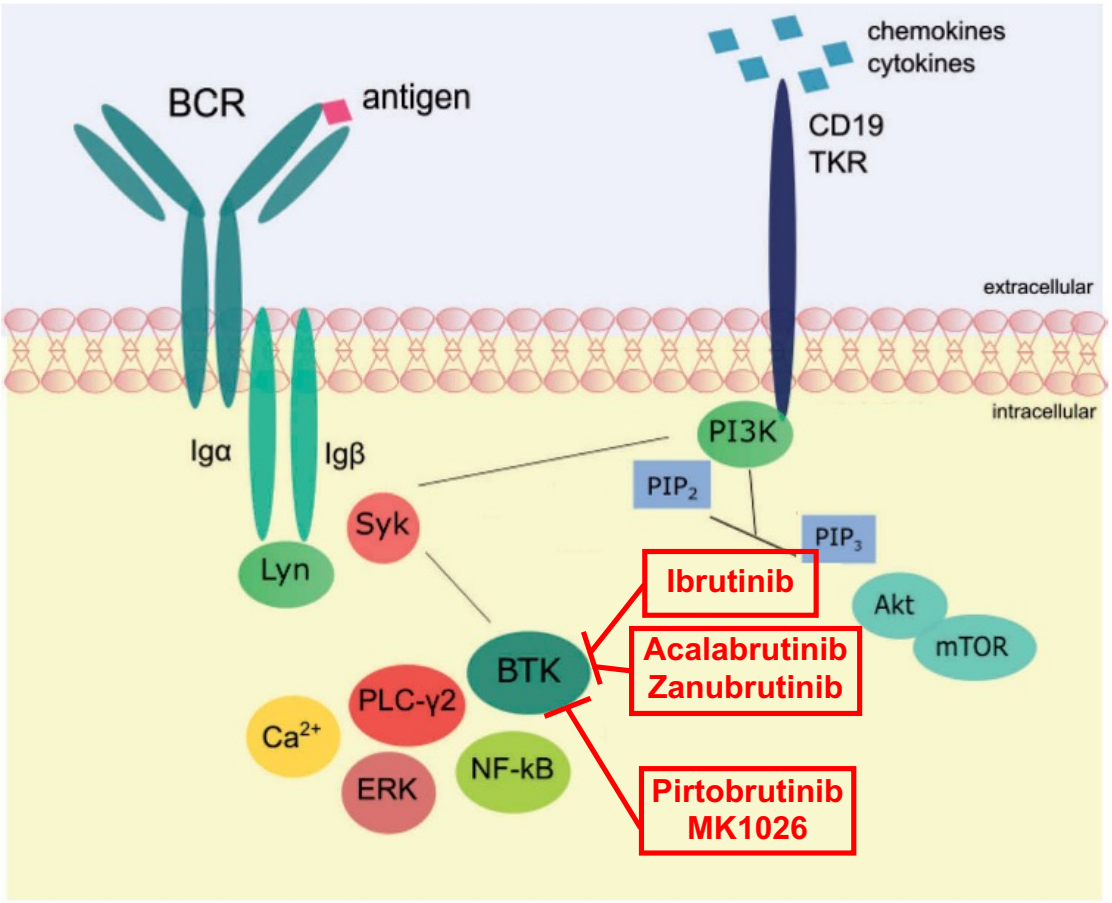


Median PFS: NR vs 15 months

7 years estimated PFS: 61% vs 9%

Ghia P et al, EHA 2021 oral presentation

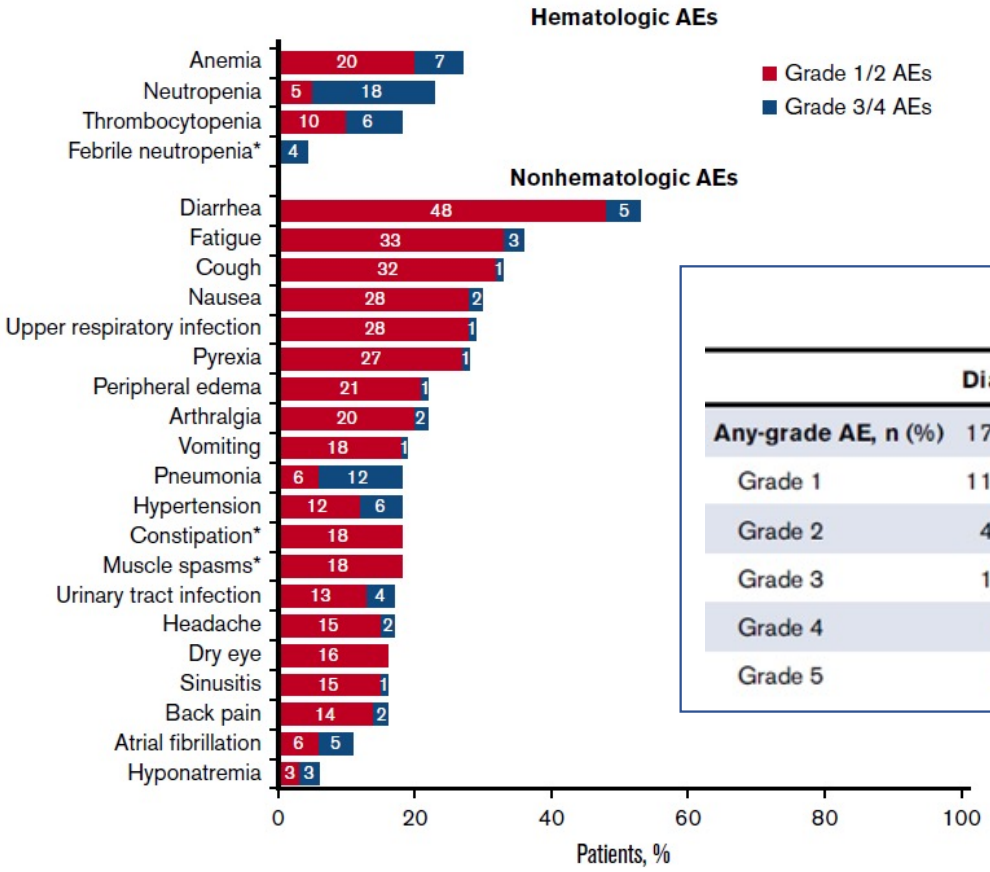
B Cell Receptor Signaling Pathway



Modified from Vitale C et al., Expert Opin Pharmacother 2017

Long term safety of ibrutinib monotherapy in CLL

Phase III RESONATE study
Phase III RESONATE-2 study → N= 330



Frequency of AEs of clinical interest

	Diarrhea	Arthralgia	Fatigue	Atrial fibrillation	HTN	Infection	Rash	Bleeding/bruising
Any-grade AE, n (%)	173 (52)	74 (22)	119 (36)	36 (11)	69 (21)	274 (83)	117 (35)	182 (55)§
Grade 1	116 (35)	45 (14)	65 (20)	5 (2)	11 (3)	24 (7)	74 (22)	130 (39)
Grade 2	42 (13)	22 (7)	44 (13)	14 (4)	34 (10)	149 (45)	32 (10)	35 (11)
Grade 3	15 (5)	7 (2)	10 (3)	16 (5)	24 (7)	81 (25)	11 (3)	14 (4)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	12 (4)	0 (0)	2 (1)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	8 (2)	0 (0)	1 (<1)

Coutre S et al, Blood Adv 2019

Ibrutinib: BTK inhibition and other targets

Ibrutinib 420 mg once daily → Sustained and complete BTK occupancy (>95%)

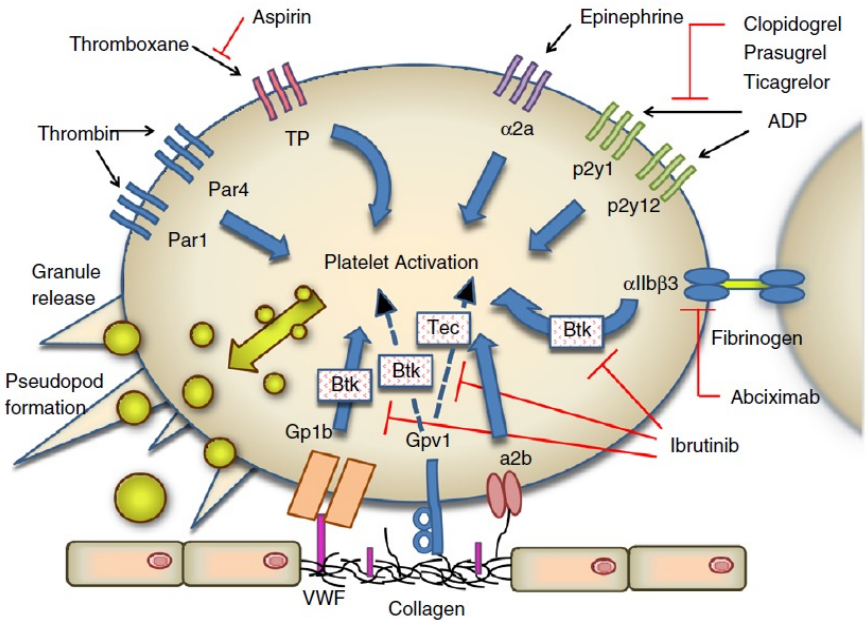
Ibrutinib also inhibits other targets at lower potency

C-terminal SRC kinase (CSK) → expressed in cardiac tissue
→ possible role in atrial fibrillation

EGFR → involved in cutaneous, vascular and gastrointestinal toxicity
→ Rash
→ Hypertension
→ Diarroeha

TEC family kinases → involved in platelet activation through glycoprotein(GP)VI signaling

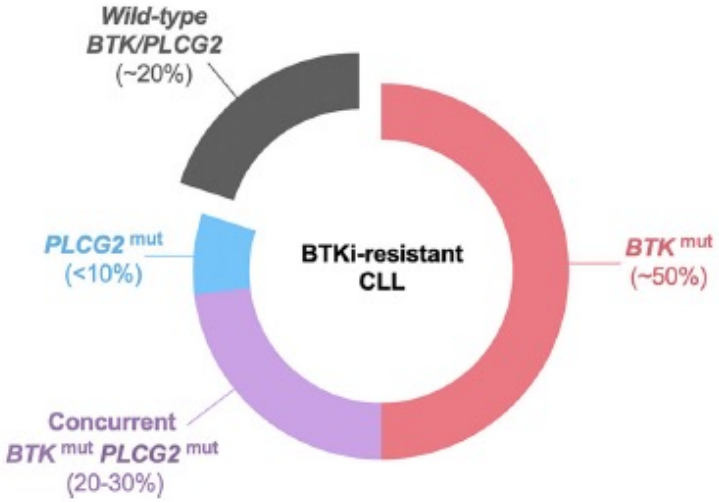
BTK has also a direct role in von Willebrand factor adhesion to GPib-IX-V *(on target effect)*



Ahn IE and Brown JR, Front Immunol 2021;
Shatzel JJ et al. J Throm Haemost 2017

BTKi resistant CLL

- BTK mutation is the most common mutation (50% of patients as BTK mutation alone and 20-30% with coexisting PLCgamma2 mutation)
- >10% of the patients have PLCG2 mutation alone
- 20% of patients do not have detectable BTK or PLCG2 mutation at progression



Ahn IE and Brown JR, Front Immunol 2021

Novel BTKi

- **Acalabrutinib**
- **Zanubrutinib** → 2nd generation BTKi

- **Pirtobrutinib**
- **MK-1026** → 3rd generation BTKi (non-covalent)

Acalabrutinib

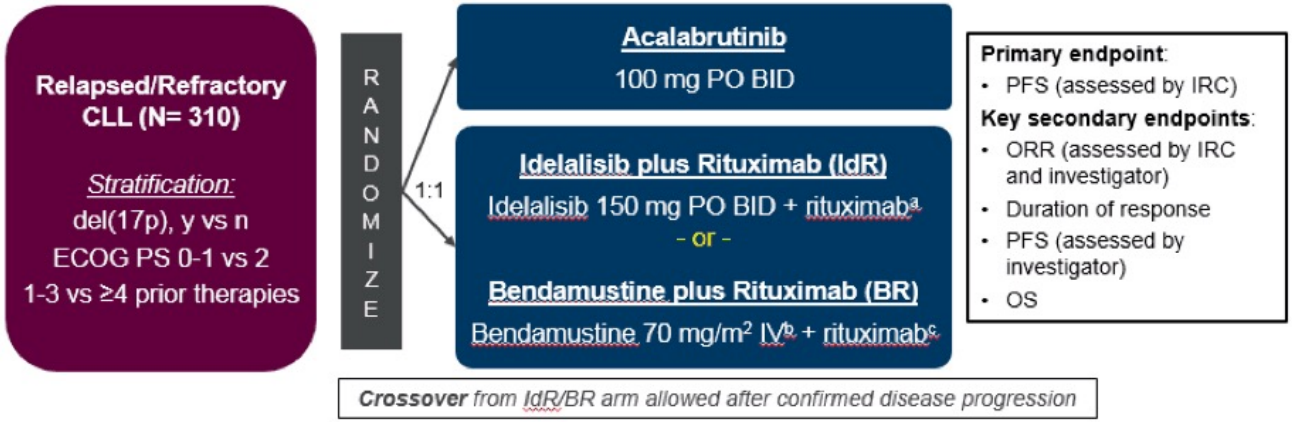
- **2nd generation covalent (irreversible) BTKi**
- Rapid oral absorption & short half-life (1 hour)→ **100 mg twice daily administration**
- **Absence of irreversible targeting to EGFR, TEC and C-terminal Src kinase**
- Weaker at inhibiting GP VI signaling and collagen-mediated platelet aggregation compared to ibrutinib

→ **Less toxic effects from inhibition of alternative kinases**

→ **complete and continuous level of drug binding to BTK** (improved BTK occupancy of 97% before dose administration)

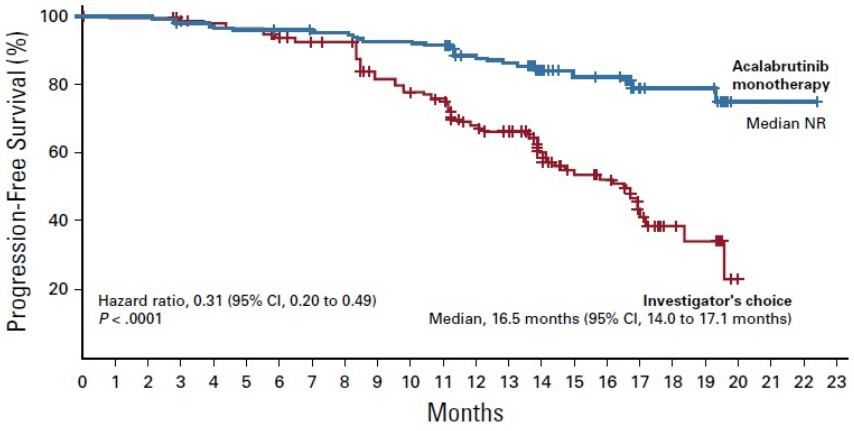
Byrd JC et al. N Engl J Med 2016

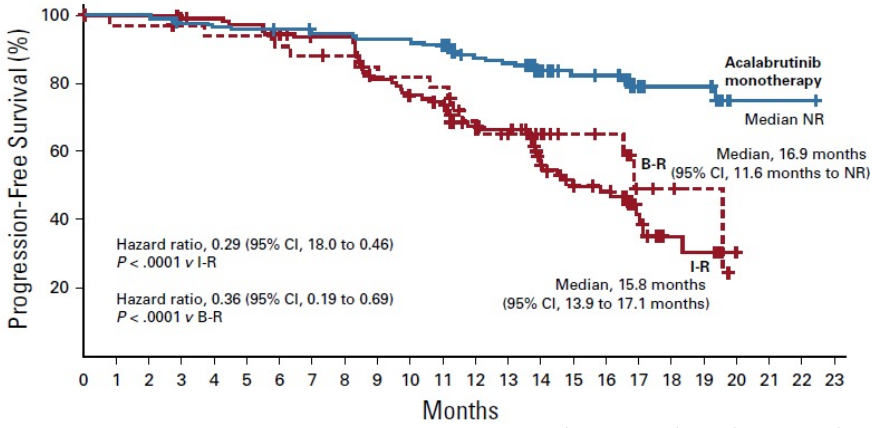
Acalabrutinib: ASCEND trial



N° of prior therapies: 1 (1-8)
IGHV UM 78%
Del17 16%
TP53 mut 24%

Median follow-up: 16.1 months
ORR 81% vs 75%
Median PFS: NR vs 16 months

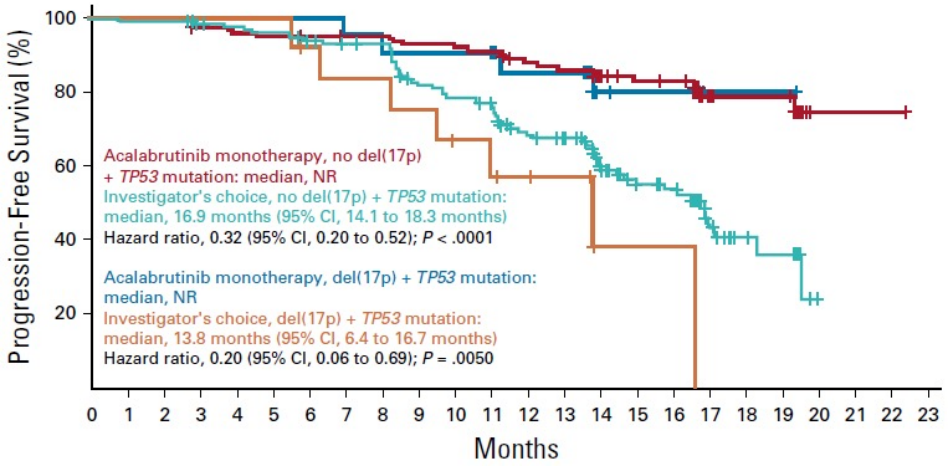


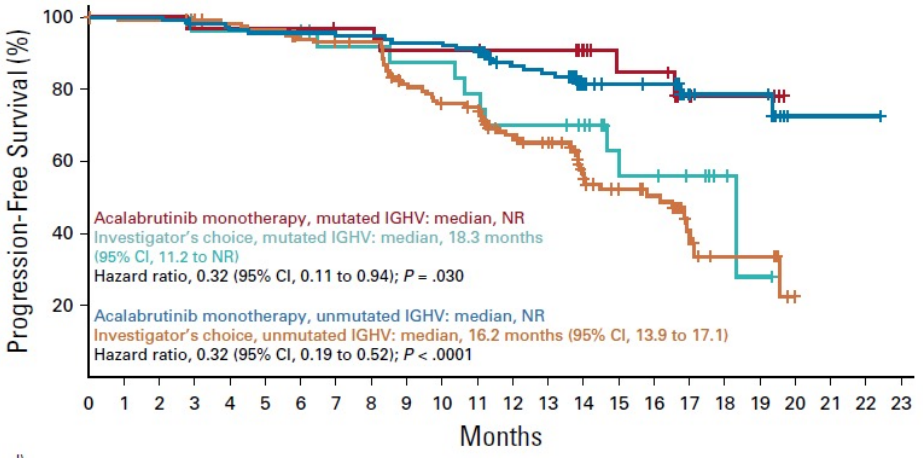


Ghia P et al. J Clin Oncol 2020

Acalabrutinib: ASCEND trial

Acalabrutinib vs investigator choice
PFS by del(17p) plus TP53 mutation status and IGHV mutation status





No del17/TP53 mut: median PFS NR vs 16.9 months

Del17+TP53mut: median PFS NR vs 13.8 months

IGHV M: median PFS NR vs 18.3 months

IGHV UM: median PFS NR vs 16.2 months

Ghia P et al. J Clin Oncol 2020

Acalabrutinib: ASCEND trial

Most common AEs observed in >10% of patients in any treatment group or ≥G3 in >5% in any treatment group

	Acalabrutinib Monotherapy (n = 154)			Idelalisib Plus Rituximab (n = 118)			Bendamustine Plus Rituximab (n = 35)		
AE	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Entire study									
All	68 (44)	48 (31)	22 (14)	11 (9)	59 (50)	42 (36)	11 (31)	8 (23)	7 (20)
Neutropenia	6 (4)	14 (9)	10 (6)	6 (5)	24 (20)	23 (19)	1 (3)	5 (14)	6 (17)
Diarrhea	26 (17)	2 (1)	0	27 (23)	26 (22)	2 (2)	5 (14)	0	0
Pyrexia	18 (12)	1 (1)	0	13 (11)	7 (6)	1 (1)	5 (14)	1 (3)	0
Cough	23 (15)	0	0	17 (14)	1 (1)	0	2 (6)	0	0
Upper respiratory tract infection	19 (12)	3 (2)	0	13 (11)	4 (3)	0	3 (9)	1 (3)	0
Headache	33 (21)	1 (1)	0	7 (6)	0	0	0	0	0
Thrombocytopenia	11 (7)	2 (1)	4 (3)	7 (6)	7 (6)	2 (2)	4 (11)	0	1 (3)
Anemia	5 (3)	16 (10)	2 (1)	2 (2)	8 (7)	0	1 (3)	3 (9)	0
Fatigue	13 (8)	2 (1)	0	10 (8)	0	0	7 (20)	1 (3)	0
Nausea	11 (7)	0	0	14 (12)	1 (1)	0	7 (20)	0	0
Pneumonia	8 (5)	8 (5)	0	4 (3)	10 (8)	0	1 (3)	1 (3)	0
Rash	10 (6)	0	0	12 (10)	4 (3)	0	2 (6)	0	0
Constipation	10 (6)	0	0	9 (8)	0	0	3 (9)	2 (6)	0
Respiratory tract infection	14 (9)	1 (1)	1 (1)	7 (6)	1 (1)	0	0	0	0
ALT increased	1 (1)	2 (1)	0	4 (3)	9 (8)	1 (1)	2 (6)	1 (3)	0
Infusion-related reaction	0	0	0	7 (6)	2 (2)	0	7 (20)	1 (3)	0
AST increased	2 (1)	1 (1)	0	5 (4)	6 (5)	0	1 (3)	1 (3)	0
Neutrophil count decreased	1 (1)	1 (1)	1 (1)	0	3 (3)	6 (5)	0	0	1 (3)
Transaminases increased	0	0	0	1 (1)	6 (5)	0	0	0	0

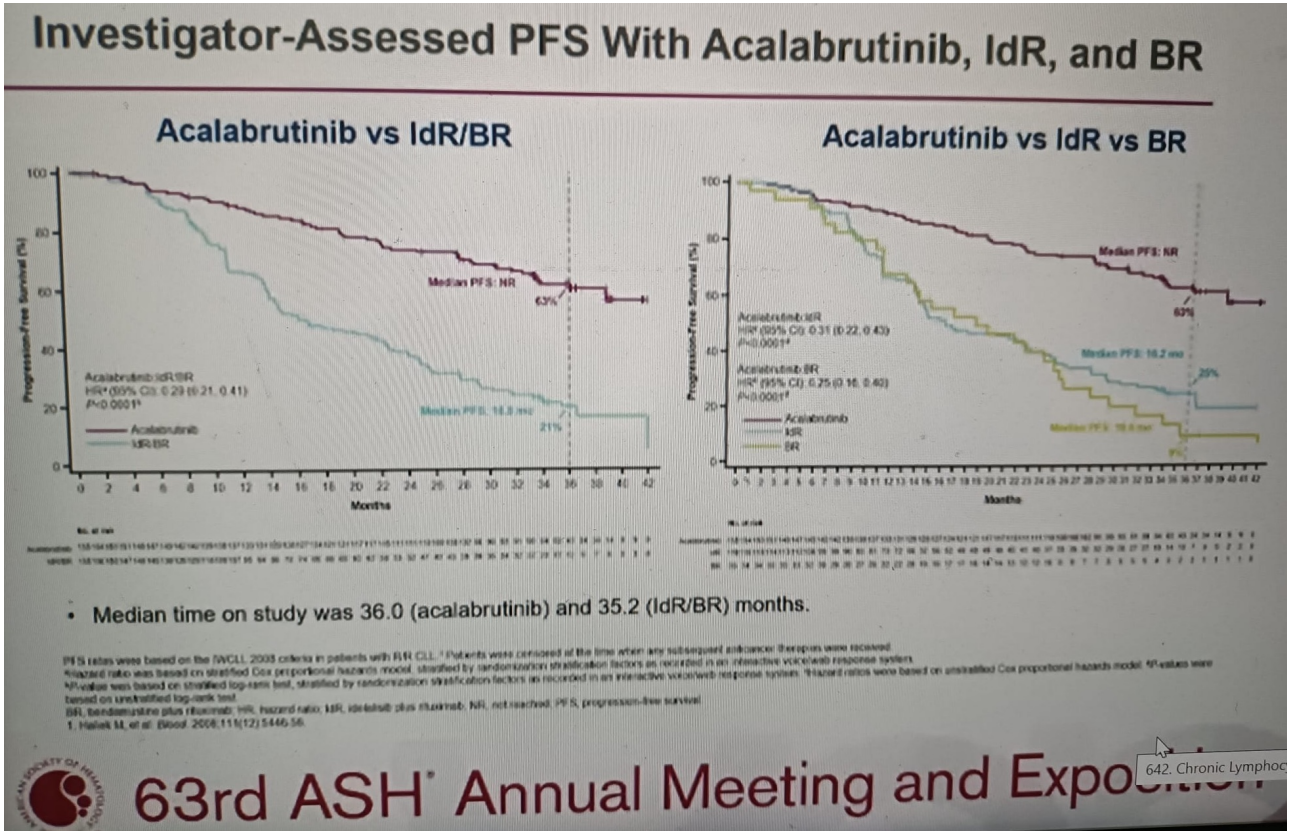
AEs leading to dose reduction
(Acala vs R-idela vs R-benda)
3% vs 24% vs 17%

AEs of clinical interest
(acala vs investigator choice)

Bleeding (any grade)
26% vs 7%
Major hemorrhage (G3-G4)
1% vs 2%
Atrial fibrillation (any grade)
5% vs 3%

Ghia P et al. J Clin Oncol 2020

ASCEND trial: 3 years update (ASH 2021)



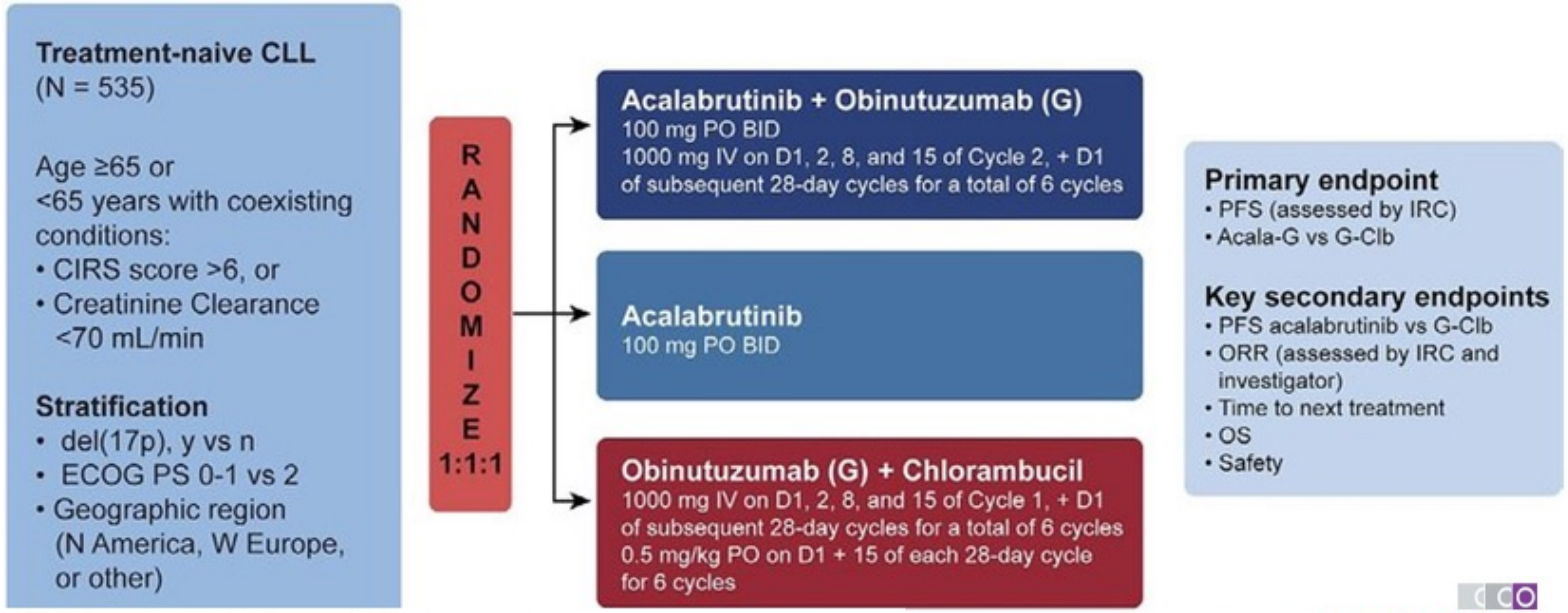
<u>Acalabrutinib 36-month PFS rate: 66%</u>

Median PFS: NR vs 16 months

Median PFS in del17 pts: NR vs 13.8 months

Wojchiek J ASH 2021 oral presentation

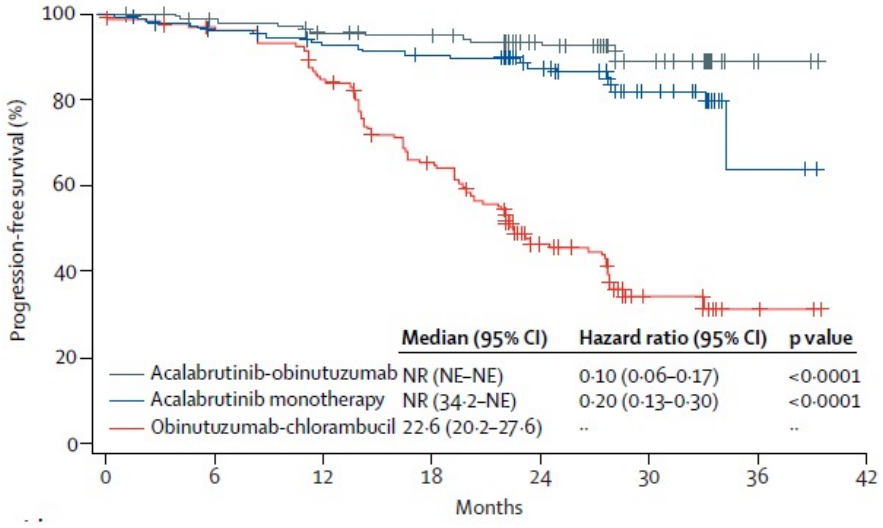
Acalabrutinib: ELEVATE-TN trial

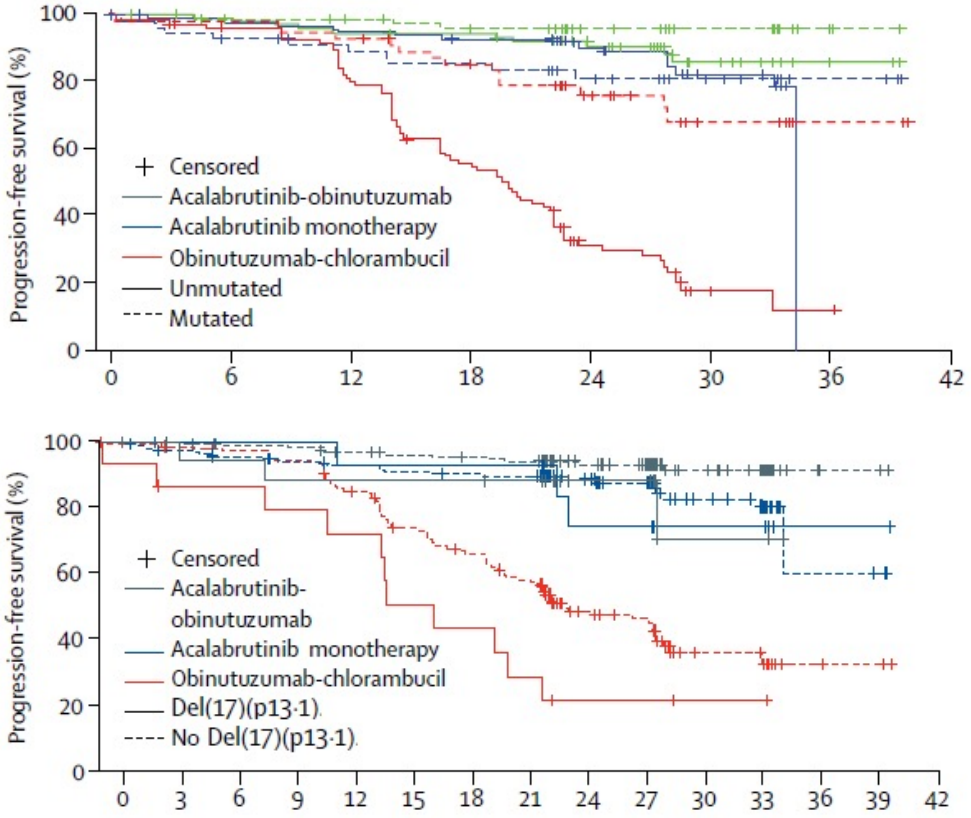


Slide credit: clinicaloptions.com

Sharman JP et al. Lancet 2020

Acalabrutinib: ELEVATE-TN trial





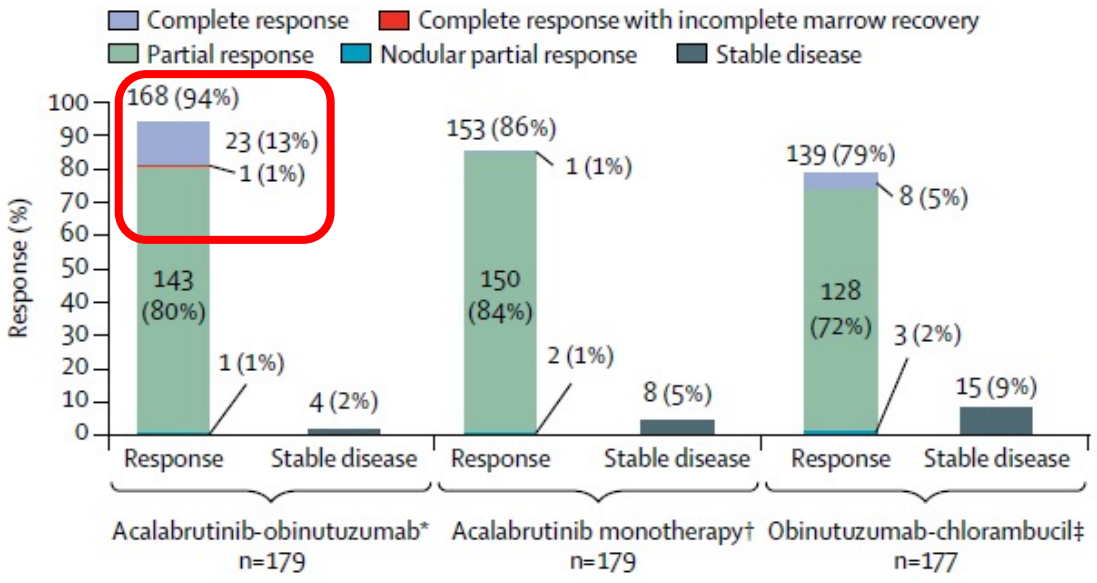
Median follow-up: 28.3 months

Median PFS:
NR vs NR vs 22.6 m

Estimated PFS @24 m:
93% vs 87% vs 47%

Sharman JP et al. Lancet 2020

Acalabrutinib: ELEVATE-TN trial



ORR: Acala + G 94%
Acala 86%
Chl + G 79%

Sharman JP et al. Lancet 2020

Acalabrutinib: ELEVATE-RR trial

Phase III ELEVATE-RR Trial of Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL

- A randomized, multicenter, open-label, noninferiority phase III trial

Patients del(17p) or del11q CLL with active disease; ≥ 1 previous line of tx (no prior exposure to a BCL-2 inhibitor or B-cell receptor signaling inhibitor); ECOG PS 0-2 (N = 533)

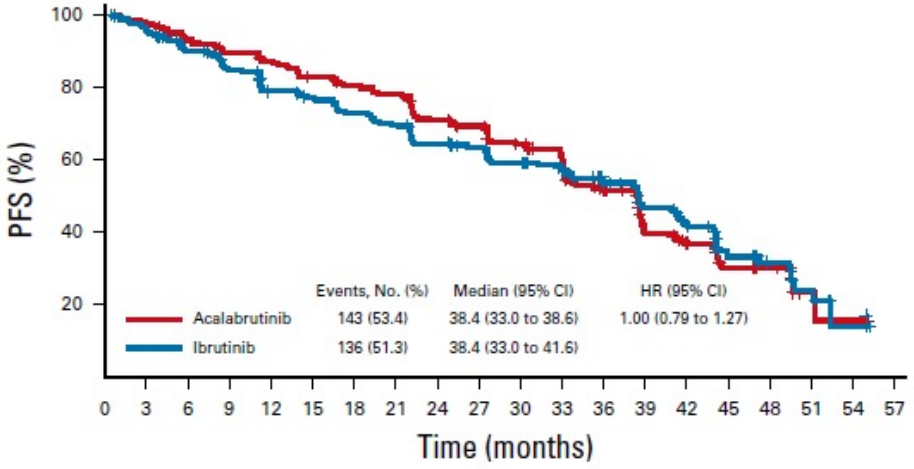
- Primary endpoint: PFS
- Secondary endpoints: OS; incidence of tx-emergent AEs, atrial fibrillation; Richter's transformation

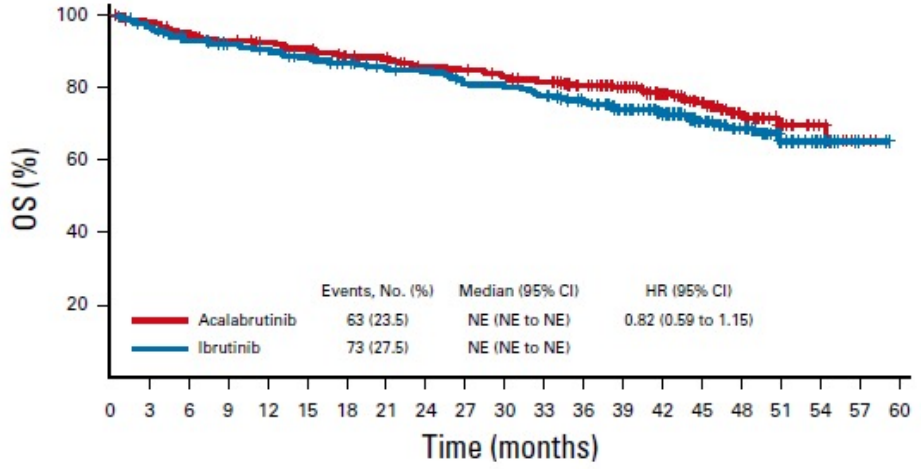
Slide credit: clinicaloptions.com

Characteristic	Acalabrutinib (n = 268)	Ibrutinib (n = 265)
No. of prior therapies		
Median (range)	2 (1-9)	2 (1-12)
1-3	234 (87.3)	237 (89.4)
4 or more	33 (12.3)	28 (10.6)
Chromosome 17p13.1 deletion	121 (45.1)	120 (45.3)
Chromosome 11q22.3 deletion	167 (62.3)	175 (66.0)
Complex karyotype[a]	124 (46.3)	125 (47.2)
TP53 mutational status		
Mutated	100 (37.3)	112 (42.3)
Unmutated	167 (62.3)	153 (57.7)
IGHV mutational status		
Mutated	44 (16.4)	28 (10.6)
Unmutated	220 (82.1)	237 (89.4)

Byrd JC et al. J Clin Oncol 2021

Acalabrutinib: ELEVATE-RR trial





Median PFS 38.4 months in both arms

ORR:
Ibrutinib 77%
Acalabrutinib 81%

Byrd JC et al. J Clin Oncol 2021

Acalabrutinib: ELEVATE-RR trial

Event	Acalabrutinib (n = 266) Any Grade	Acalabrutinib (n = 266) Grade ≥ 3	Ibrutinib (n = 263) Any Grade	Ibrutinib (n = 263) Grade ≥ 3
Diarrhea[a,b]	92 (34.6)	3 (1.1)	**121 (46.0)**	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	**4 (1.5)**	53 (20.2)	0
Cough[a]	**77 (28.9)**	2 (0.8)	56 (21.3)	1 (0.4)
Upper respiratory tract infection	71 (26.7)	5 (1.9)	65 (24.7)	1 (0.4)
Pyrexia	62 (23.3)	8 (3.0)	50 (19.0)	2 (0.8)
Anemia	58 (21.8)	31 (11.7)	49 (18.6)	34 (12.9)
Neutropenia	56 (21.1)	52 (19.5)	65 (24.7)	60 (22.8)
Fatigue[b]	54 (20.3)	**9 (3.4)**	44 (16.7)	0
Arthralgia[a]	42 (15.8)	0	**60 (22.8)**	2 (0.8)
Hypertension[a,b]	23 (8.6)	11 (4.1)	**60 (22.8)**	**23 (8.7)**
Nausea	47 (17.7)	0	49 (18.6)	1 (0.4)
Pneumonia	47 (17.7)	28 (10.5)	43 (16.3)	23 (8.7)
Thrombocytopenia	40 (15.0)	26 (9.8)	35 (13.3)	18 (6.8)
Dyspnea	37 (13.9)	6 (2.3)	23 (8.7)	1 (0.4)
Contusion[a]	31 (11.7)	0	**48 (18.3)**	1 (0.4)
Vomiting	28 (10.5)	1 (0.4)	36 (13.7)	3 (1.1)
Peripheral edema	26 (9.8)	0	38 (14.4)	1 (0.4)
Rash	26 (9.8)	2 (0.8)	33 (12.5)	0
Myalgia	25 (9.4)	2 (0.8)	27 (10.3)	1 (0.4)
Atrial fibrillation[a]	24 (9.0)	12 (4.5)	**41 (15.6)**	9 (3.4)
Urinary tract infection[a]	22 (8.3)	3 (1.1)	**36 (13.7)**	6 (2.3)
Back pain[a]	20 (7.5)	0	**34 (12.9)**	2 (0.8)
Epistaxis	19 (7.1)	1 (0.4)	28 (10.6)	1 (0.4)

Most common AEs observed in >10% (any grade) or ≥5% (G3 or higher) of patients in either treatment arm

Discontinuation because of AEs:
Acalabrutinib 14.7%
Ibrutinib 21.3%

Treatment discontinuation because of cardiovascular events was 5-fold higher with ibrutinib compared to acalabrutinib

Byrd JC et al. J Clin Oncol 2021

Acalabrutinib in CLL patients who are intolerant to ibrutinib

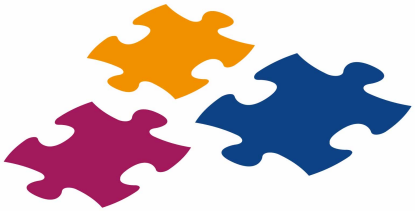
33 CLL patients
Median duration of prior ibrutinib treatment: 11.6 months
Median time from ibrutinib discontinuation to acalabrutinib start 47 days
Median f.up 19 months

23 patients remained on acalabrutinib
10 discontinued (progressive disease → 5 pts; AEs → 3 pts)

Of 61 ibrutinib-related AEs associated with intolerance:
72% did not recur
13% recurred at a lower grade with acalabrutinib

ORR: 76%

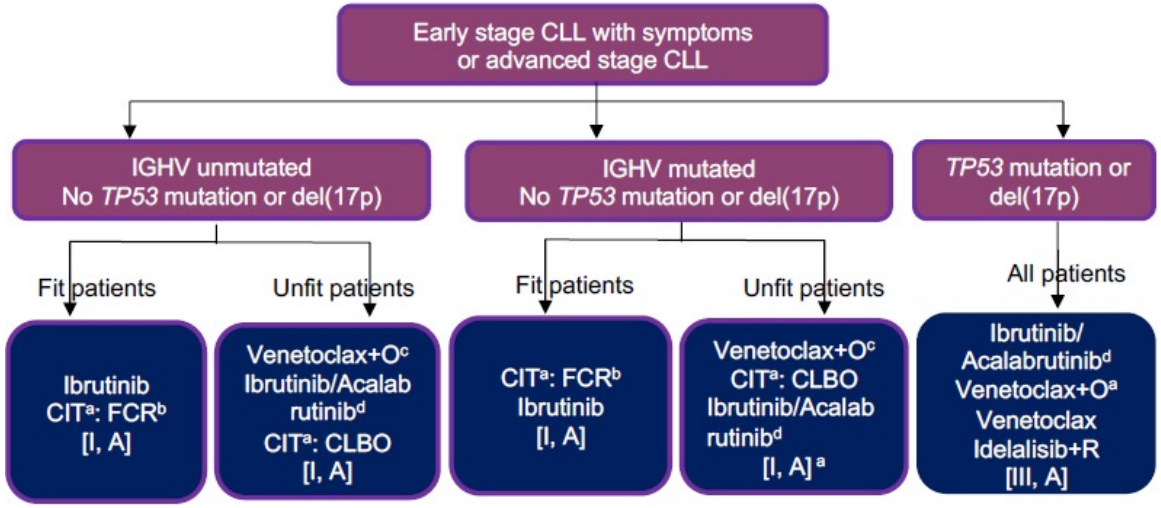
Among 25 responders: median PFS not reached; 1-year PFS 83.4%



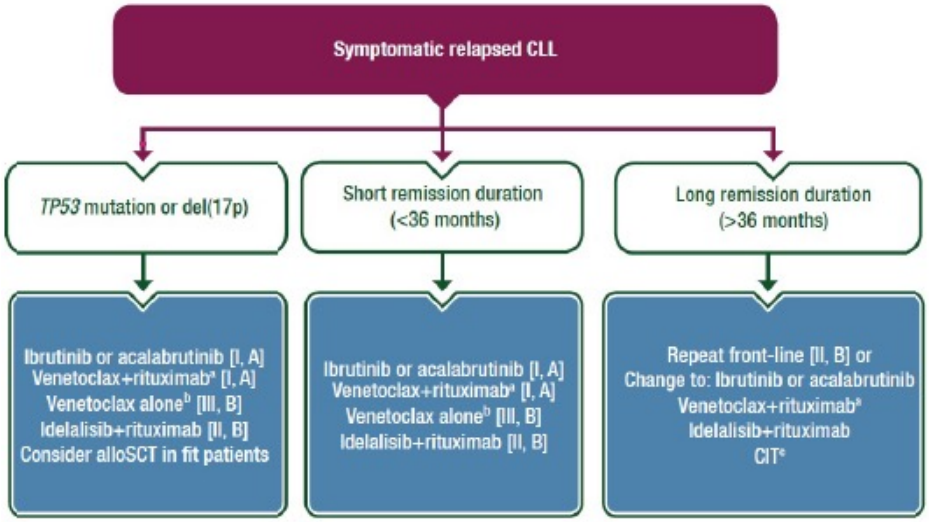
Awan FT et al. Blood Adv 2019

ESMO clinical practice guidelines 2021

Treatment-naive



Relapsed/refractory



CIT: chemoimmunotherapy; Obin: obinutuzumab ; CLBO: Chlorambucil plus Obinutuzumab; R: rituximab; [a] Chemoimmunotherapy as alternative treatment only if no TP53 dysfunction and reasons against continuous treatment with ibrutinib or non-availability; [b] BR might be considered alternatively in patients above the age of 65 years; [c] If available; [d] if approved and available.

Eichhorst B et al. Ann Oncol 2021

Zanubrutinib (BGB-3111)

- **2nd generation covalent (irreversible) BTKi**

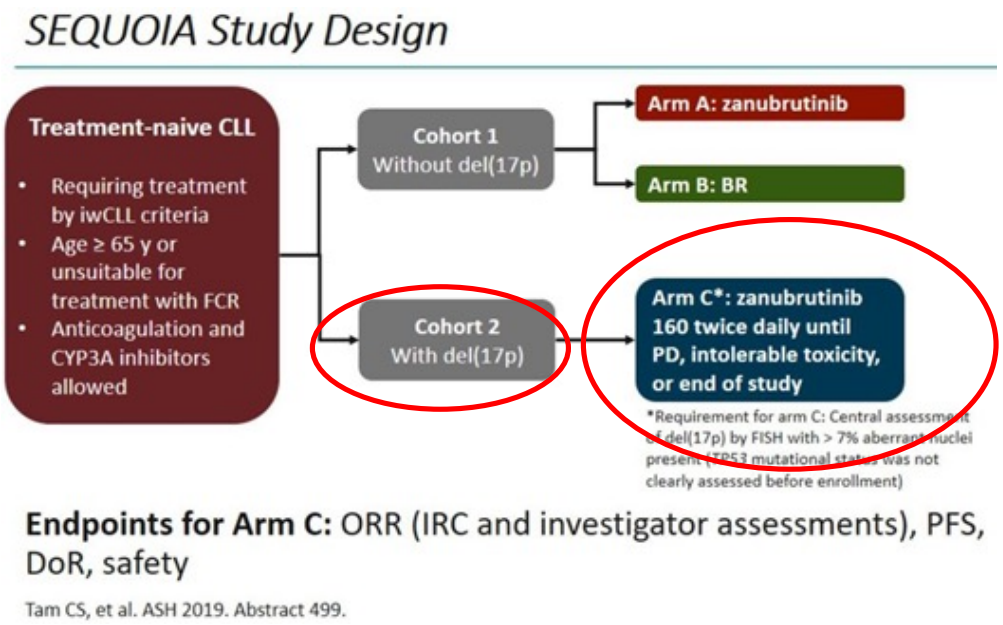
- Short half-life, but longer than acalabrutinib (4 hours vs 1 hour)
  - → **160 mg twice daily administration**
  - → **Blocks newly synthesized BTK as well as preexisting BTK protein**

- **Absence of irreversible targeting to EGFR and C-terminal Src Kinase** (does have TEC inhibition)
- Allowed coadministration with azole antifungals at a reduced dose, **proton pump inhibitors and acid reducing agents**)

→ **Less toxic effects**
→ **Blockade of BTK resynthesis**
→ **Favorable drug-drug interaction profile**

Zanubrutinib: SEQUOIA trial

Open-label, multi center, randomized phase III study

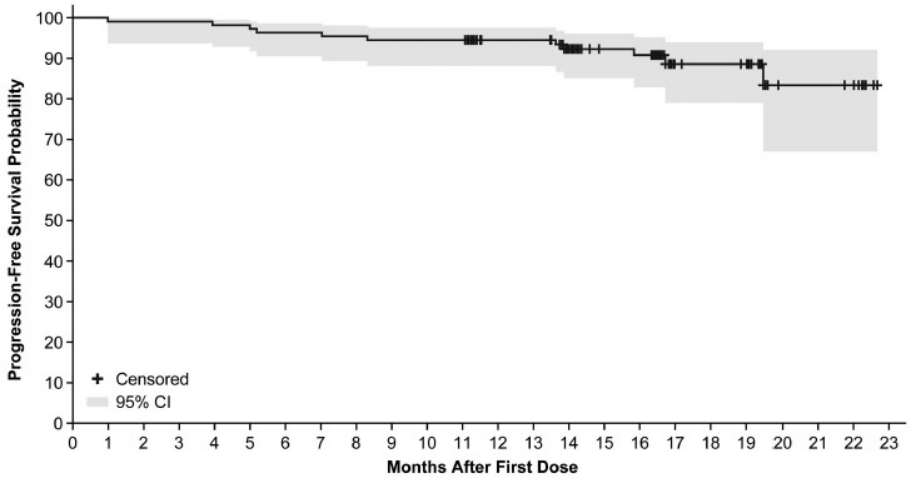


Endpoints for Arm C: ORR (IRC and investigator assessments), PFS, DoR, safety

Tam CS, et al. ASH 2019. Abstract 499.

<u>Arm C (n= 109)</u>
TN CLL/SLL with del(17p)

ORR 94.5%
Estimated PFS @18 months: 88.6%



Tam CS et al. Haematologica 2021

Zanubrutinib: SEQUOIA trial

Most common adverse events regardless of causality. Adverse events of any grade occurring in ≥ 5% of patients and all grade ≥3 adverse events occurring in ≥2% of patients are shown.

Term	Any Grade	Grade 1/2	Grade 3 n (%)	Grade 4	Grade 5
Patients with at least one AE	106 (97.2)	53 (48.6)	44 (40.4)	7 (6.4)	2 (1.8)
Hematologic AE					
Neutropenia	13 (11.9)	3 (2.8)	7 (6.4)	3 (2.8)	0 (0)
Neutrophil count decreased	6 (5.5)	2 (1.8)	1 (0.9)	3 (2.8)	0 (0)
Nonhematologic AE					
Contusion	22 (20.2)	22 (20.1)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	21 (19.3)	21 (19.3)	0 (0)	0 (0)	0 (0)
Diarrhea	18 (16.5)	17 (15.6)	1 (0.9)	0 (0)	0 (0)
Nausea	16 (14.7)	16 (14.7)	0 (0)	0 (0)	0 (0)
Constipation	15 (13.8)	15 (13.8)	0 (0)	0 (0)	0 (0)
Rash	15 (13.8)	15 (13.8)	0 (0)	0 (0)	0 (0)
Back pain	14 (12.8)	13 (11.9)	1 (0.9)	0 (0)	0 (0)
Cough	13 (11.9)	13 (11.9)	0 (0)	0 (0)	0 (0)
Arthralgia	12 (11.0)	12 (11.0)	0 (0)	0 (0)	0 (0)
Fatigue	11 (10.1)	10 (9.2)	1 (0.9)	0 (0)	0 (0)
Dyspepsia	10 (9.2)	10 (9.2)	0 (0)	0 (0)	0 (0)
Headache	9 (8.3)	8 (7.3)	1 (0.9)	0 (0)	0 (0)
Pneumonia	9 (8.3)	5 (4.6)	3 (2.8)	0 (0)	1 (0.9)
Abdominal pain	8 (7.3)	8 (7.3)	0 (0)	0 (0)	0 (0)
Dyspnea	8 (7.3)	8 (7.3)	0 (0)	0 (0)	0 (0)
Epistaxis	8 (7.3)	7 (6.4)	1 (0.9)	0 (0)	0 (0)
Hematuria	8 (7.3)	6 (5.5)	2 (1.8)	0 (0)	0 (0)
Nasopharyngitis	8 (7.3)	8 (7.3)	0 (0)	0 (0)	0 (0)
Pruritus	8 (7.3)	8 (7.3)	0 (0)	0 (0)	0 (0)
Pyrexia	8 (7.3)	7 (6.4)	1 (0.9)	0 (0)	0 (0)
Hypertension	7 (6.4)	5 (4.6)	2 (1.8)	0 (0)	0 (0)
Hematoma	6 (5.5)	6 (5.5)	0 (0)	0 (0)	0 (0)
Musculoskeletal pain	6 (5.5)	5 (4.6)	1 (0.9)	0 (0)	0 (0)

<u>AEs of clinical interest:</u>

Atrial fibrillation = 2.4%

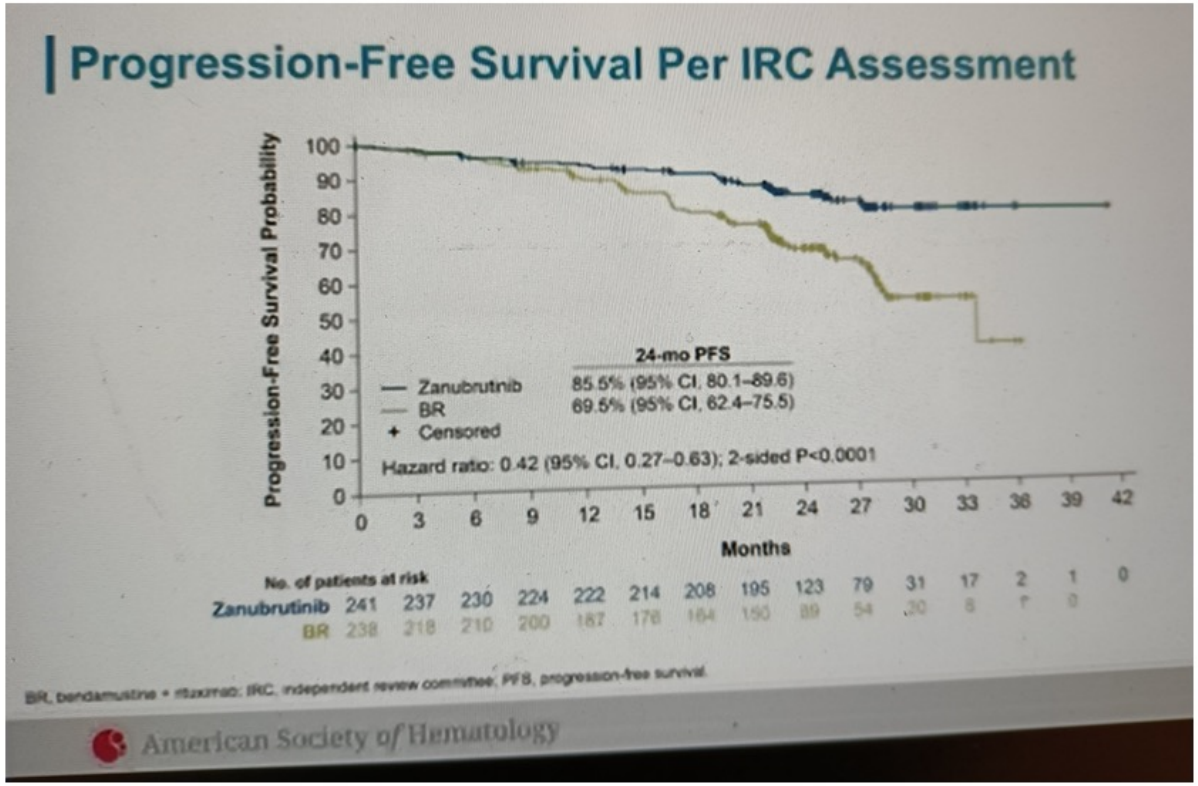
Bleeding (any type, any grade) = 47.7%

Major hemorrhage (G≥3) = 5.4%

[Antiplatelet or anticoagulant (including warfarin): 43% of pts]

Tam CS et al. Haematologica 2021

Zanubrutinib: SEQUOIA trial (ASH 2021)



<u>24-months PFS:</u>
85.5% vs 69.5%

Tam CS et al. Haematologica 2021

Zanubrutinib: ALPINE trial

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

Key Exclusion Criteria
- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R 1:1

Arm A
Zanubrutinib 160 mg BID

Arm B
Ibrutinib 420 mg QD

Stratification Factors
- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

Pre-planned interim analysis scheduled 12 months after the first 415/652 patients were enrolled

Hillmen P. et al EHA 2021 LB1900

Zanubrutinib: ALPINE trial

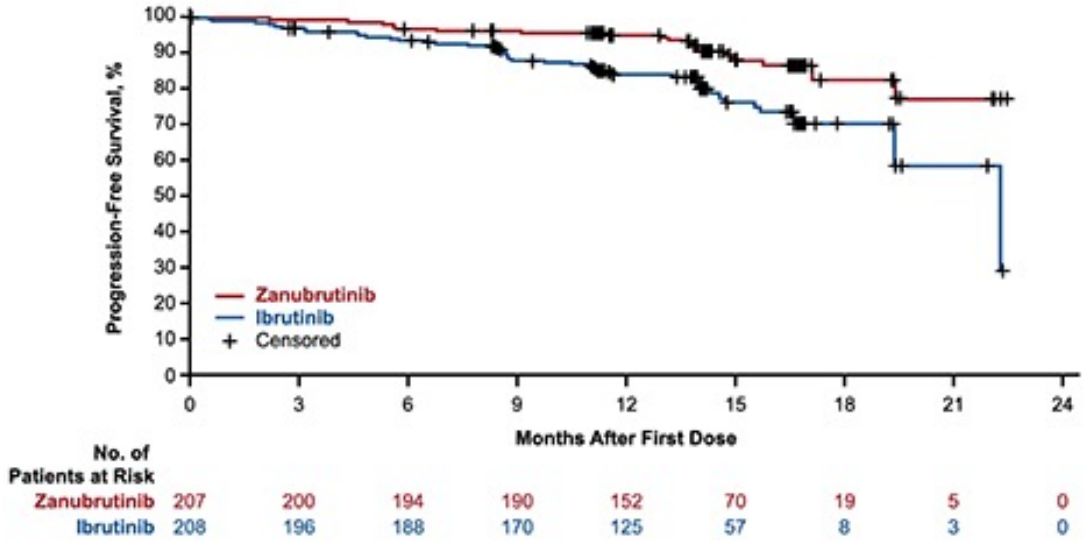
Median follow-up: 15 months

Zanubrutinib vs ibrutinib:

Efficacy

ORR 78.3% vs 62.5%

12-mo PFS: 94.9% vs 84.0%



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.

Safety

Atrial fibrillation/flutter: 2.5% vs 10.1%

Major bleeding: 2.9% vs 3.9%

Neutropenia 28.4% vs 21.7%

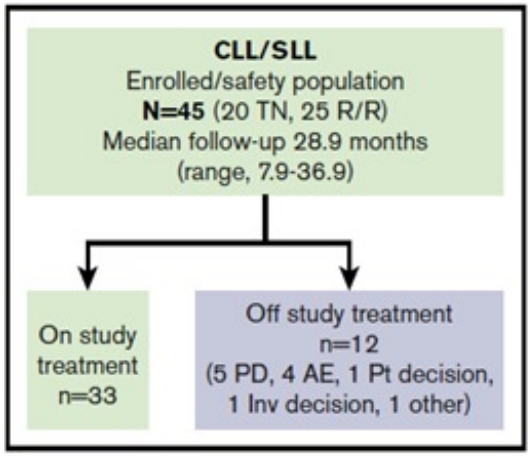
Grade ≥3 infections 12.7% vs 17.9%

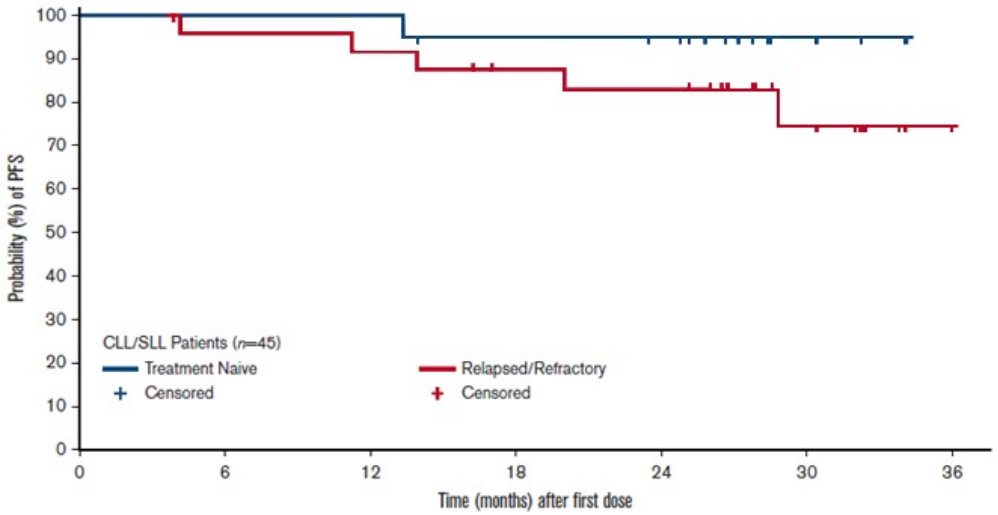
Adverse events leading to discontinuation 7.8% vs 13.0%

Hillmen P. et al EHA 2021 abstract LB1900

Phase 1 trial: zanubrutinib + obinotuzumab

Zanubrutinib plus obinotuzumab in TN or R/R CLL & TN follicular lymphoma



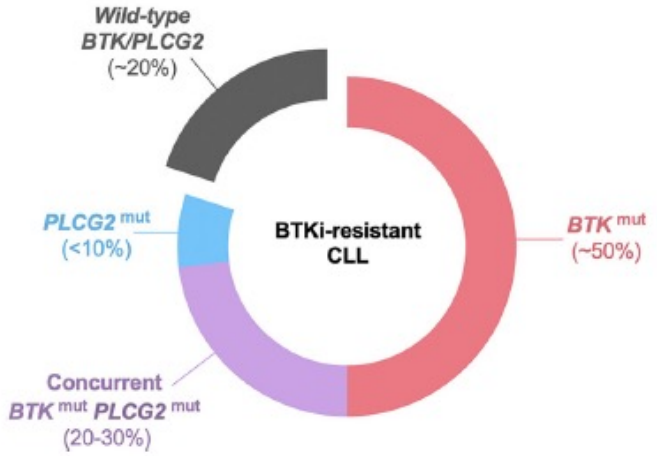


ORR 100% (30% CR) for TN patients
92% (28% CR) for R/R patients

Tam CS et al. Blood Adv 2020

3rd generation non-covalent BTKi

	Pirtobrutinib (LOXO-305)	MK-1026
IC_{50}*	3.15 nM (BTK WT) 1.42 nM (BTK C481)	0.85 nM (BTK WT) 0.39 nM (BTK C481)
Biochemical IC_{50} (Selectivity)*	BTK C481 1.42nM (1x) ITK 103nM (3521x) EGFR >1,000nM (>700x) TEC 1,234nM (869x)	BTK C481 0.39nM (1x) ITK >10,000nM (>10,000x) TEC 5.8nM (14.9x) LYN 19nM (48.7x) SYK, not specified MEK1/ERK, indirect
Clinical trials in CLL and B cell malignancies	Phase 1, 2	Phase 1, Phase 2 pending
Comment	Highly selective	Active against *PLCG2* mutation

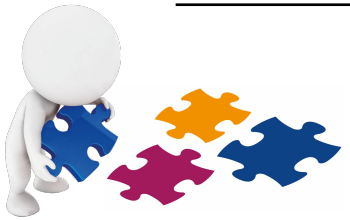


Pirtobrutinib

- Most specific to BTK with little to no effect on other targets
- **Effective in the presence of BTK C481 mutation**

MK-1026

- Inhibits SYK and LYN; indirectly inhibits MEK1/ERK
- **Effective in the presence of BTK C481 mutation and PLCγ2 mutation**



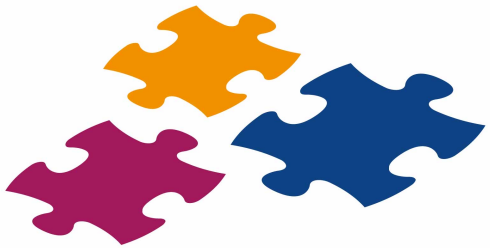
Ahn IE and Brown JR, Front Immunol 2021

Pirtobrutinib in B-cell malignancies: phase 1 / 2 trial

B-cell malignancies: ≥ 2 previous lines of therapy
Protocol amendment → patients with CLL/SLL: ≥ 1 previous line of therapy that included a BTKi

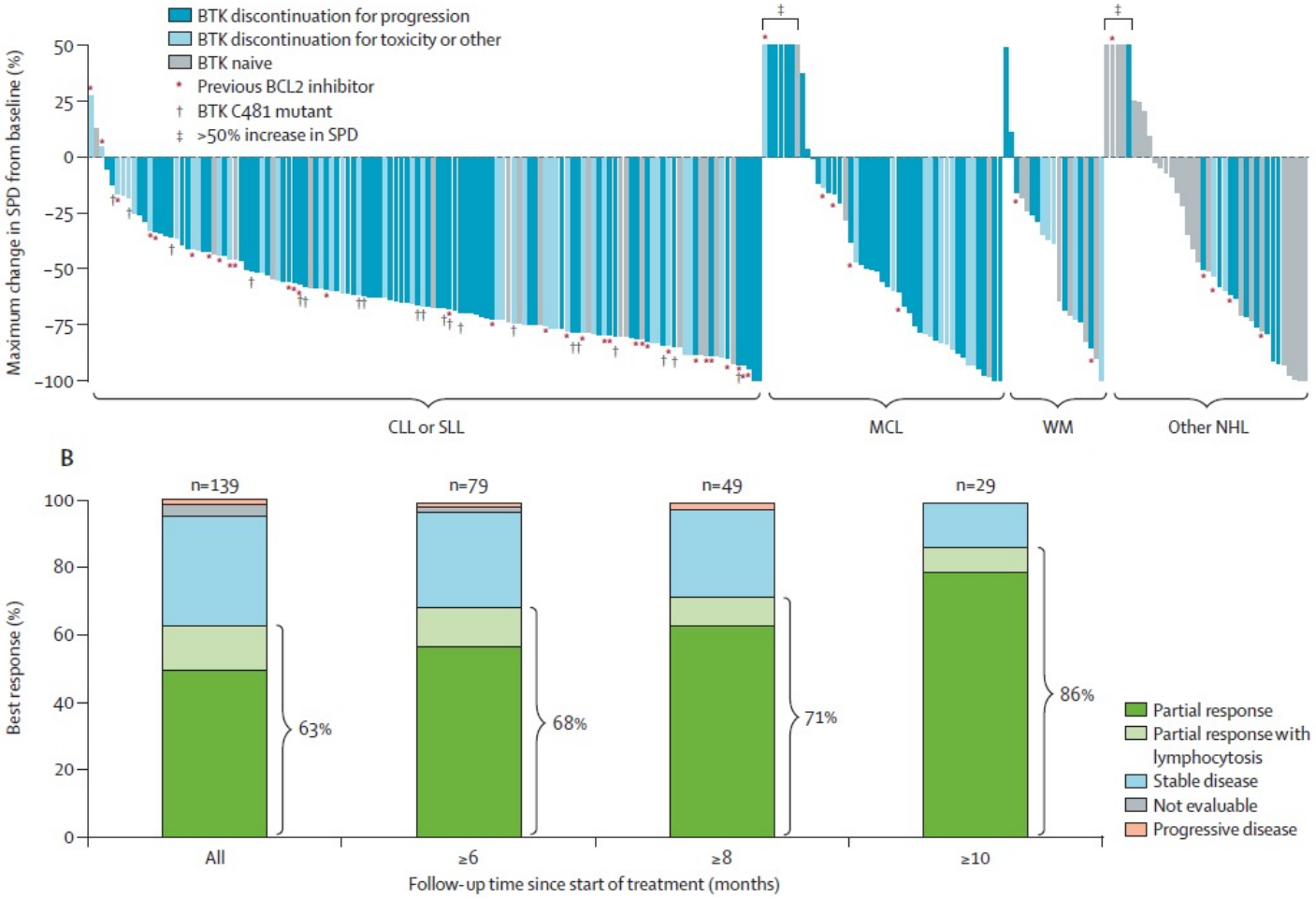
	All (n=323)	CLL or SLL (n=170)
Age, years	68 (62–74)	69 (62–73)
Number of previous lines of systemic therapy		
All patients	3 (2–5)	3 (2–5)
BTK pretreated	3 (2–5)	4 (2–5)
Previous therapy		
BTK inhibitor	245 (76%)	146 (86%)
Chemotherapy	282 (87%)	140 (82%)
Anti-CD20 antibody	302 (94%)	153 (90%)
BCL2 inhibitor	81 (25%)	57 (34%)
PI3K inhibitor	51 (16%)	36 (21%)
Lenalidomide	45 (14%)	14 (8%)
Autologous stem-cell transplant	22 (7%)	0
Allogeneic stem-cell transplant	8 (3%)	3 (2%)
CAR T-cell therapy	22 (7%)	10 (6%)
Reason discontinued any previous BTK inhibitor‡§		
Progressive disease	173 (71%)	98 (67%)
Toxicity or other¶	70 (29%)	48 (33%)

- Pirtobrutinib orally once daily in 28-day cycles
- Seven dose levels explored in the phase 1 cohort (203 patients)
- **<u>200 mg once per day</u>** in the phase 2 cohort (120 CLL patients)



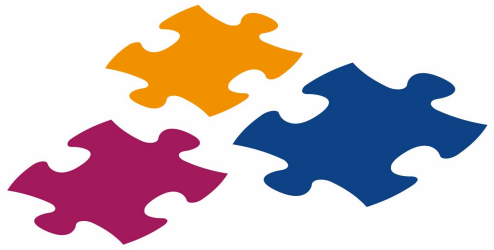
Mato AR et al. Lancet 2021

Pirtobrutinib in B-cell malignancies: phase 1 / 2 trial



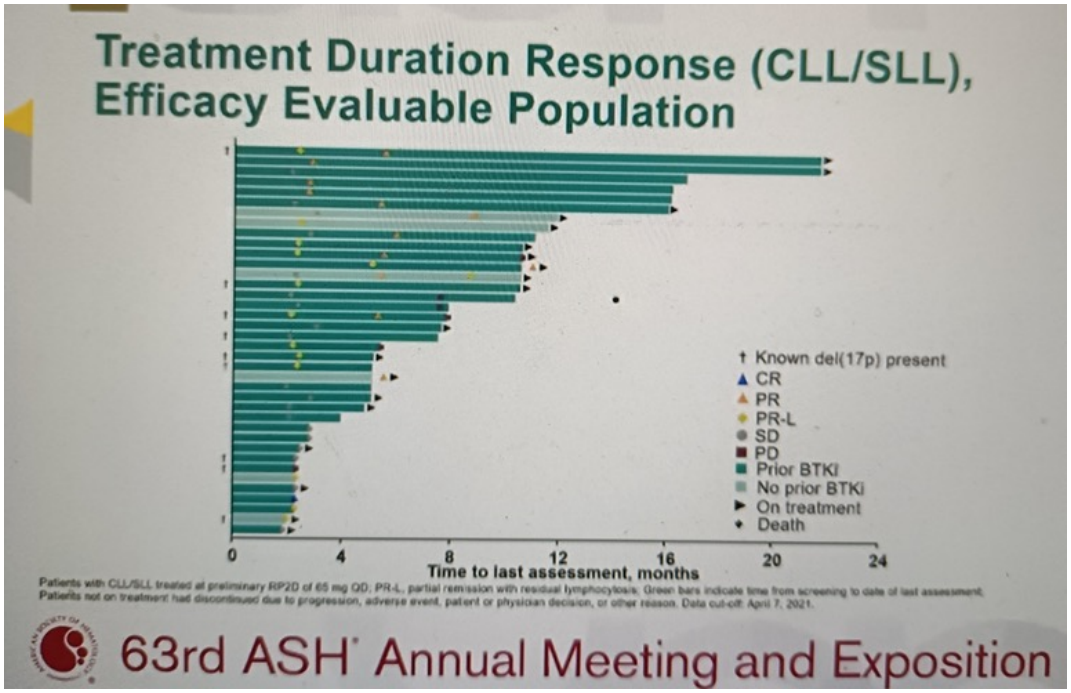
<u>Efficacy in CLL patients (median f.up 6 months)</u>

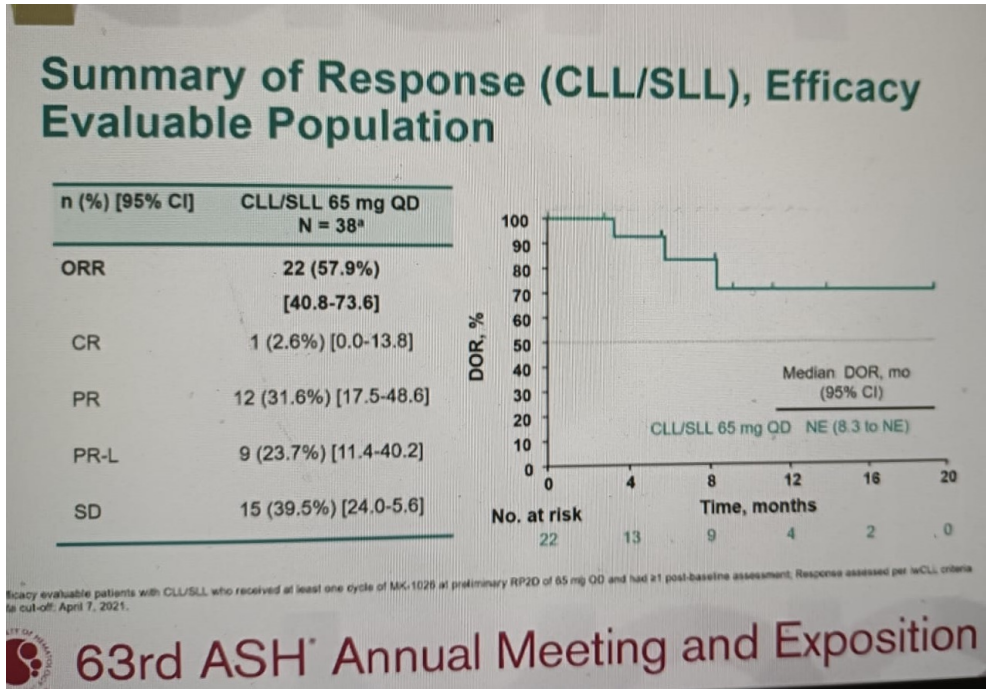
- ORR 63%
- **ORR in BTK-pretreated patients: 62%**
- **ORR was similar in patients with or without BTK C481 mutation**



Mato AR et al. Lancet 2021

MK-1026 in B-Cell Malignancies (ASH 2021)





Phase 2 dose of MK-1026: 65 mg once daily
<u>51 patients with CLL</u>
Median number of prior therapies: 4 (1-18)
<u>84% of patients had prior BTKi therapy</u>
<u>63% had C481s BTK mutation</u>

Median f.up 4,5 months
ORR 57.9%

Woijach J ASH 2021 oral presentation

Conclusions

- Patients with TP53 aberrations have comparable PFS to non-TP53 aberrant patients when treated with BTK inhibitors
- Second generation BTK inhibitors are more specific to BTK with little effect on other targets → improved safety profile
- First data on third generation (non covalent) BTK inhibitors show efficacy against BTK-mutated CLL
- Longer follow-up are needed to determine whether more effective and selective blockade of BTK translates to deeper and more durable response

Grazie per l'attenzione!