Treatment options for a patient with ibrutinib-resistant CLL

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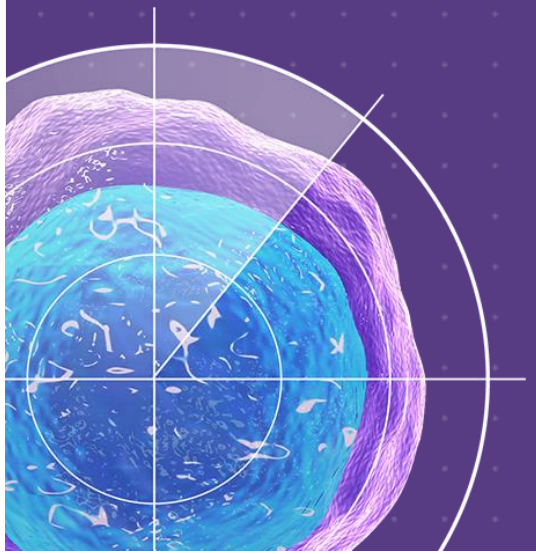

Disclosures

	Research funding	Consultancy
Celgene	√	√
Gilead	√	√
AstraZeneca	√	√
AbbVie	√	√
Roche	√	√
Janssen	√	√
Novartis	√	√
Takeda	√	√
TG Therapeutics		√
Loxo		√
BeiGene		√

Patient case

- 66-year-old male with CLL
- At diagnosis:
  - Lymphocytosis and anemia
  - Bone marrow: 88% CLL cells
  - Rai stage III, symptomatic disease
  - ECOG PS 1
  - Unmutated *IGHV*
  - Impaired renal function
- Treated with venetoclax plus obinutuzumab
  - Relapsed within 30 months
  - Acquired *TP53* mutation

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; *IGHV*, immunoglobulin heavy chain variable region.

Predictive markers for targeted therapies[1–4]

	Ibrutinib		Venetoclax (+ anti-CD20)
	PFS	CR	PFS
Bulky disease (>5 cm)	No	Yes	Yes
Prior therapies (>1)	Yes	Yes	Refractory to BCRi
Del17p/*TP53*^{mut}	Yes	No	Yes
NOTCH1^{mut}	No	No	Yes
Complex karyotype	Yes*	No	Yes†

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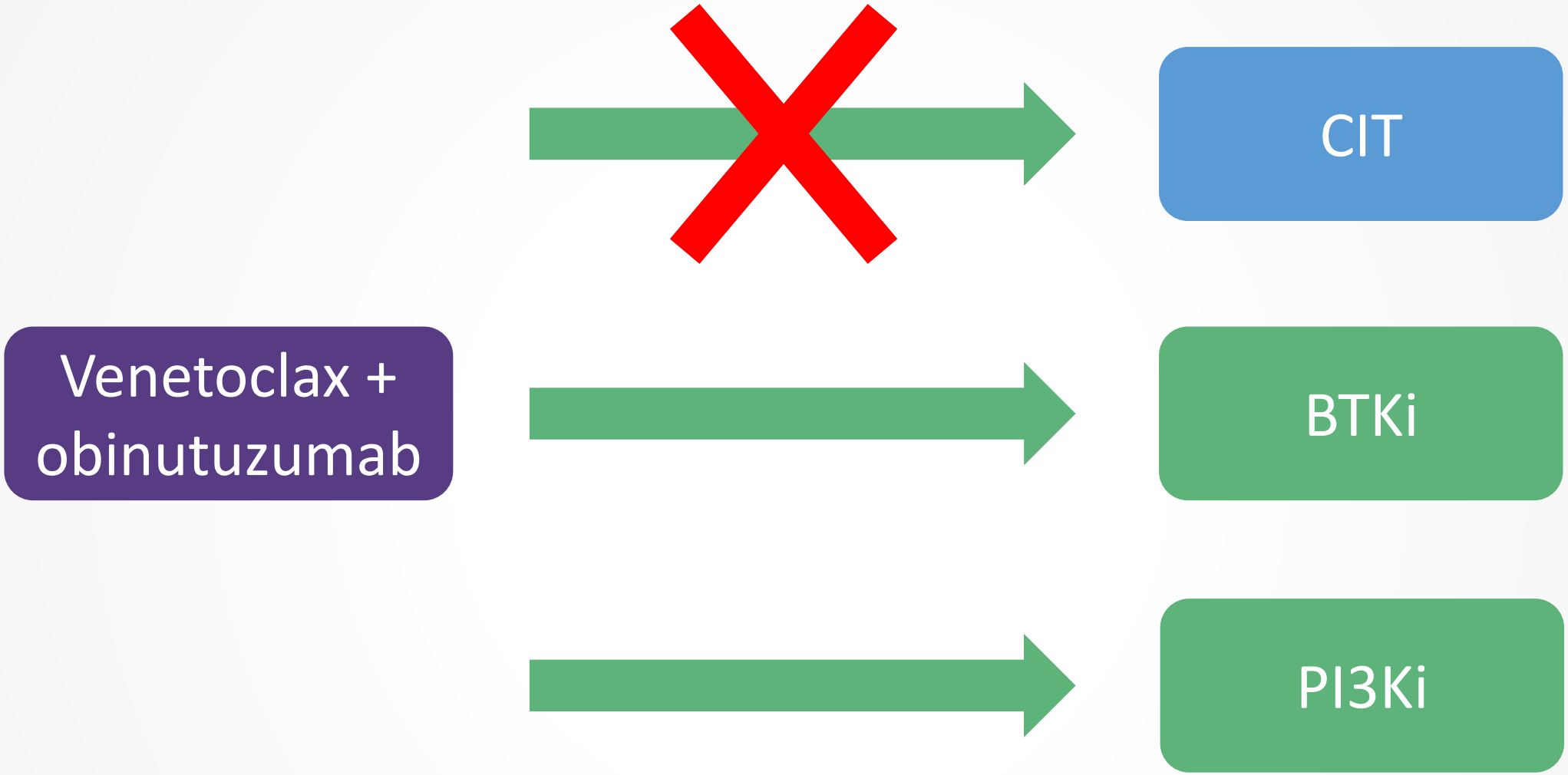
BCRi, B-cell-antigen receptor inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; del17p, chromosome 17p deletion; mut, mutation; PFS, progression-free survival.
*In relapsed/refractory CLL.
†Not with venetoclax plus obinutuzumab.
1. O'Brien SM, et al. *JAMA Oncol.* 2018;4(5):712-716. **2.** O'Brien SM, et al. *Blood.* 2018;131(17):1910-1919. **3.** Roberts AW, et al. *Blood*. 2019;134(2):111-122. **4.** Al Sawaf O, et al. Abstract #S106; 24th EHA Annual Congress. Jun 19, 2019; Amsterdam, NL.



CIT, chemoimmunotherapy; BTKi, Bruton's tyrosine kinase inhibitor; PI3Ki, phosphoinositide 3-kinase inhibitor.

Response to subsequent therapies following venetoclax discontinuation

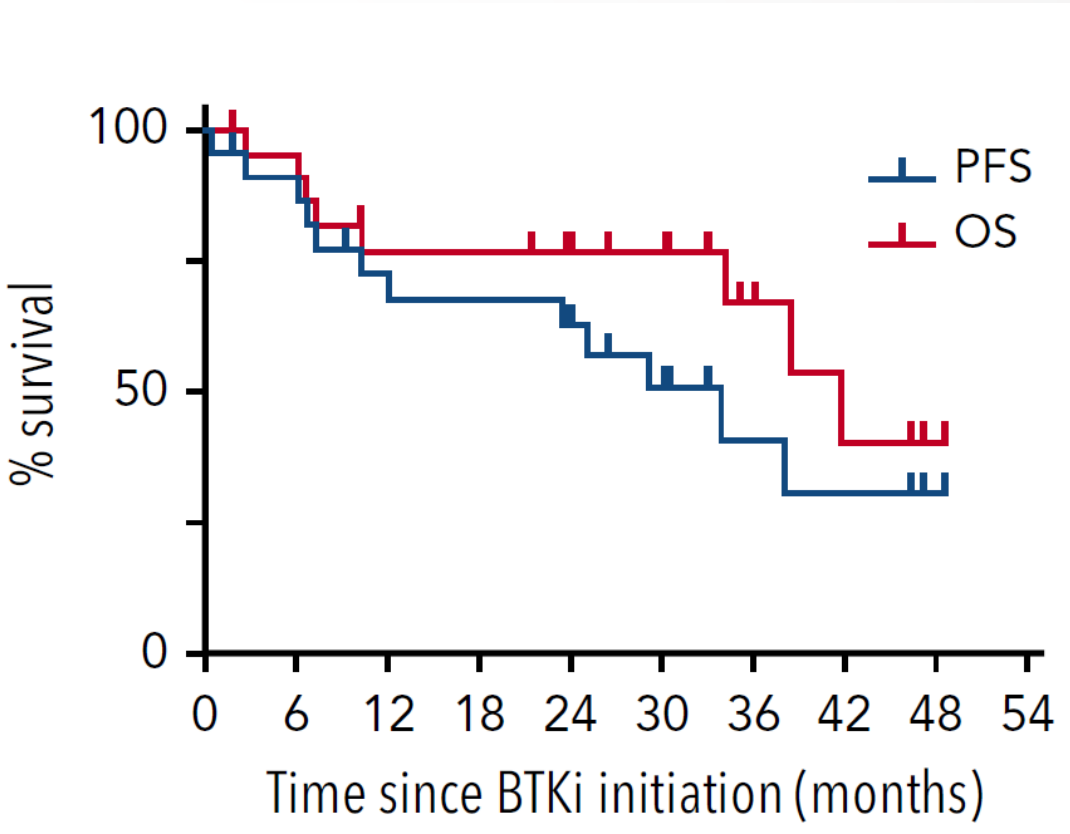
Subsequent therapy	BTKi	BTKi	PI3Ki	CAR-T	Anti-CD20 abs
Agents	Ibrutinib Acalabrutinib	Ibrutinib Acalabrutinib Non-covalent BTKi	Idelalisib Duvelisib	Anti-CD19	Rituximab Obinutuzumab Ofatumumab
Pre-Ven exposure	BTKi-naïve	BTKi-exposed 33% BTKi-intolerant 66% BTKi-resistant	PI3Ki-naïve	BTKi-exposed	
Patient number	44	30	17	18	19
Lines of therapy pre-Ven, median (range)	2 (0–8)	4 (1–11)	4 (1–6)	4 (1–10)	3 (1–9)
ORR, %	83.9	53.4	46.9	66.6	32
CR	9.0	10.0	5.9	33.3	16
PR	56.8	26.7	35.2	33.3	16
PRL	18.1	16.7	5.8	0	0
SD	11.6	23.3	23.7	5.7	32
PD	4.5	23.3	29.4	27.7	37
Median PFS (months)	32	12	5	9	2
Adverse event, %	14.3	8.3	25	—	15.4

abs, antibodies; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; ORR, overall response rate; PFS, progression-free survival; PI3Ki, phosphoinositide 3-kinase inhibitor; PR, partial response; PRL, partial response with lymphocytosis; Ven, venetoclax.

Mato AR, et al. *Clin Cancer Res.* 2020;26:3589-96.

BTK inhibitor therapy after progression on venetoclax

	N = 23*
ORR, n (%)	20 (91)
CR, n	4
PR/PRL, n	16
Median PFS	34 months
Median OS	42 months



BTKi, Bruton's tyrosine kinase inhibitor; CR, compete response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRL, partial response with lymphocytosis.
*21 patients received ibrutinib and two patients received zanubrutinib.
Lin VS, et al. *Blood*. 2020;135(25):2266-2270.

Patient case

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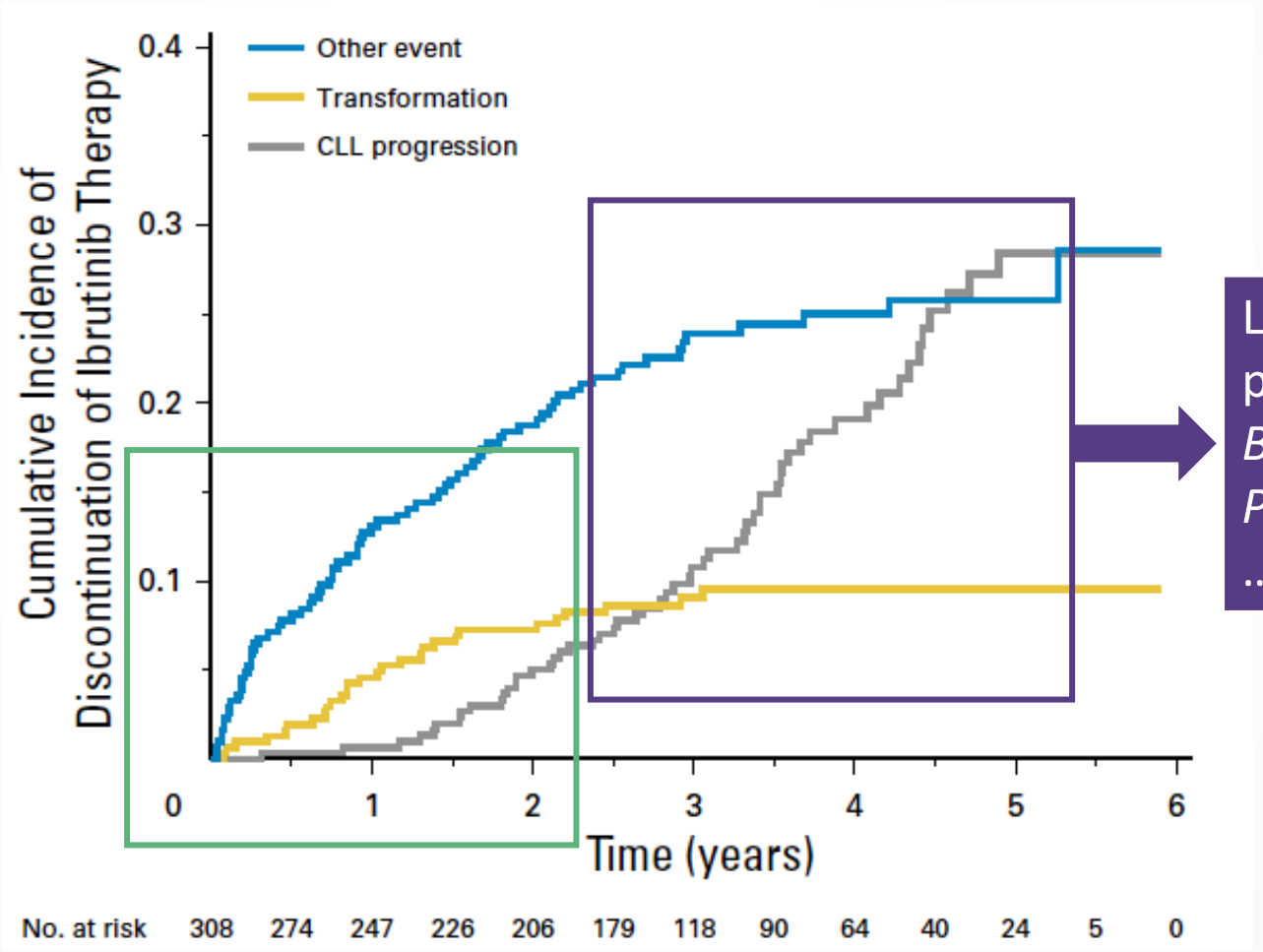
- At diagnosis:
  - Lymphocytosis and anemia
  - Bone marrow: 88% CLL cells
  - Rai stage III, symptomatic disease
  - ECOG PS 1
  - Unmutated *IGHV*
  - Impaired renal function
- Treated with venetoclax plus obinutuzumab
  - Relapsed after 30 months
  - Acquired *TP53* mutation
- **Treated with ibrutinib 420 mg/day**
  - Developed resistance after 20 months of ibrutinib treatment
  - Complex karyotype
  - Still unfit

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; *IGHV*, immunoglobulin heavy chain variable region.

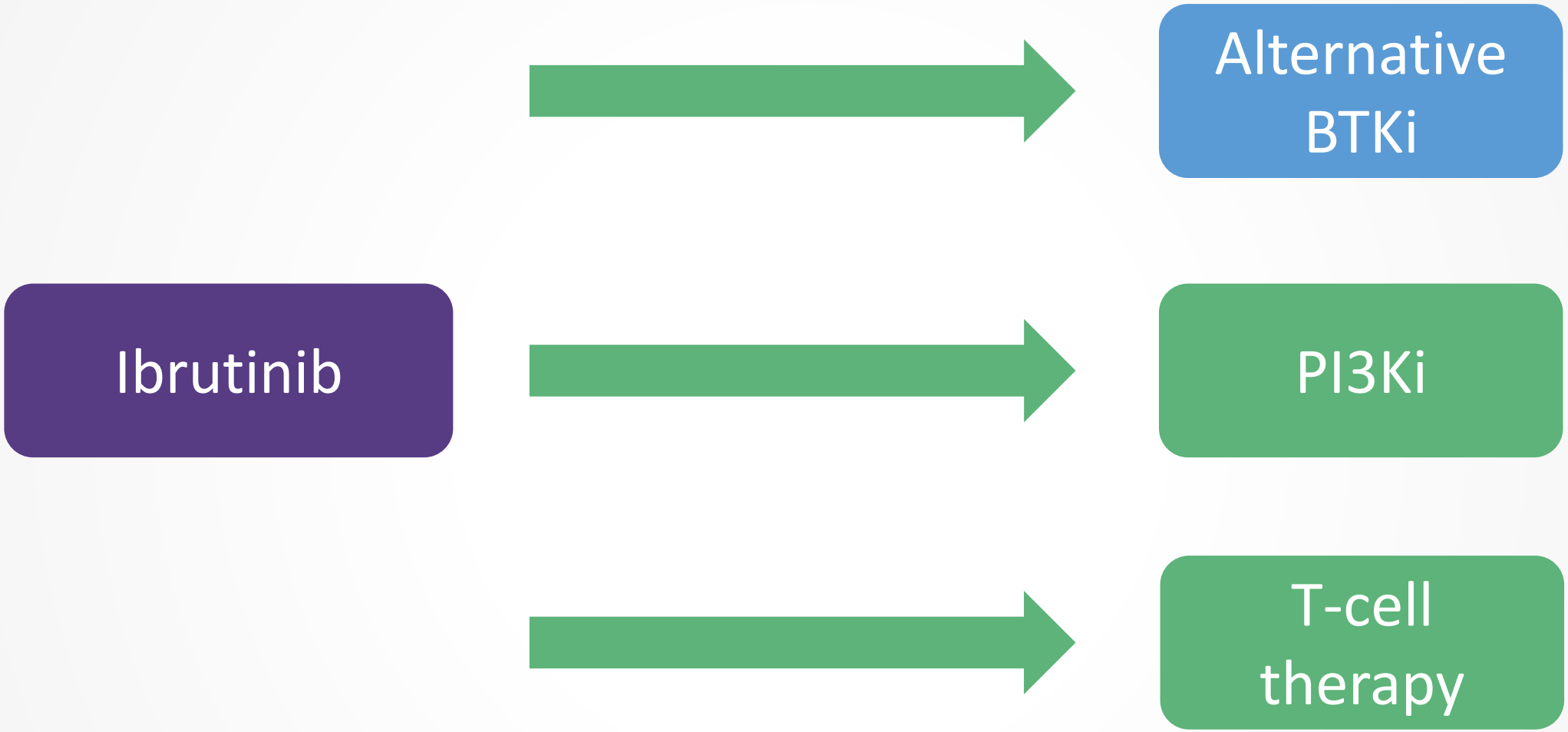
Resistance to ibrutinib

4–30% of patients.
More frequent with:
- *TP53*^{mut}
- complex karyotype



Late progression:
BTK^{C481Smut}
PLCG2^{mut}
…

BTK, Bruton's tyrosine kinase; mut, mutation; *PLCG2*, 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2.
Woyach, et al. *J Clin Oncol*. 2017;35(13):1437-1443.



BTKi, Bruton's tyrosine kinase inhibitor; PI3Ki, phosphoinositide 3-kinase inhibitor.

Alternative BTK inhibitors for R/R CLL[1,2]

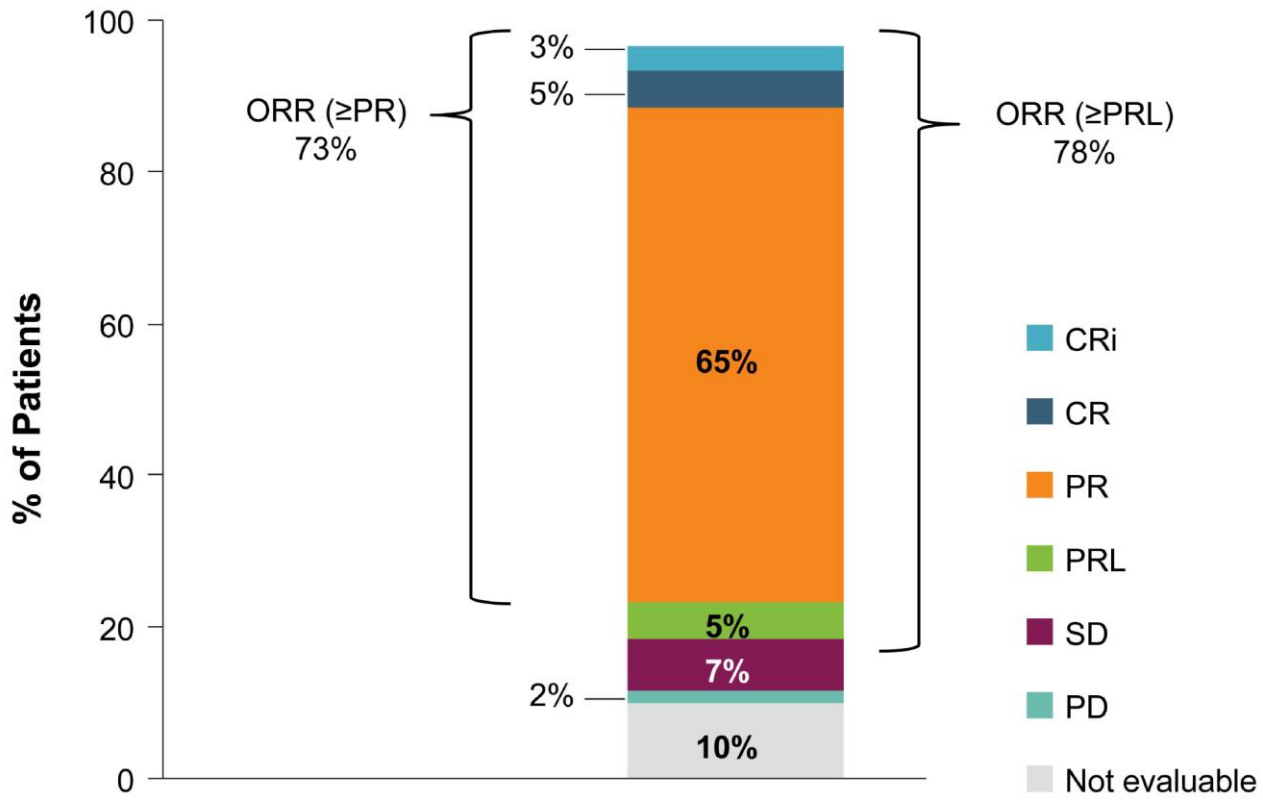
BTKi	Approval status	BTK binding	BTK selectivity	Inhibition of other TKs	
Acalabrutinib	Approved	**Covalent** Irreversible at Cys481	Higher BTK selectivity than ibrutinib	Lower than ibrutinib	• Inactive against C481S-mutated *BTK* (binding site Cys481) • Indicated when "off-target" toxicity
Zanubrutinib	Investigational				
Tirabrutinib	Investigational				
Spebrutinib	Investigational				
Branebrutinib	Investigational				
M7583	Investigational				
ARQ-531	Investigational	**Non-covalent** Reversible		TEC, ITK, SRC…	• Active against WT *BTK* and **C481S-mutated *BTK* (not PLCγ2)** • "Off-target" toxicity
Pirtobrutinib (LOXO-305)	Investigational				

BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; C481S, cysteine 481 to serine; CLL, chronic lymphocytic leukemia; ITK, interleukin-2-inducible T cell kinase; PLCγ2, phospholipase C gamma 2; R/R, relapsed/refractory; SRC, sarcoma proto-oncogene tyrosine-protein kinase; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TK, tyrosine kinase; WT, wildtype.

1. Rule S, Chen RW. *Exp Rev Hematol.* 2018;11(9):749-756. **2.** Kim HO. *Arch Pharm Res.* 2019;42(2):171-181.

Ibrutinib intolerance *vs* resistance

- Phase II study of acalabrutinib for ibrutinib-intolerant patients with R/R CLL



	N = 60
Median PFS	Not reached
Estimated 24-month PFS	72%
Median OS	Not reached
Estimated 24-month OS	81%

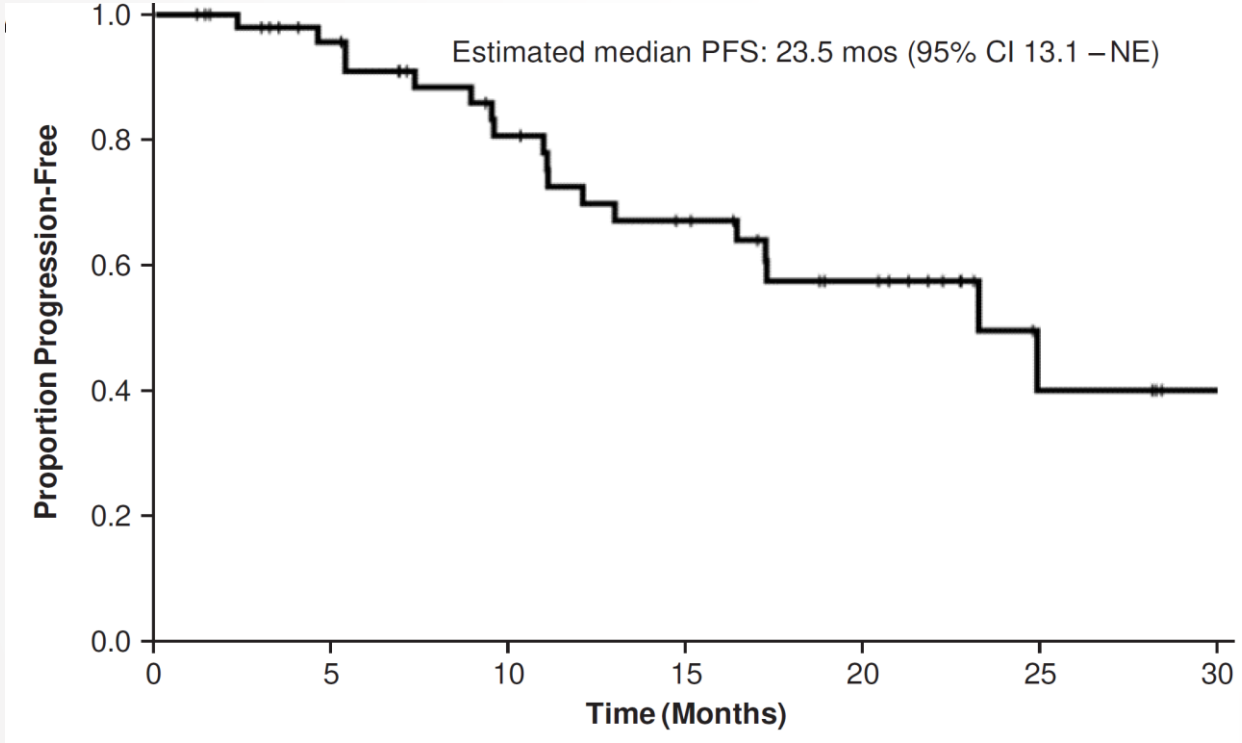
- Study was not designed to test efficacy of acalabrutinib in patients with therapeutic resistance
- Most patients (95%) had no mutation in *BTK*/*PLCG2*

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, compete response; CRi, CR with incomplete hematologic recovery; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; *PLCG2*, 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2; PR, partial response; PRL, PR with lymphocytosis; R/R, relapsed/refractory; SD, stable disease.

Rogers KA, et al. *Hematologica.* 2021. Online ahead of print. DOI: 10.3324/haematol.2020.272500

Investigational PI3K inhibitor: umbralisib

- Phase II study of umbralisib (PI3Kδ/CK1ε inhibitor) in BTKi/PI3Ki-intolerant patients with CLL



AEs of special interest	Grade 1	Grade 2	Grade 3	Grade 4
Colitis	–	2%	–	–
Pneumonitis	2%	2%	–	–
Transaminitis	4%	4%	2%	–

- Six patients (12%) discontinued umbralisib due to an AE

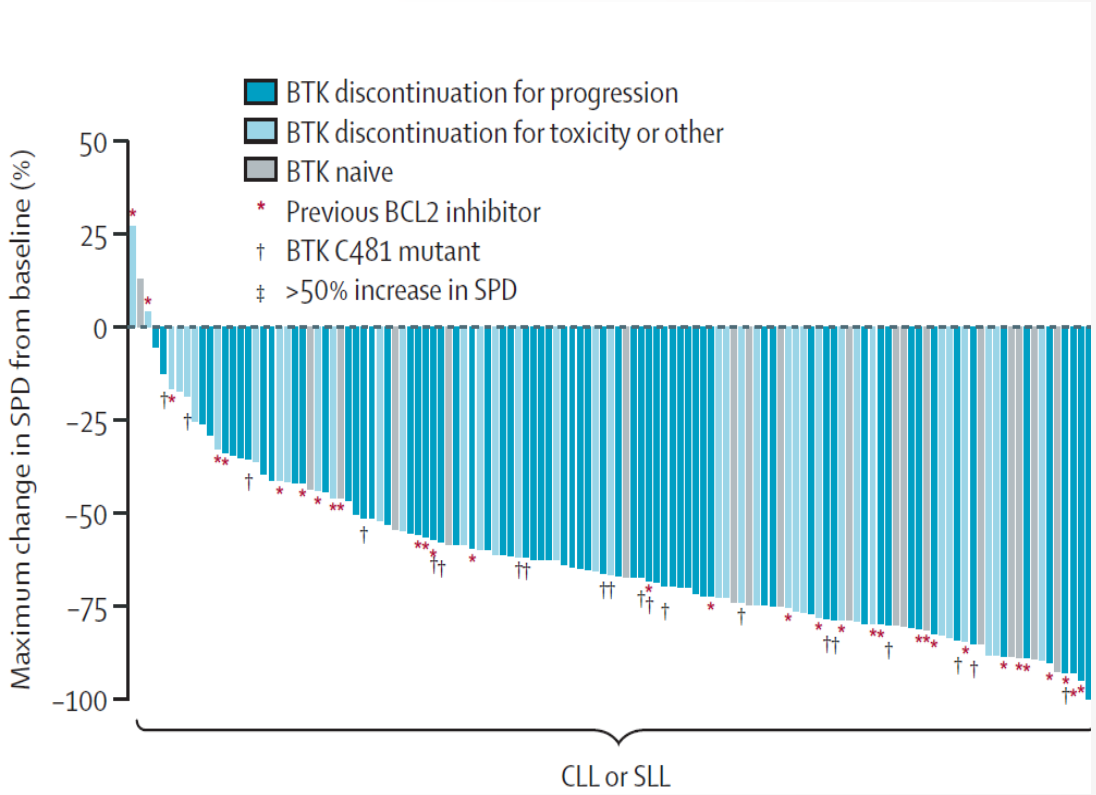
AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; CK1, casein kinase 1; CI, confidence interval; CLL, chronic lymphocytic leukemia; mos, months; NE, not evaluable; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase, PI3Ki, PI3K inhibitor.

Mato AR, et al. *Blood*. 2020. Online ahead of print. DOI: 10.1182/blood.2020007376

Alternative BTK inhibitors for ibrutinib-resistant patients

- Phase I/II study of pirtobrutinib (LOXO-305), a reversible (non-covalent) BTK inhibitor in R/R CLL

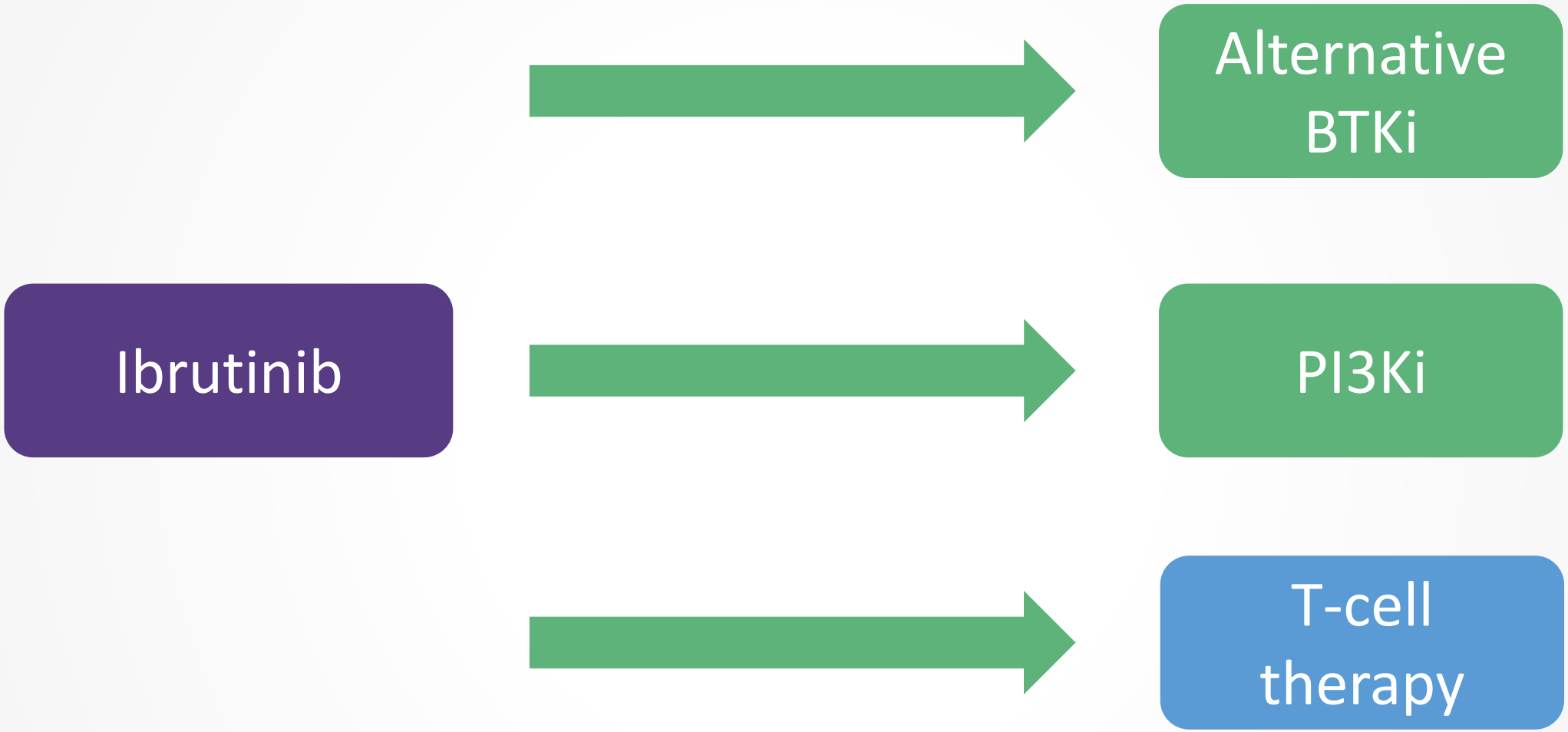
	n*	ORR
All patients	139	63% (55–71)
Prior BTKi	121	62% (53–71)
Prior BCL2i	48	65% (50–78)
Prior BTKi and BCL2i	45	64% (49–78)
BTK mutational status		
C481 mutant	24	71% (49–87)
Wild type	65	66% (53–77)



BCL2i, B-cell lymphoma 2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; CLL, chronic lymphocytic leukemia; ORR, overall response rate; R/R, relapsed/refractory; SPD, sum of products of diameters.

*Efficacy evaluable patients.

Mato AR, et al. *Lancet.*2021;397:892-901.



BTKi, Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor; PI3Ki, phosphoinositide 3-kinase inhibitor.

CAR T-cell therapy

- Phase I TRANSCEND-CLL-004 trial of liso-cel for patients with R/R CLL
  - Median 18-month follow-up

Response	All evaluable patients (n = 22)	Patients refractory to BTKi and venetoclax (n = 10)
ORR	82% (95% CI, 59.7–94.8)	80% (95% CI, 44.4–97.5)
CR/CRi	45%	60%
PR/nPR	36%	20%
uMRD ($\leq 10^{-4}$)	**n = 20**	**n = 9**
Blood	75%	78%
Bone marrow	65%	67%

Adverse events	All evaluable patients (n = 23)	Patients refractory to BTKi and venetoclax (n = 11)
Common Grade 3/4 TEAEs, %		
Thrombocytopenia	70	55
Anemia	78	73
Neutropenia	57	45
Leukopenia	43	18
AEs of special interest, %		
Grade 3 CRS	9	18
Grade ≥3 NEs	22	27

AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; CR, complete response; CRi, CR with incomplete hematologic recovery; CRS, cytokine release syndrome; liso-cel, lisocabtagene maraleucel; NE, neurological event; nPR, nodular PR; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TEAE, treatment-emergent adverse event; uMRD, undetectable minimal residual disease.

Siddiqi T, et al. *Blood.* 2020;136(Supplement 1):40-41.

My approach to this clinical case…..

- 66 year-old patient with CLL:
  - Comorbidities, frail
  - UM-*IgHV genes, TP53* gene abnormality and CK
  - Double refractory to venetoclax + obinutuzumab and ibrutinib

1. Investigate mechanisms of resistance to Ibrutinib:
   1. PET/CT to rule out a Richter transformation
   2. Mutational analysis of the BTK pathway
2. Reconsider comorbidities and potential allo-SCT
3. Treatment with a non-covalent BTKi → pirtobrutinib
4. Alternatively → clinical trial with a CAR-Tor a T-cell engager (CD20-CD3, ROR1-CD3, CD19-CD3)

allo-SCT, allogeneic stem cell transplantation; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; CLL, chronic lymphocytic leukemia; PET/CT, positron emission tomography–computed tomography.

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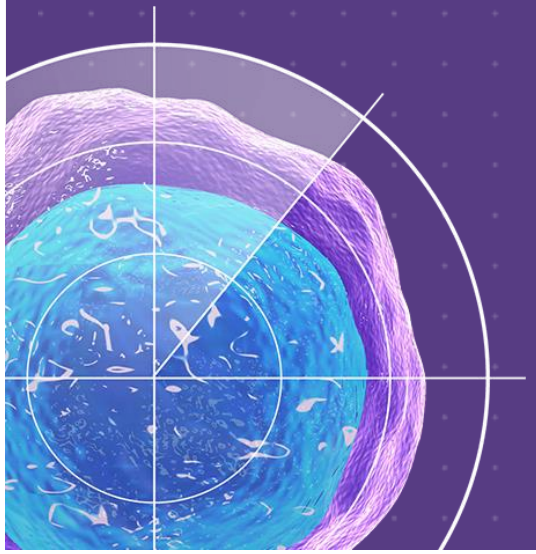
Thank you



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