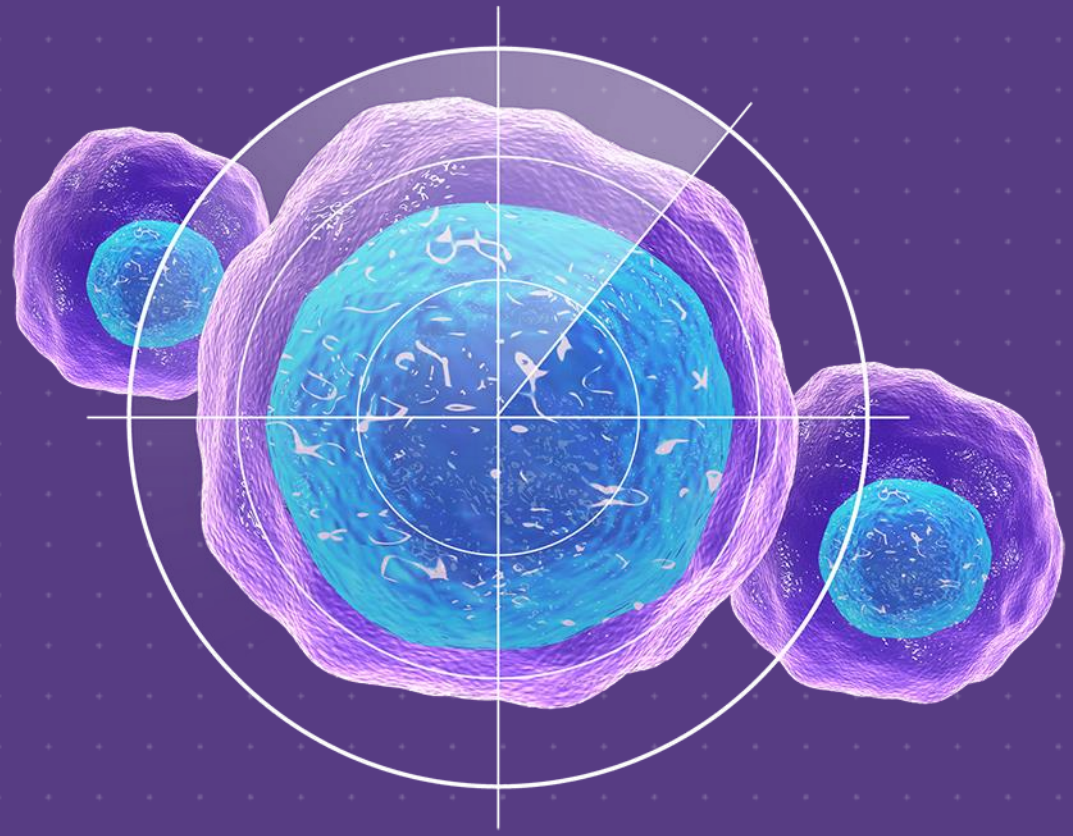
LymphomaHub

VIRTUAL SATELLITE SYMPOSIUM

How I treat relapsed/refractory disease – DLBCL and CLL

November 8, 2020



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Case 2:
Patient with R/R CLL – European perspective

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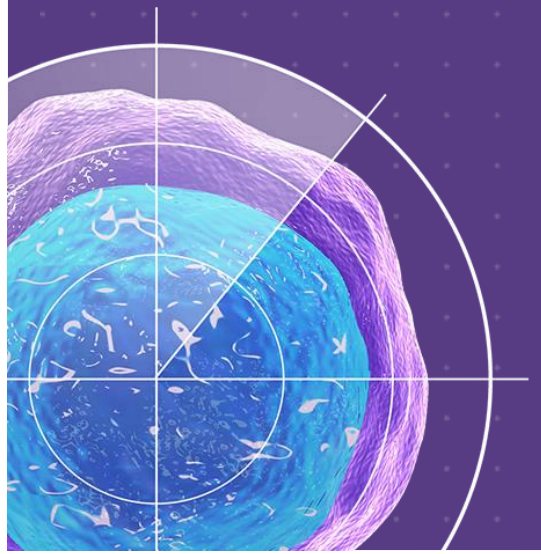


Conflict of interest disclosure

- I hereby declare the following potential conflicts of interest concerning my presentation:

- Consultancy / Advisor: AbbVie, Celgene, Gilead, Janssen, Novartis, Takeda, AstraZeneca, Roche, TG Therapeutics, Loxo, BeiGene

- Research funding: AbbVie, Celgene, Gilead, Janssen, Novartis, Takeda, AstraZeneca, Roche

No share ownership, patents or board membership

Clinical case

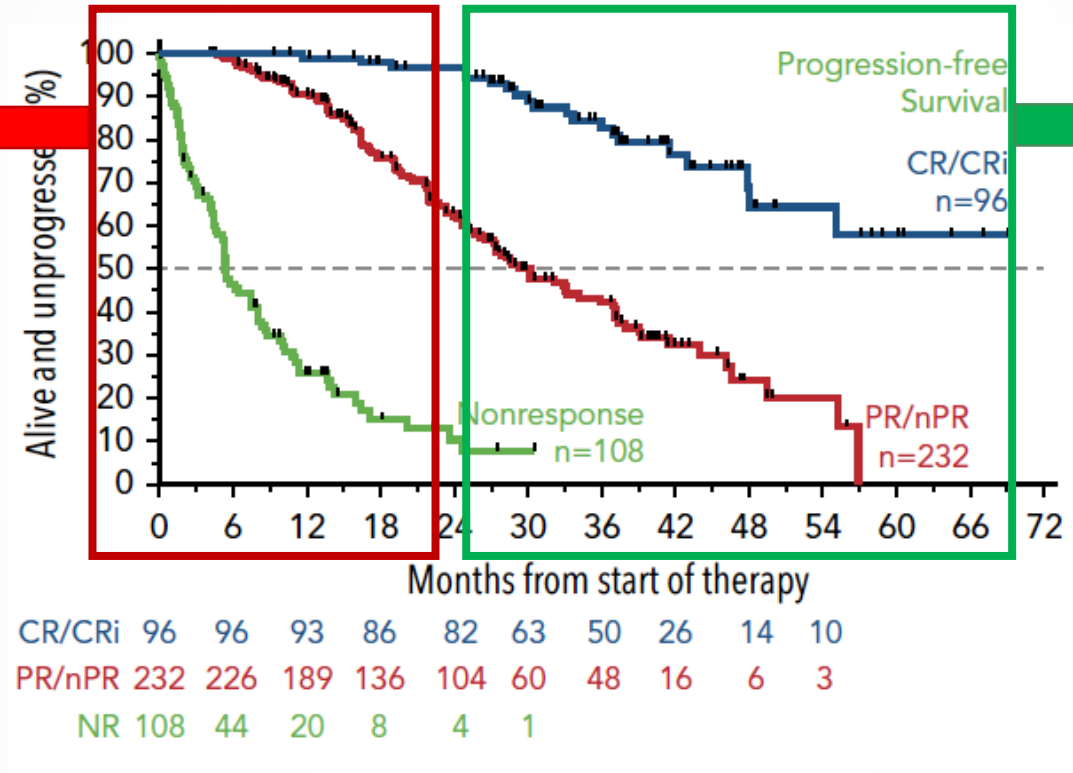
CLL patient case (relapse after venetoclax – rituximab)

- 72-year-old female, ECOG PS 1
- Patient has mild renal insufficiency (creatinine 1.6 mg/dL with creatinine clearance of 40 mL/min)
- Lymphocytosis (WBC 114,000, Hb 10.5 g/dL, platelets 100 × 10^9/L) and adenopathy, BM: 84% CLL cells
- CD19+, CD5++, CD20+, CD23+++
- Genetics: FISH: trisomy 12, *IGHV*-mutated, *TP53*-mutated
- Previous therapies:
  - Monitored for 2 years until development of symptoms
  - Was started on Bendamustine – Rituximab → relapsed 2.5 years later with *TP53* mutation
  - Was started on Venetoclax – Rituximab, and is now progressing after 1.5 years of treatment

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Clinical Oncology Group performance score; FISH, fluorescence *in situ* hybridization; IGVH, immunoglobulin variable heavy chain gene mutation.

Mechanisms of progression under venetoclax[1,2]

- Highly proliferative CLL
- Richter transformation
- Bulky disease
- *TP53*^{mut}



- Low burden CLL
- BTKi sensitive

- *Specific resistance mechanisms*
  - *BCL2*^{mut} (G101V)
  - *Upregulation prosurvival BCL-X$_L$/MCL-1*
  - *Loss of BAX/BAK*

1. Blombery P*, et al. Cancer Discov.* 2019;9(3):342; **2.** Anderson MA, et al. Presented at XVIII iwCLL; Sep 20–23, 2019, Edinburgh, GB.
BTKi, Bruton's tyrosine kinase inhibitor; CR, complete response; CRi, CR with incomplete hematologic recovery; mut, mutation; NR, nonresponse; PR/nPR, partial response/near PR.

Predictive markers for targeted therapies[1,2,3,4]

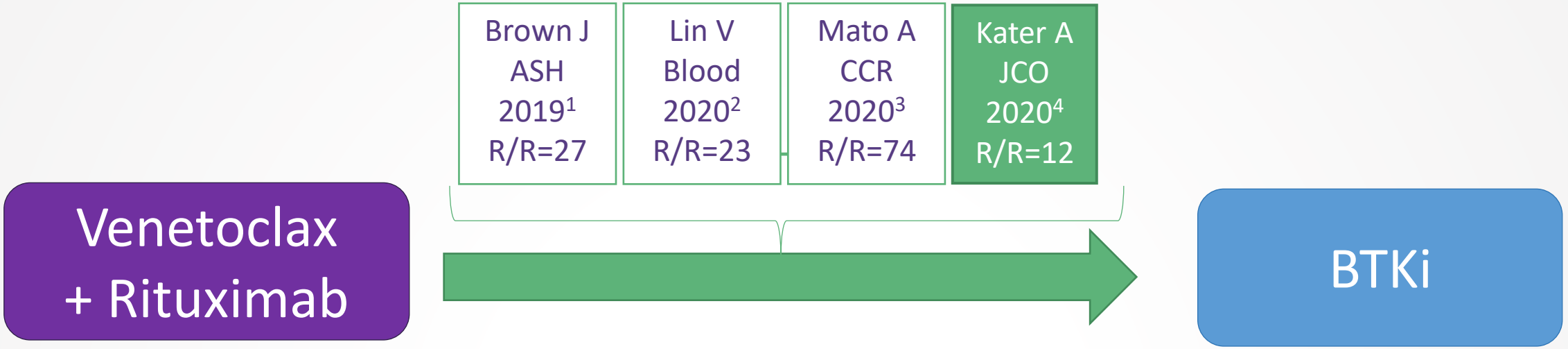
Markers	Ibrutinib		Venetoclax (+ anti-CD20)
	PFS	CR	PFS
Bulky disease (> 5 cm)	No	Yes	Yes
Prior therapies (> 1)	Yes	Yes	Refractory to BCRi
Del17p / *TP53*^{mut}	Yes	No	Yes
NOTCH1^{mut}	No	No	Yes
Complex karyotype	Yes*	No	Yes†

?

1. O'Brien SM, *et al. JAMA Oncol.* 2018;4(5):712; **2.** O'Brien SM, *et al. Blood.* 2018;131(17):1910; **3**. Al Sawaf O, *et al*. Abstract #S106. EHA 2019; Amsterdam, NL; **4.** Roberts AW, *et al. Blood*. 2019;134(2):111.

BCRi, B-cell-antigen receptor inhibitor; CR, complete response; del17p, chromosome 17p deletion; mut, mutation; PFS, progression-free survival.

*in relapse/refractory CLL; †not with venetoclax plus obinutuzumab

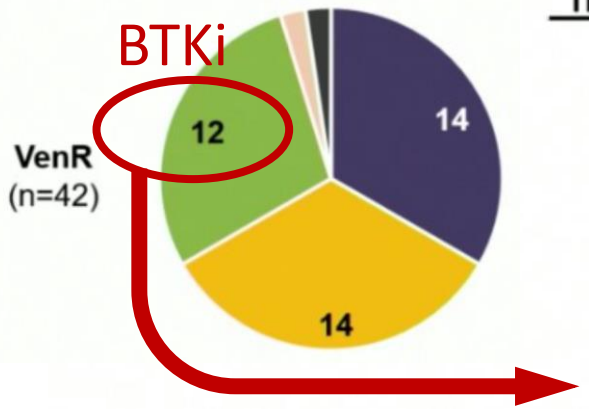


Subsequent therapy[3]	BTKi	BTKi pre-exposed	PI3Ki	CAR T	Anti-CD20
Agents	Ibrutinib Acalabrutinib	Ibrutinib Acalabrutinib Non-covalent BTKi	Idelalisib Duvelisib	Anti-CD19	Rituximab Obinutuzumab Ofatumumab
N	44	30	17	18	19
ORR	84%	53%	47%	67%	32%
CR	9%	10%	6%	33%	16%
PD	5%	23%	29%	28%	37%
Median PFS (months)	32	12	5	9	2

1. Brown J, *et al. Blood.* 2019;134(Supplement_1):4320. **2.** Lin VS, *et al. Blood*. 2020;135(25):2266. **3.** Mato AR, *et al. Clin Cancer Res.* 2020;26(14):3589; **4.** Kater AP, et al. J Clin Oncol. 2020; JCO2000948.
BTKi, Bruton's tyrosine kinase inhibitor; CAR T, chimeric antigen receptor T-cell therapy; CR, complete response ; ORR, overall response rate; PD, progressive disease; PI3Ki, phosphoinositide 3-kinase inhibitor; PFS, progression-free survival; R/R, relapsed/refractory.

Ibrutinib in R/R CLL previously treated with venetoclax in the MURANO study[1,2]

Responses to therapy after progression: Ibr post-Ven



Time on Ibr	Best response to Ibr	Reason for discontinuation
190*	PR	
215	PR	New treatment (idelalisib + R)
250	Not available	Death (PD)
359*	PR	
364*	PR	
374*	PR	
431*	PR	
458	PR	Death (PD)
470*	PR	
665*	CR	
683*	Not available	
1304	PR	PD

Response rate Ibr post-Ven:
10/10 (100%)
(in evaluable patients)

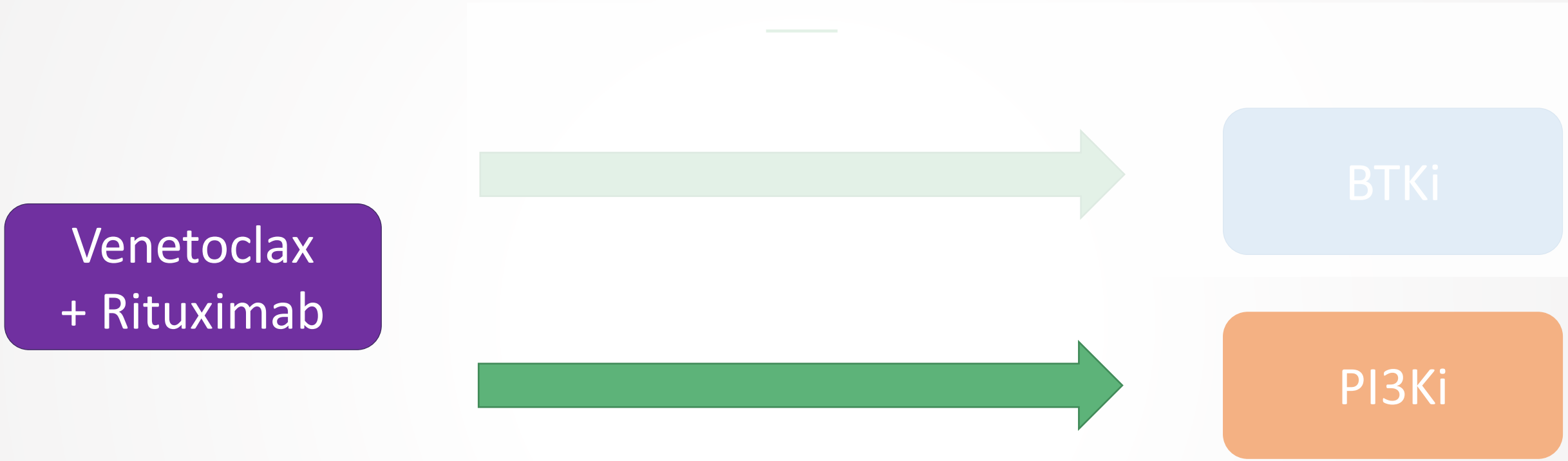
1. Seymour J, *et al. Blood* 2019;134(Supplement_1):355. **2.** Kater AP, *et al. J Clin Oncol.* 2020; JCO2000948.
BTKi, Bruton's tyrosine kinase inhibitor; CR, complete response; Ibr, ibrutinib; PD, progressive disease; PR, partial response; R, rituximab; Ven, venetoclax.

New BTK inhibitors[1,2]

BTKi	BTK binding	BTK selectivity	Inhibition of other TKs	Additional features
Acalabrutinib	**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				
Tirabrutinib				
Spebrutinib				
Branebrutinib				
M7583				
Vecabrutinib	**Non-covalent** Reversible		TEC, SRC, EGFR…	• Active against WT *BTK* and **C481S-mutated *BTK* (not PLCγ2)** • "Off-target" toxicity
ARQ-531			TEC, ITK, SRC…	
LOXO-305				

1. Rule S & Chen RW. *Expert Rev Hematol.* 2018;11(9):749; **2.** Kim HO. *Arch Pharm Res.* 2019;42(2):171.

BTK, Bruton's tyrosine kinase; BTKi, BTK inhibitor; C481S, cysteine 481 to serine; EGFR, epidermal growth factor receptor; ITK, interleukin-2-inducible T-cell kinase; SRC, sarcoma proto-oncogene tyrosine-protein kinase; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TK, tyrosine kinase.



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

Response to subsequent therapies following venetoclax discontinuation[1]

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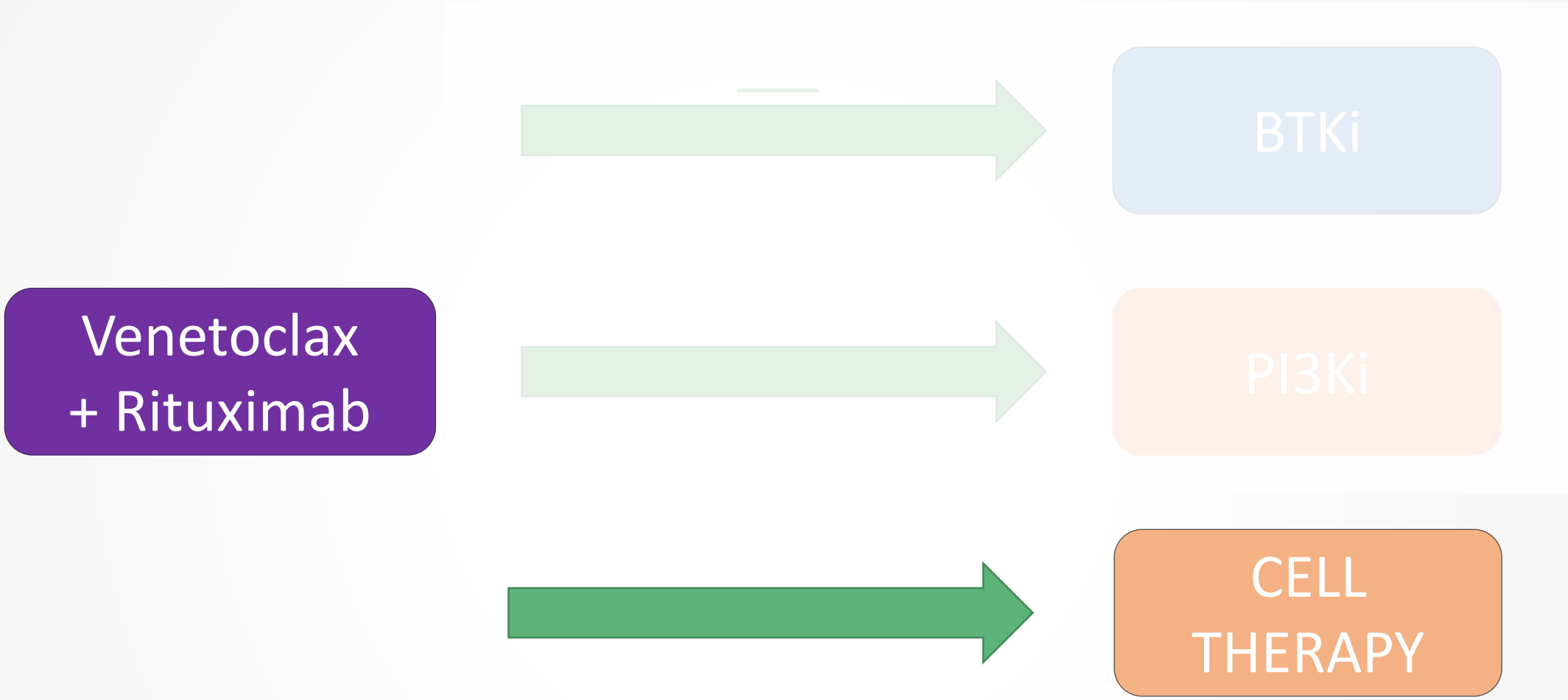
CR	9%	10%	6%	33%	16%
PD	5%	23%	29%	28%	37%
Median PFS (months)	32	12	5	9	2

- Median age: 66 years
- Prior treatments: 3
- *TP53* disruption: 56%
- Unmutated *IGHV*: 82%

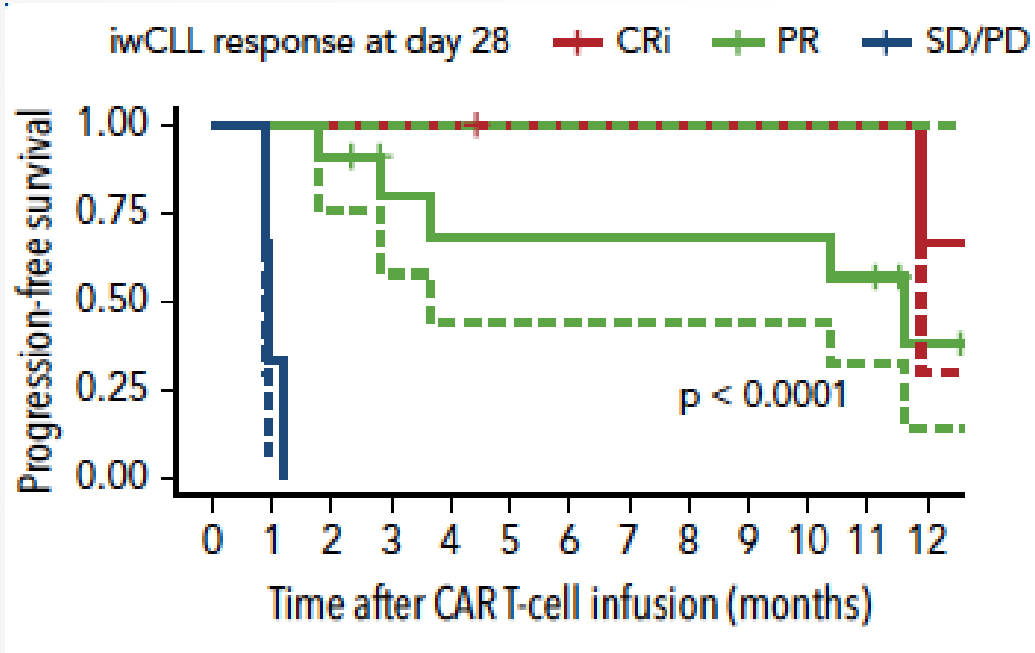
1. Mato AR, *et al. Clin Cancer Res.* 2020;26(14):3589.

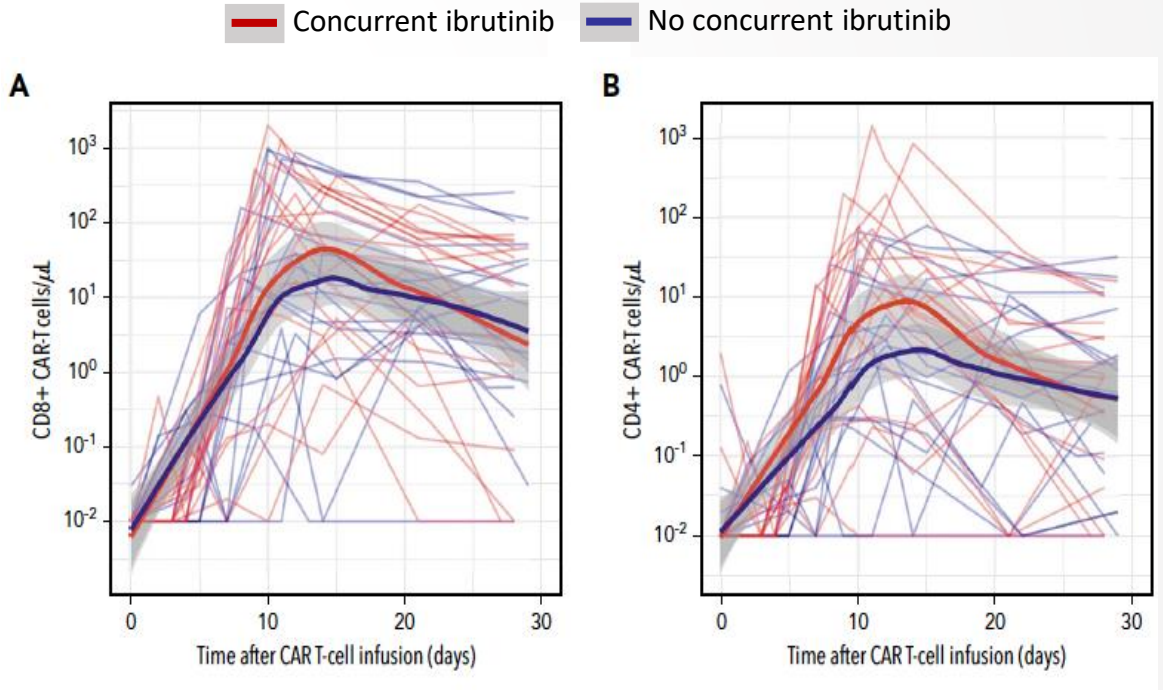
BTKi, Bruton's tyrosine kinase inhibitor; CAR T, chimeric antigen receptor T-cell therapy; CR, complete response; ORR, overall response rate; PD, progressive disease; PI3Ki, phosphoinositide 3-kinase inhibitor; PFS, progression-free survival.



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

CD19-targeted CAR T with concurrent ibrutinib[1]





Prior venetoclax → 11/19

1. Gauthier J, *et al. Blood*. 2020;135(19):1650.

CAR T, chimeric antigen receptor T-cell therapy; CRi, complete response with incomplete hematologic recovery; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; PD, progressive disease; PR; partial response; SD, stable disease.

My approach to this clinical case….

Exclude Richter t.

→ PET/CT + bone marrow examination

Thorough biological assessment

(CK, other genetic lesions)

Salvage therapy with BTKi (ibrutinib)

Early signs of ibrutinib failure

- CAR T trial available?
- Clinical trial
- Consider for allo-SCT (72-year-old)?
  - Age / comorbidities[1]
  - 'Quality' of the donor
  - Desires of the patient
- PI3Ki, other BTKi,…

1. Sorror ML, *et al. Blood.* 2005;106(8):2912.

Allo-SCT, allogeneic stem cell transplant; BTKi, Bruton's tyrosine kinase inhibitor; CAR T, chimeric antigen receptor T-cell therapy; CK, complex karyotypes; PET/CT, positron emission tomography–computed tomography; Richter t., Richter transformation.

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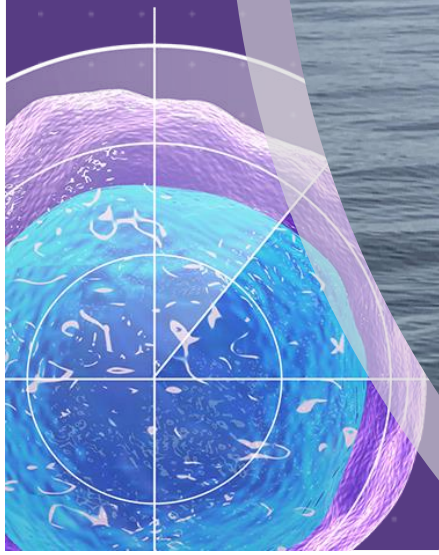
Thank you



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