Development of resistance to B-Cell Receptor inhibition

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Disclosures

	Research funding	Consultancy
BMS	√	√
Gilead	√	√
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Novartis	√	√
Takeda	√	√
TG Therapeutics		√
Kite	√	√
Lilly		√
BeiGene	√	√
Advantage		√
Allogene		√

No share ownership, patents or board membership

Outline

1. Patterns and biological mechanisms of resistance to BTKi

2. Predicting resistance to targeted therapies

3. Contending with resistance to iBTK

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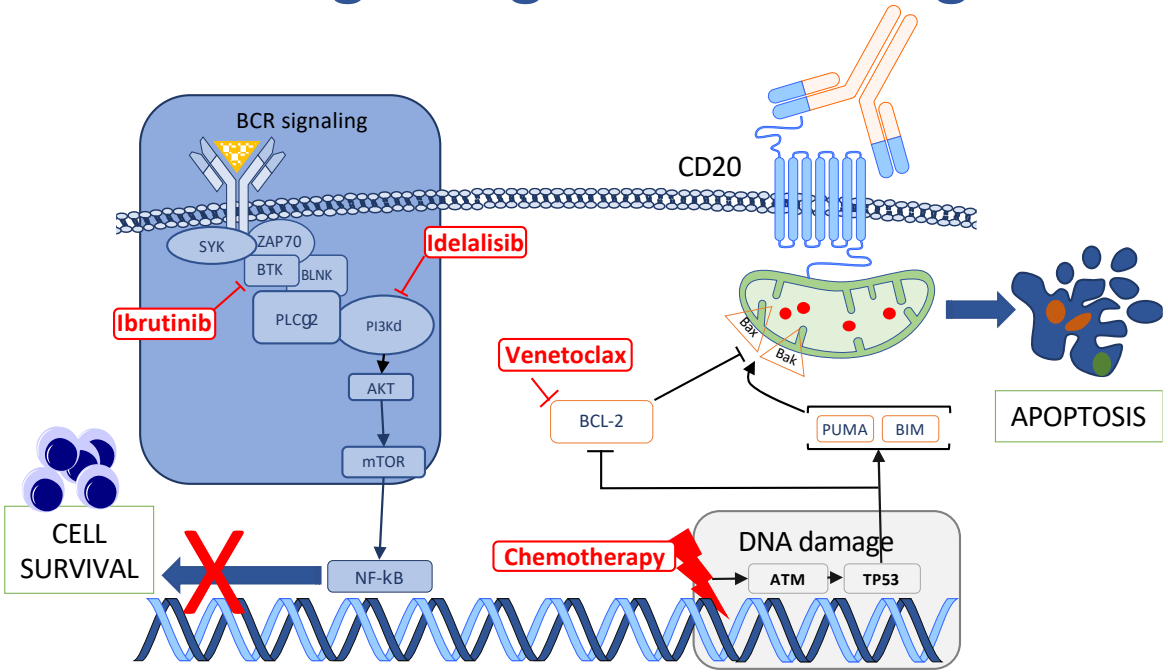
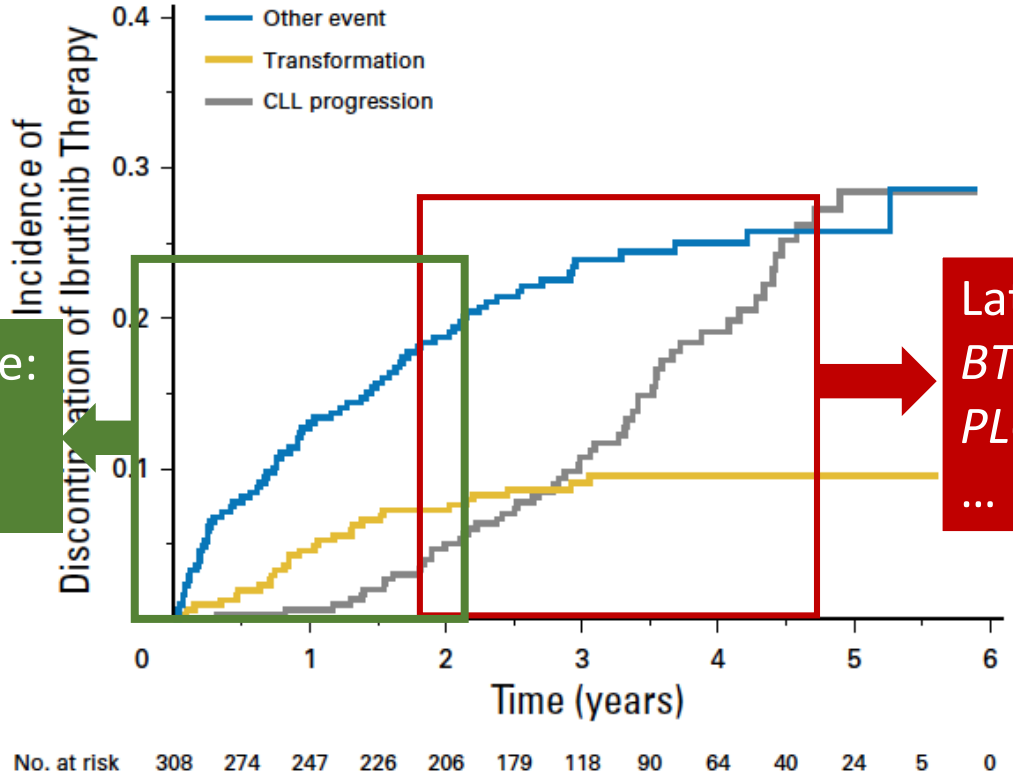
Relevance of BCR signaling in B-cell malignancies



Adapted from Bosch & Hallek, Blood, 2018

Resistance to ibrutinib

Primary resistance:
'Accelerated' CLL
Richter Sdr



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

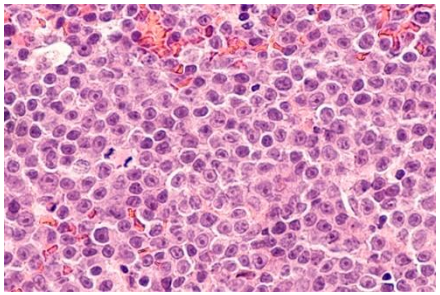
Woyach, JCO 2017

Ibrutinib in CLL: PD under treament

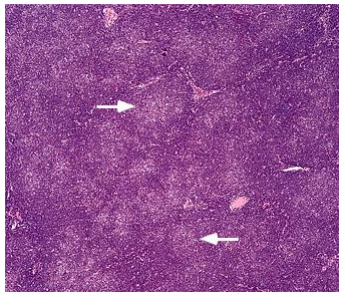
	Poland [1]	UK[2]	France[3]	USA[4]	Resonate-2
N	224	315	428	621	136
Median age	63	69	70	62	73
Previous treatment	3 (1-10)	2(1-14)	3 (0-10)	NR	-
Median FU (months)	10	16	3	17	60
PFS	79% at 12 m	NR	NR	35 m (median)	NR
OS	82% at 12 m	77% at 16m	NR	75% at 30 m	80% 60m
Resistance	10%	10%	5%	10%	4%

1. Iskierka-Jażdżewska E, et al. *Leuk Lymphoma.* 2017;58:2485-2488; 2. UK CLL Forum. *Haematologica,* 2016; 101:1563-1572; 3. Ysebaert et al. *Am J Hematol*. 2017;92:E166-E168; 4. Mato AR, et al. *Haematologica*. 2018;103:1511-1517. Burger et al, Leukemia 2020

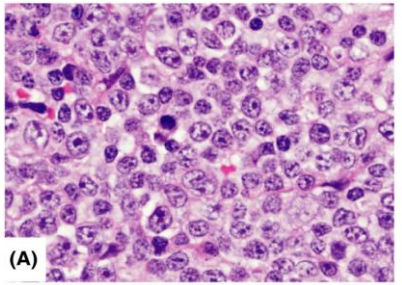
Patterns of histological transformation in CLL



Richter Sdr.#



Accelerated CLL#



Pseudo Richter*

#Images from presenter; * Slonim et al; Br J Haematol 2020

Resistance to ibrutinib

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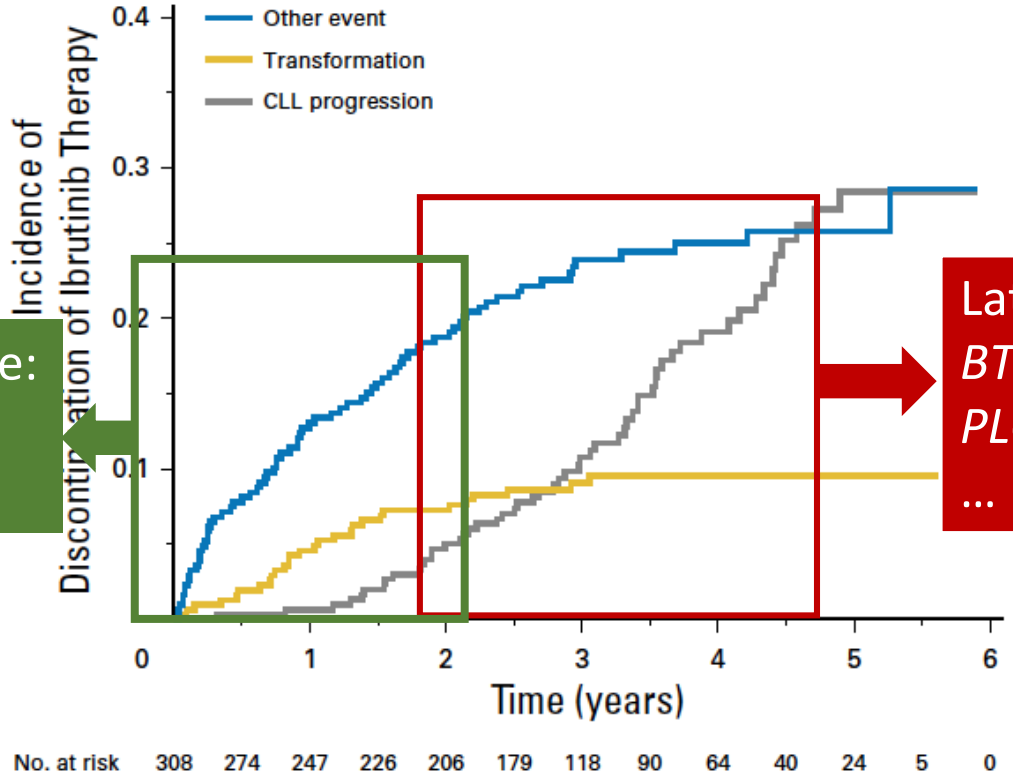
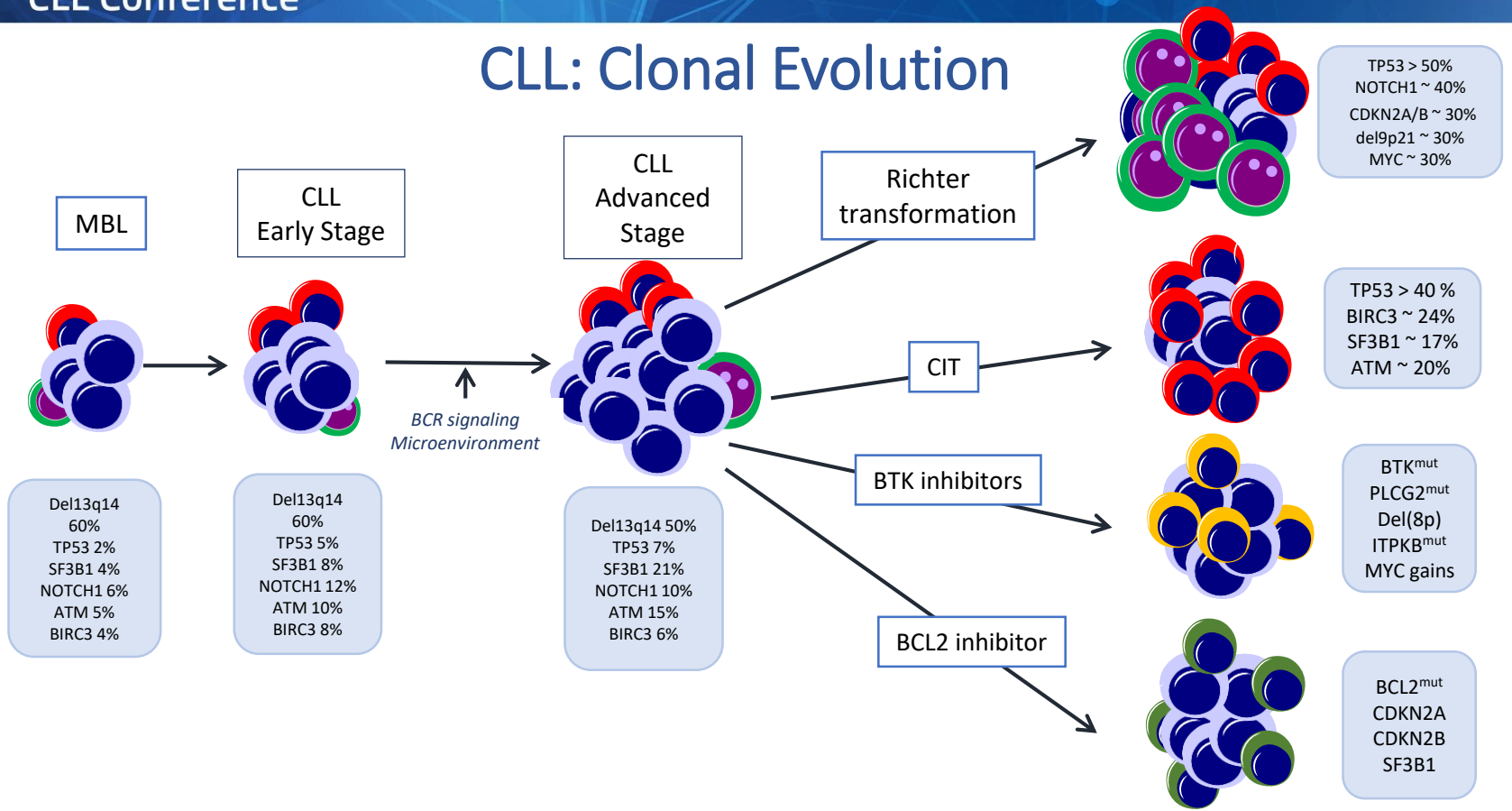
Richter Sdr



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

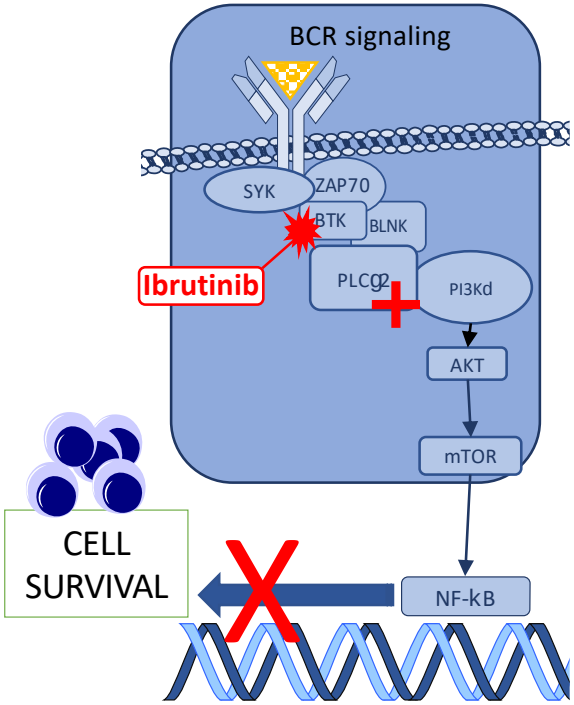
Woyach, JCO 2017

CLL: Clonal Evolution



Adapted from Bosch & Dalla-Favera, NRCO 2020

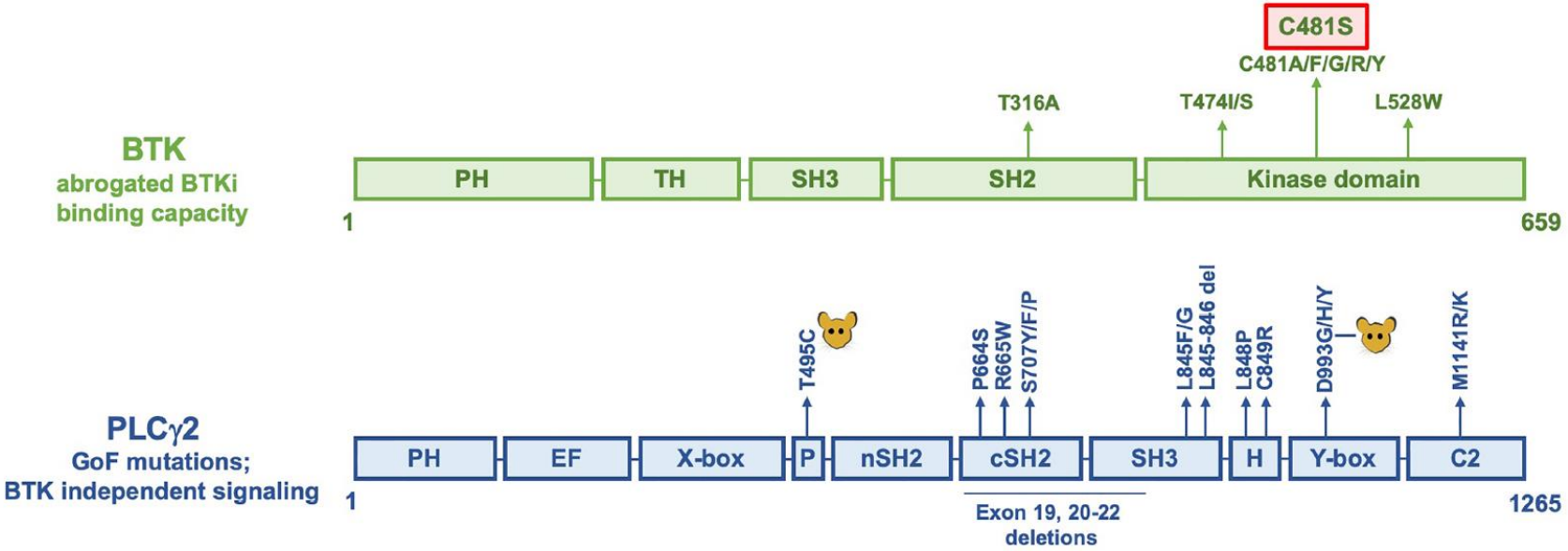
Resistance to Covalent BTKi



- >70% resistance to covalent BTKi → $BTK^{C481S/R}$ or PLCγ2 (6%)
- Other genetic mechanisms of resistance?
  - $SF3B1^{Mut}$
  - $NOTCH1^{Mut}$
  - Del8p
  - MYC gains
  - +2p (XPO-1?)

Adapted from Bosch & Dalla-Favera, Nature RCO 2020; Landau et al, Nat Commun 2017; Burger et al, Nat Commun 2016; Liu et al, Blood 2015;

BTK mutations induced by covalent BTKi



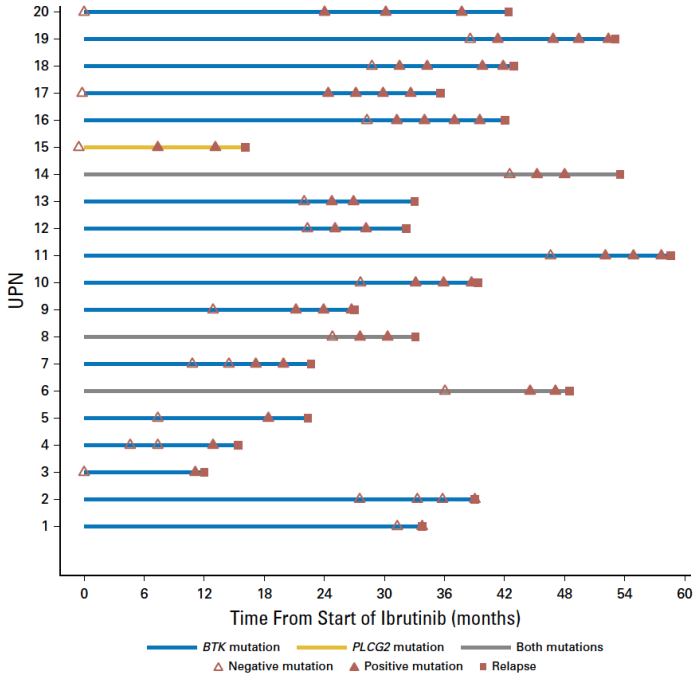
Adapted from Smith & Burger, Front Immunol 2021

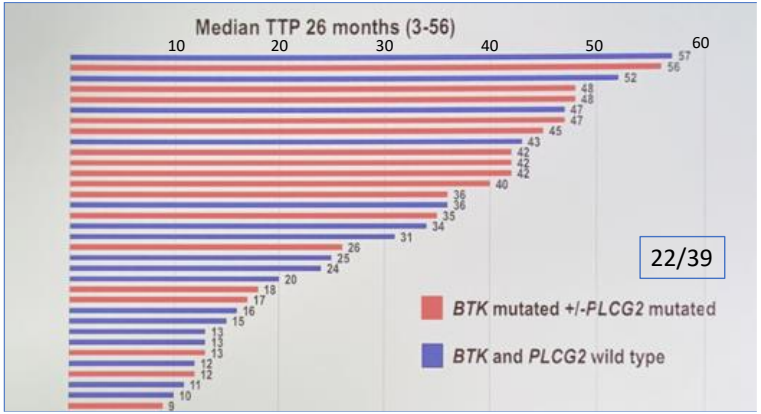
C481S BTK mutation

- Ablates covalent binding of BTK inhibitors[1,2]
- In some cases, induces a kinase-dead protein[3]
- Can be detected prior onset of treatment[4]
- Reported with ibrutinib, acalabrutinib or zanubrutinib
- Reported also in MCL[5], MZL[6], WM[7]

[1]Woyach et al, NEJM 2014; [2]Furman et al, NEJM 2014; [3]Hamasay et al, Leukemia 2017; Burger et al, Nat Commun 2017; [5]Chiroy et al, Cancer Disc 2014; [6]Epperla et al; Blood Adv 2019; [7]Jimenez et al, Br J Haematol 2020

Characteristics of BTK and PLCγ2 mutations





- BTK^{mut} preceded clinical progression in **9 months**
- VAF is usually low and not correlates with PD
  - Compartiment effect (progression in LN)
  - Mutated cells protect WT cells from ibrutinib effect (seen in WM)?

Woyach et al. JCO 2017; Woyach et al, IWCLL 2019

Non-genetic mechanisms of resistence to BTKi

- Richter transformation (selection of pre-existing clones)
- Microenvironment contribution
  - MYC overexpression
  - Activated MAPK pathway (*Fotrestieri et al., EHA 2020*)
  - Activated PI3K/AKT pathway
  - Overexpression of CD79b (DLBCL)

- Down-regulation of BTK expression *(Gandhi et al, Leukemia 2016)*

Acquisition of novel BTK mutation (Leu528Trp) with zanubrutinib

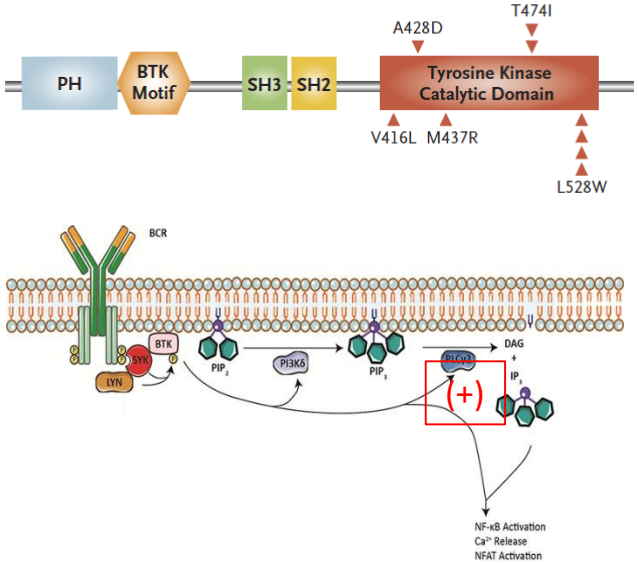
BTK Leu528Trp and Cys481 mutations are present in different cells in zanubrutinib progressors

Leu528Trp ablates binding of:

- Zanubrutinib
- Ibrutinib
- Pirtobrutinib

Blombery et al, Blood Adv 2022; Zhu et al, ASH 2022

Acquisition of novel BTK and PLCγ2 mutations with continuous pirtobrutinib



Wang E. et al. NEJM Feb 24, 2022

- Mutations leading to pirtobrutinib resistance (Naeem et al, Blood Adv 2022)
- Detected prior pirtobrutinib, under ibrutinib or acalabrutinib (Naeem et al, Blood Adv 2022)
- Dead kinase activity, but they retain downstream AKT phosphorylation → mechanism to be elucidated
- Sensitivity to BTK degraders (*in vitro*) (Montoya et al, ASH 2022)

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1. Patterns and biological mechanisms of resistance to BTKi

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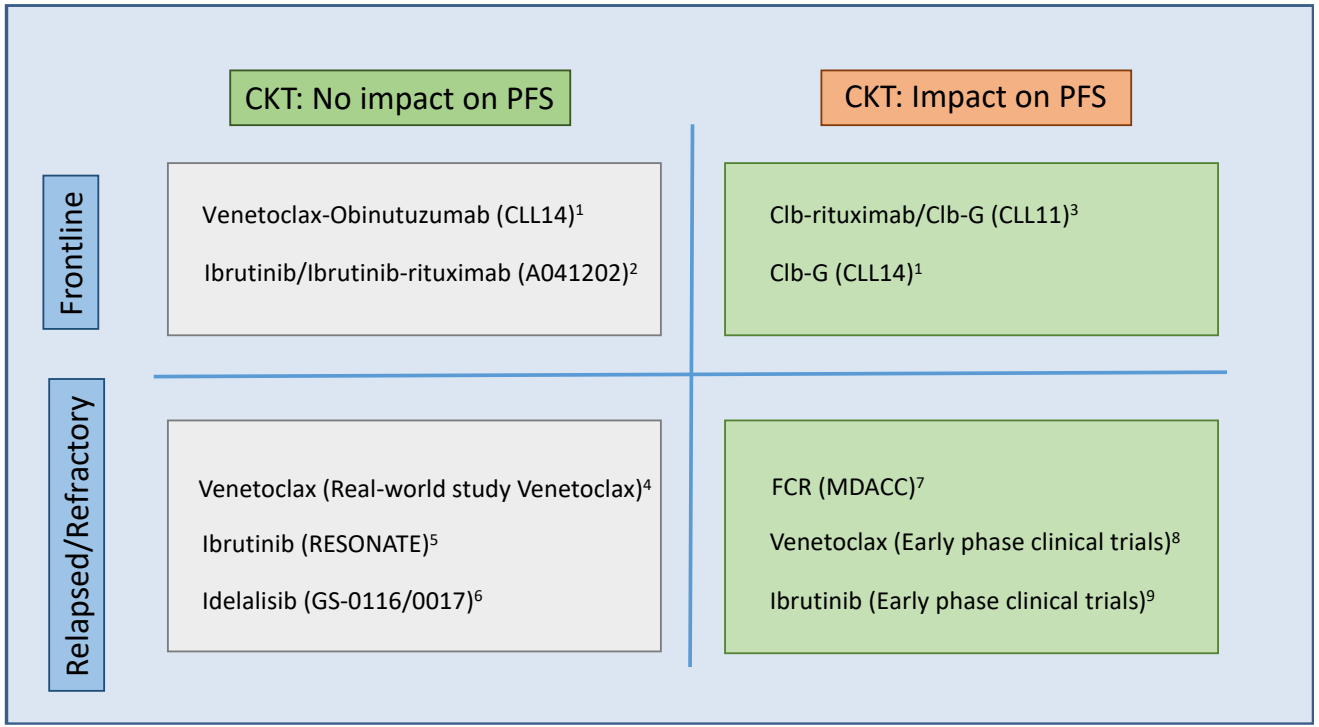
Predictive markers for targeted therapies

	Covalent BTKi		Venetoclax (+ anti-CD20)
	PFS	CR	PFS
Bulky disease (> 5 cm)	No	Yes	Yes
Prior therapies (> 1)	Yes	Yes	R to BCRi
Del17p / *TP53*^{mut}	Yes	No	Yes
NOTCH1^{mut}	No	No	Yes
BIRC3^{mut}	No	No	Yes?
Complex karyotype	Yes*	No	Yes**

(*) in R/R CLL / (**) not with VenG)

O'Brien et al, JAMA Oncol 2019; O'Brien et al, Blood 2018; Roberts et al, Blood 2019; Al-Sawaf et al, EHA 2019; Tausch et al, EHA 2021



[1]Al-Sawaf O. et al, *Blood* 2020; [2]Woyach JA et al, *NEJM* 2018; [3]Herling et al, *Blood* 2016; [4]Mato et al, *Haematologica* 2018; [5]Brown et al, *Leukemia* 2018; [6]Kreuzer et al, *Leukemia* 2019; [7]Badoux et al, *Blood* 2011; [8]Anderson et al, *Blood* 2017; 9O'Brien et al, *Blood* 2018

Abrisqueta & Bosch, Blood 2020

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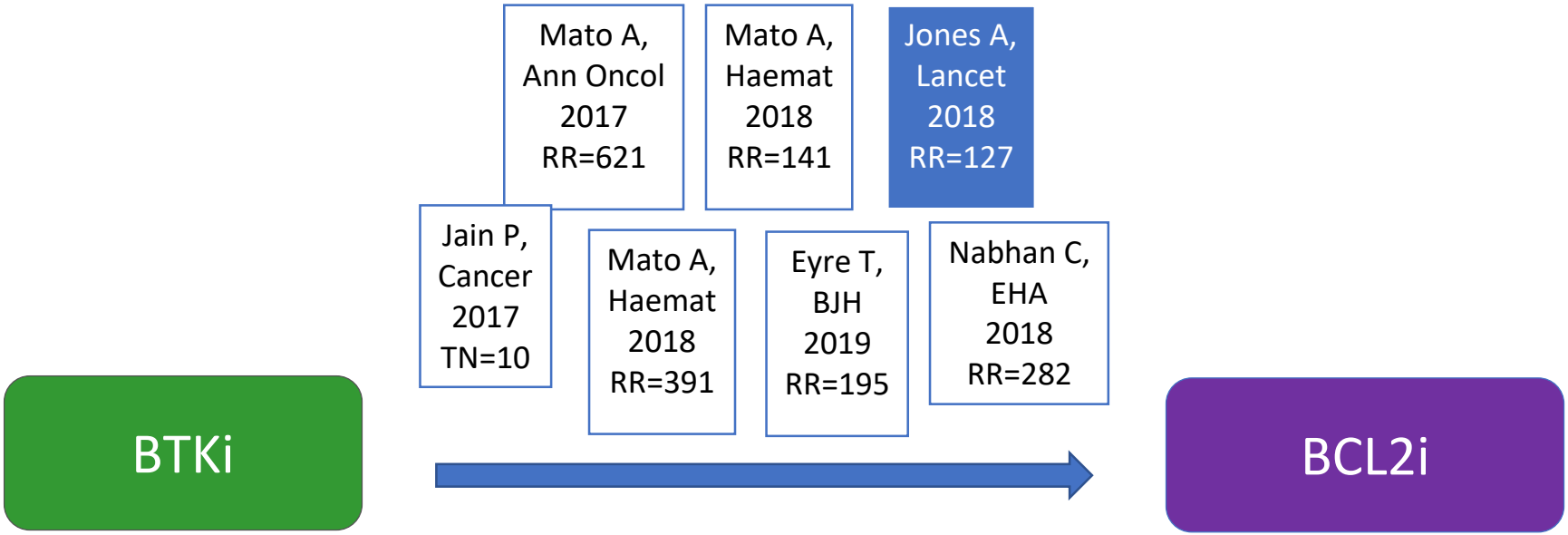


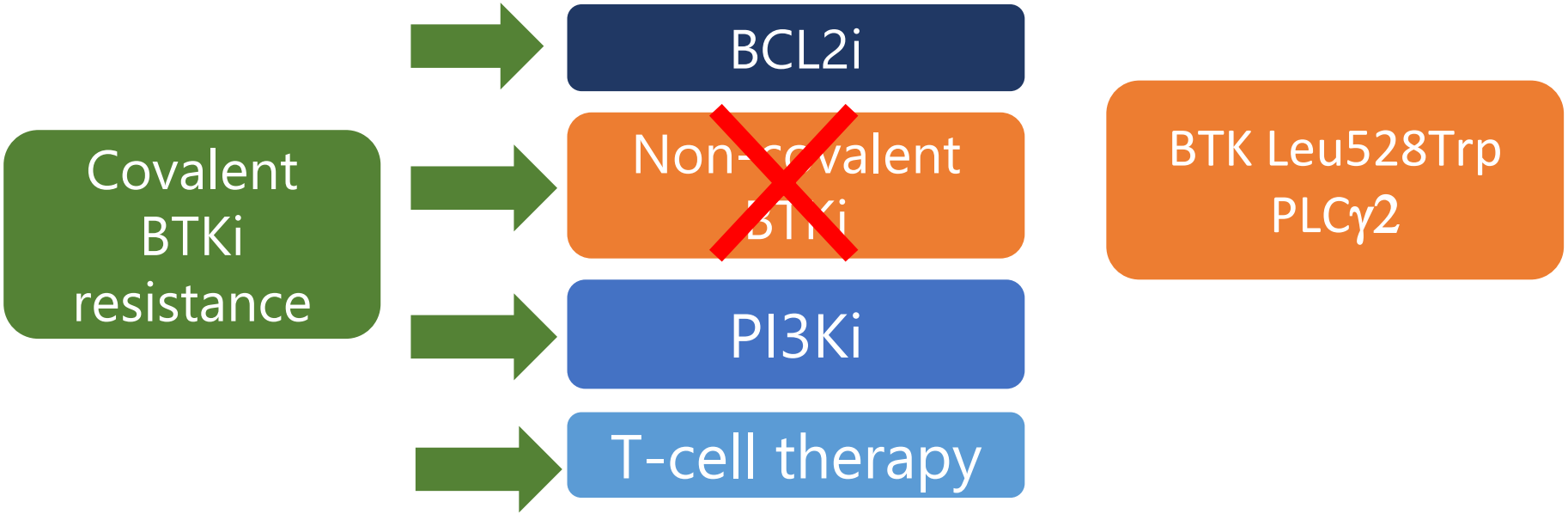
Retrospective cohorts & registry data

Outcome After Discontinuation of First BCR Kinase Inhibitor

First kinase inhibitor (KI)	Cause of failure of first KI	Second treatment (n)	ORR to second treatment	Outcome of second treatment	Median FU
[1]Ibrutinib Idelalisib	Toxicity, 51% CLL, 29% Other, 20%	Idelalisib (22) Ibrutinib (16) Venetoclax (13)	28% 64% 76%	PFS 9 mo PFS NR (if toxicity was cause of first KI failure)	14 mo
[2]Ibrutinib	CLL, 100%	Venetoclax (91)	65% (CR, 9)	PFS 25 mo	14 mo
[3]Ibrutinib Idelalisib	Toxicity 44%, CLL 54%	Venetoclax (98)	85% (CR 23)	1-y PFS, 65%	15.6 mo
[4]Ibrutinib		Venetoclax (107)	69% (CR, 17.7)		
[5]Idelalisib	CLL, 100%	Venetoclax (36)	67% (CR, 9)	1-y PFS, 79%	

1. Mato AR, et al. *Ann Oncol*. 2017;28:1050-56; 2. Jones JA et al. *Lancet Oncol*. 2018;19:65-75; 3. Eyre TA, et al. *Br J Haematol*. 2019;185:656-69; 4. Mato AR, et al. *Haematologica*. 2018;103:1511-1517; 5. Coutre S, et al. *Blood*. 2018;131:1704-11.

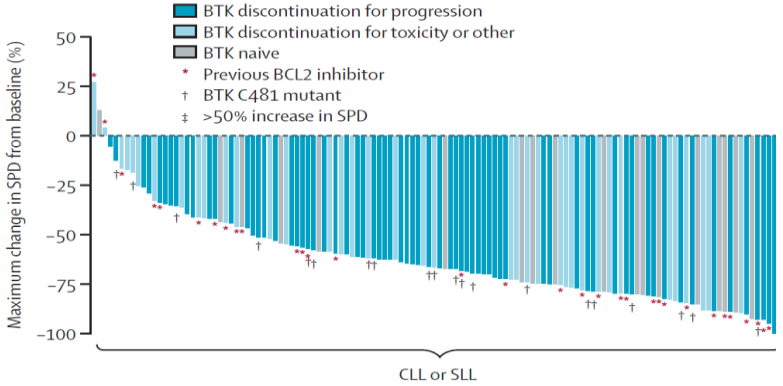
NR, not reported.

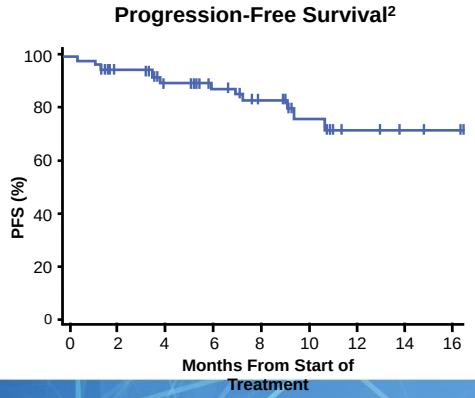

Covalent BTKi resistance
BCL2i
Non-covalent BTKi
PI3Ki
T-cell therapy
BTK Leu528Trp
PLCγ2

Phase 1b/2

Phase I/II study of pirtobrutinib (LOXO-305), a reversible (non-covalent) BTKi in RR 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)





Mato AR, et al. *Lancet.* 2021;397:892-901. NCT03740529

Summary of efficacy and safety of CD19 targeted CAR T in combination with ibrutinib

	N=	TP53 ab	Ibrutinib-R	Construct	ORR (%)	CR (%)	uMRD	PFS @ 2 y	CRS	NE
[1]Gautier J et al	19	74%	100%	4-1BB	83%	71%	85%	60%	75% (vs. 95%)	26% (vs 42%)
[2]Wierda W et al	23	39%	100%	Liso-cel 4-1BB	90%	59%	86%	70%	78%	30%
[3]Gill S et al	19	6/20pts	100%	Hu-CART19 4-1BB		50%	72%	>80%	18/19	5/19

1. Gautier J et al. Blood 2020
2. Wierda WG, et al. Presented at ICML 2021; presentation 86
3. Gill S, et al. Blood Adv.2022. 2022007317

Conclusions

Resistance to BTKi

- drug exerts continous therapeutic pressure on tumoral clones
- Usually resistance is genetic
- All covalent BTKi present similar mechanisms of resistance
- Richter transformation must be ruled out

Patients resistant can be salvaged by using alternative targeted therapies

Third generation BTKi (non-covalent) are active in (most of) resistant covalent BTKi cases

T-cell therapies (CAR-T, Allo-SCT, Bi-specific monoclonal antibodies) should be planned in this setting

Funding

Instituto de Salud Carlos III

Vall d'Hebron Barcelona Campus Hospitalari

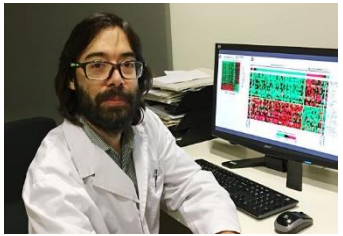
Persones (Talent, Coneixement, Professionals, Institucions)

PERIS 2016 2020
Pla estratègic de recerca i innovació en salut

aecc Contra el Cáncer

VHIO
VALL D'HEBRON Institut d'Oncologia

GELLC
Grupo Español de Leucemia Linfocítica Crónica



Pau Abrisqueta