National Heart, Lung, and Blood Institute

Biology of CLL (at Progression): How Does That Inform Treatment?

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Disclosures:

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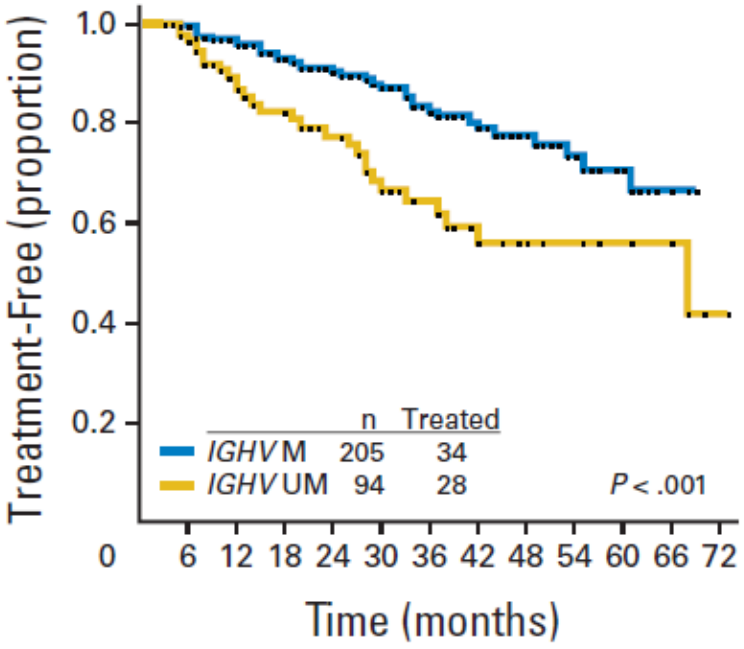
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers Bureau	N/A
Honoraria	N/A
Scientific Advisory Board	N/A

I will be discussing the following off label use

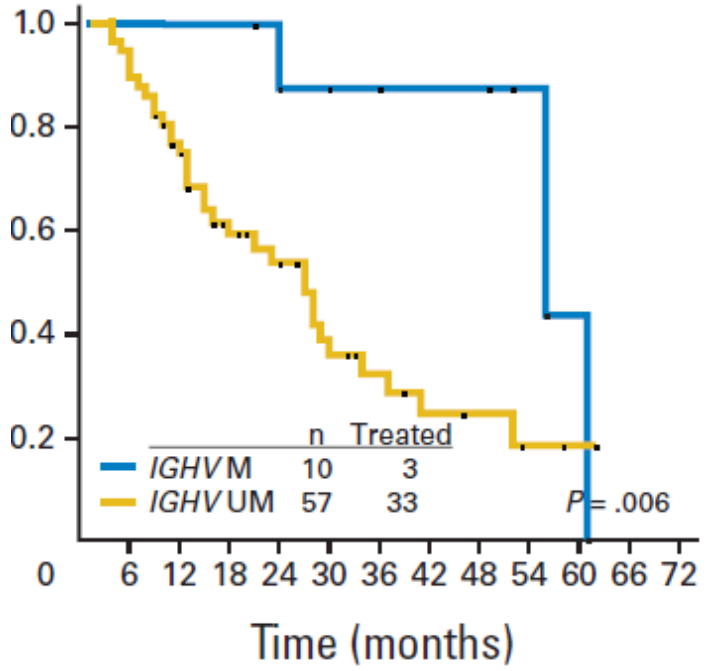
Progression from diagnosis to 1st treatment

by IGHV status and FISH cytogenetics

in del13q CLL

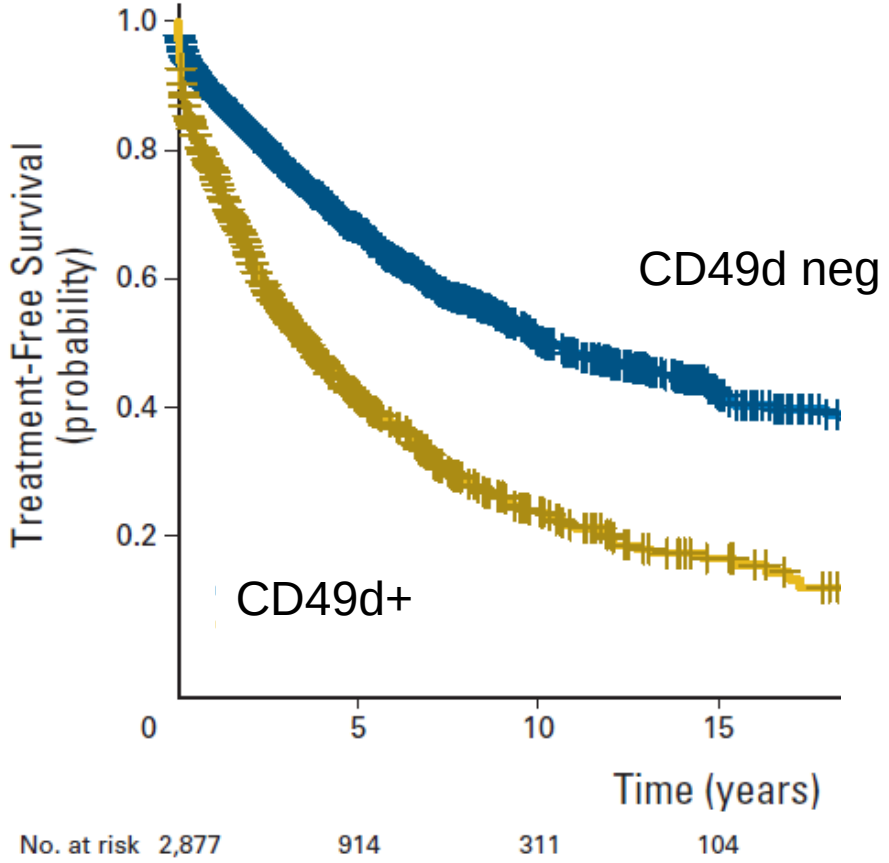


in del11q CLL



Wierda et al, JCO 2011

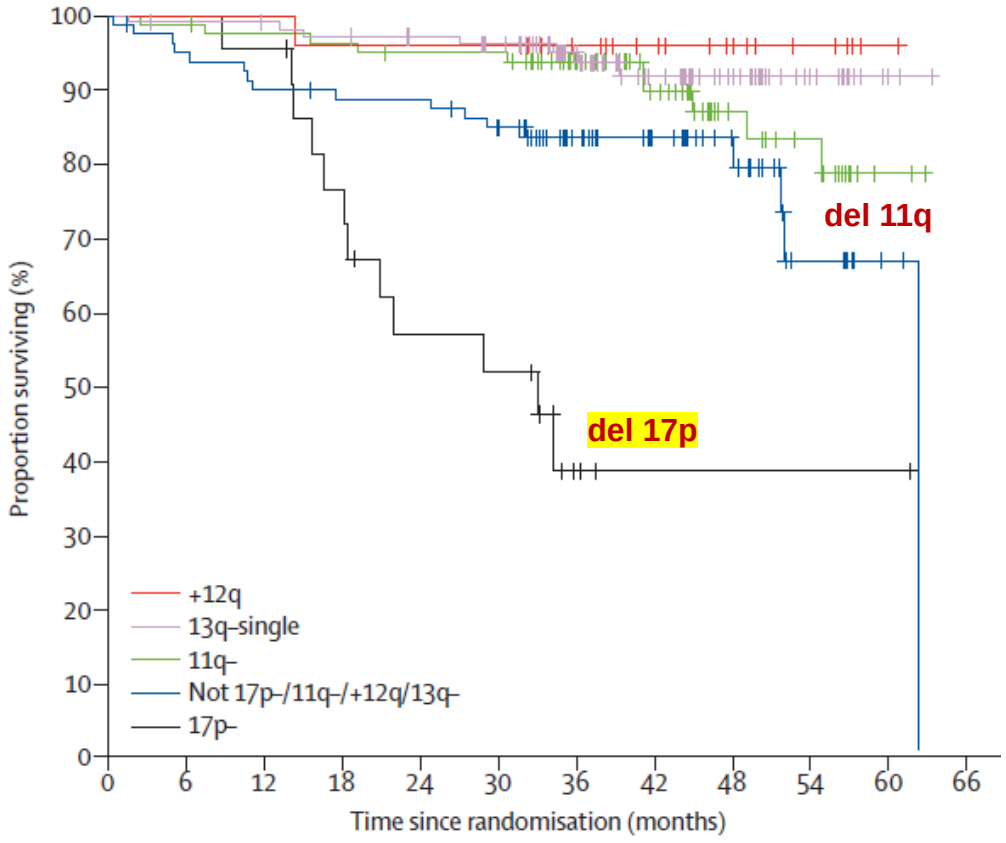
by CD49d



Bulian et al, JCO 2014

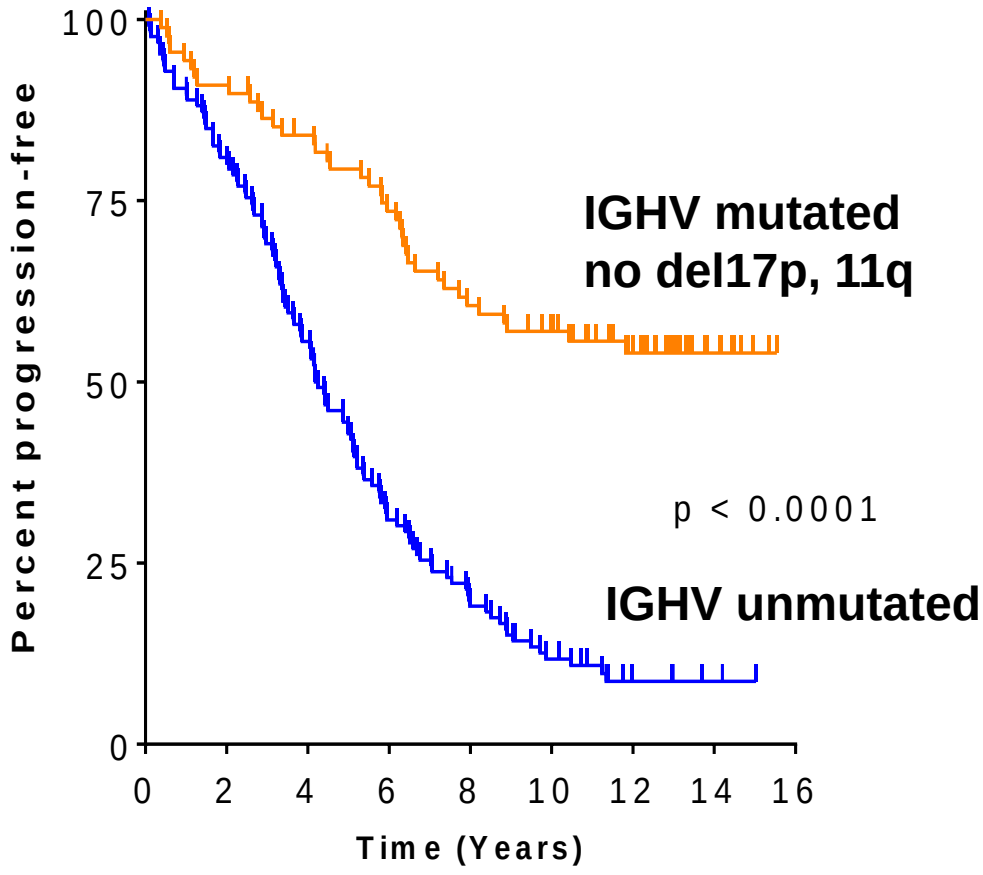
Outcome with first-line chemoimmunotherapy

Overall survival post FCR



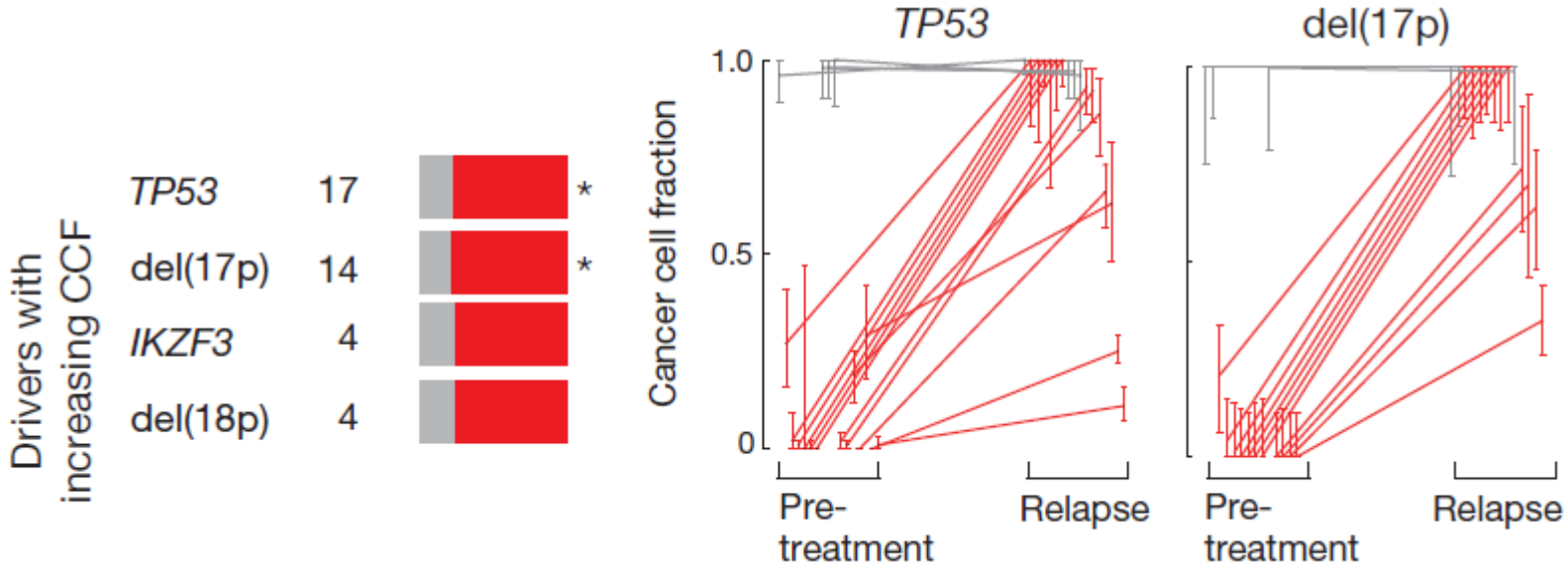
Hallek et al. Lancet, 2010

Long term remissions post FCR



Thompson et al, Blood 2015

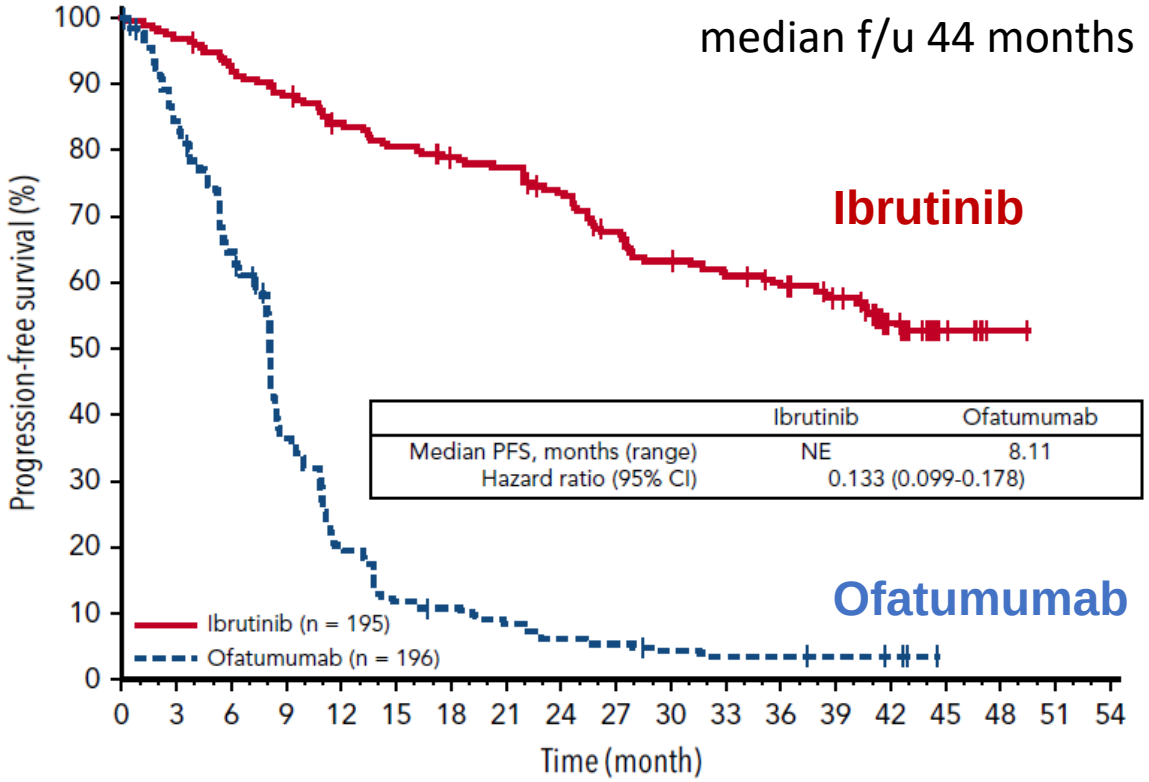
Selection of clones carrying TP53 aberrations during chemoimmunotherapy



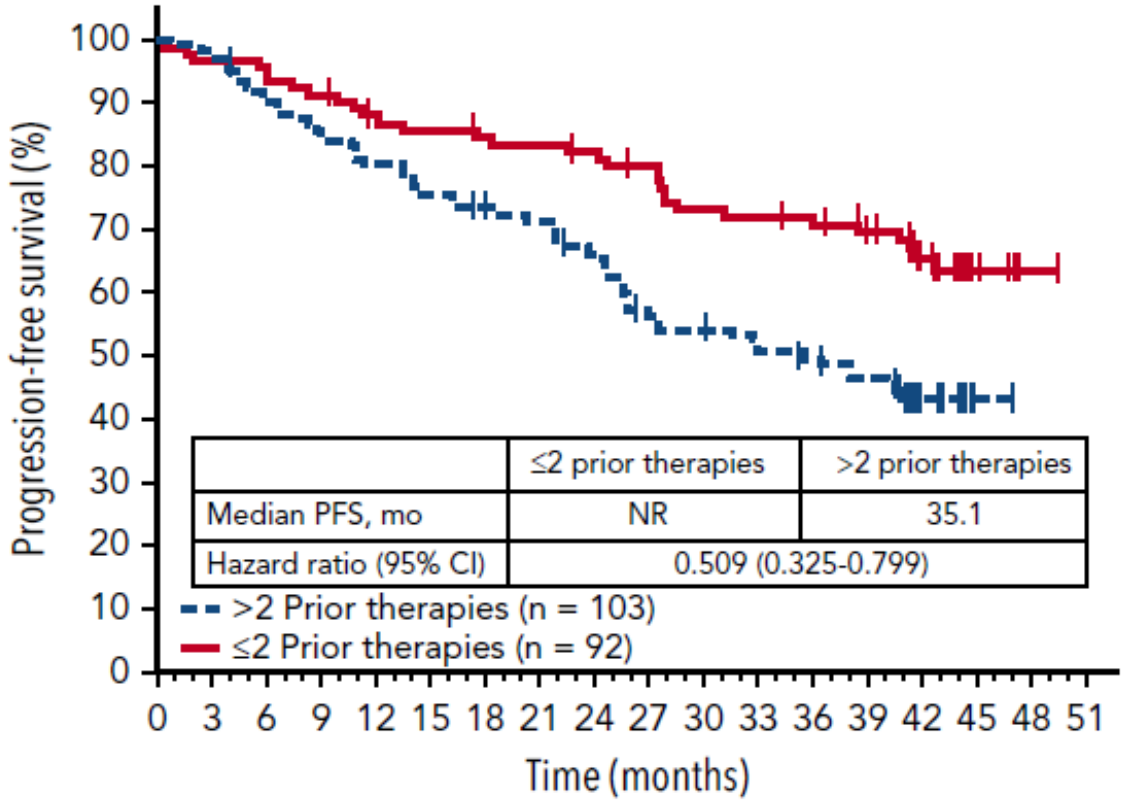
Landau et al, Nature 2015

Ibrutinib vs ofatumumab in relapsed/refractory CLL : Resonate study

Progression-free survival by study arm



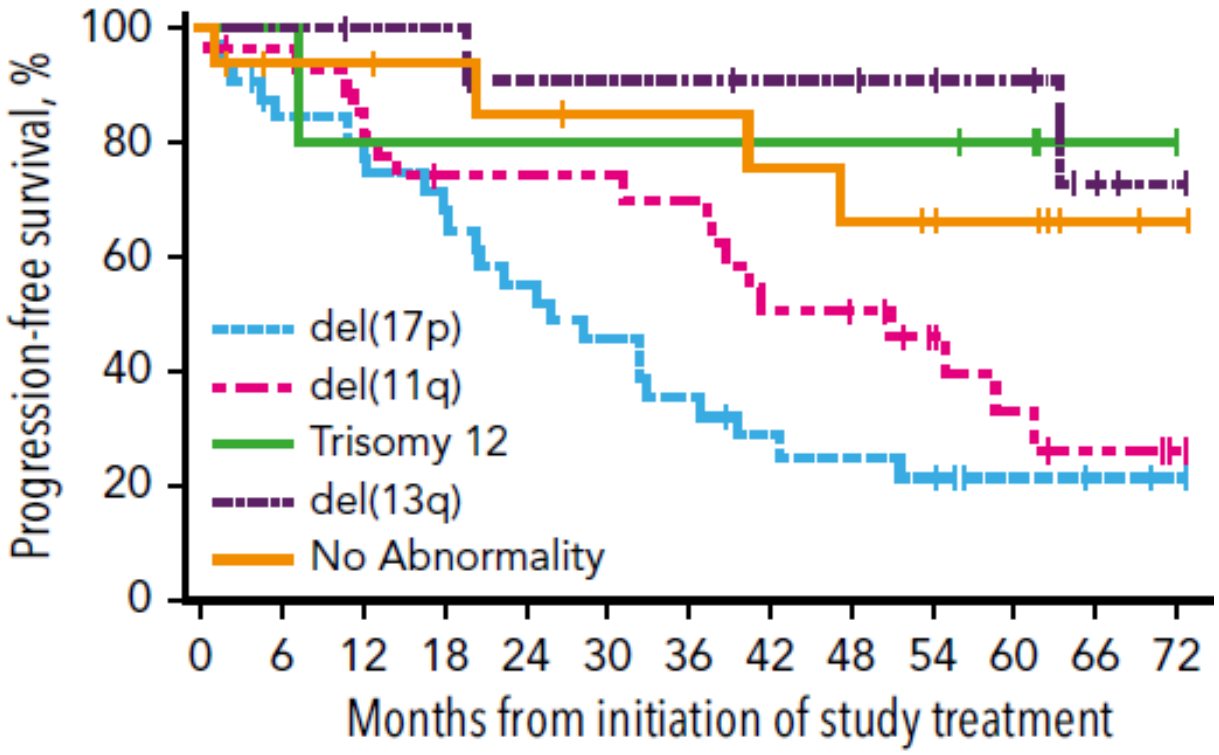
PFS by prior lines of therapy



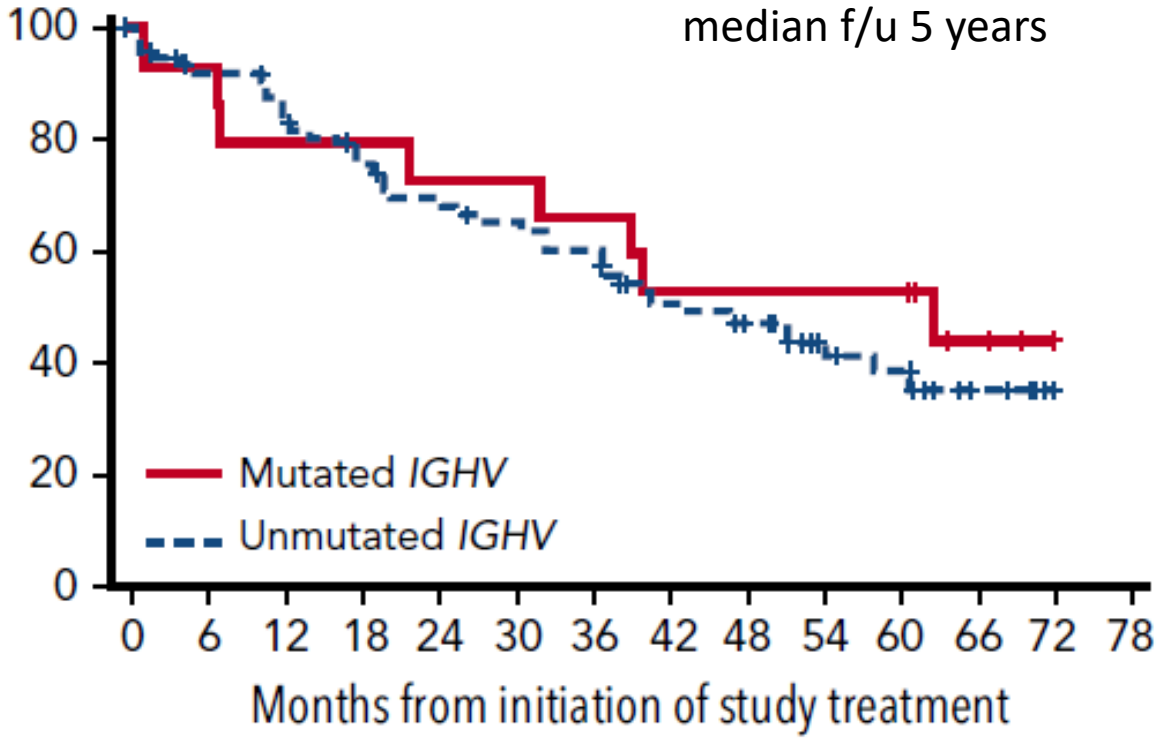
Byrd et al. Blood 2019

Outcome with ibrutinib in relapsed/refractory CLL : phase 1b/2 study

PFS on ibrutinib by cytogenetics



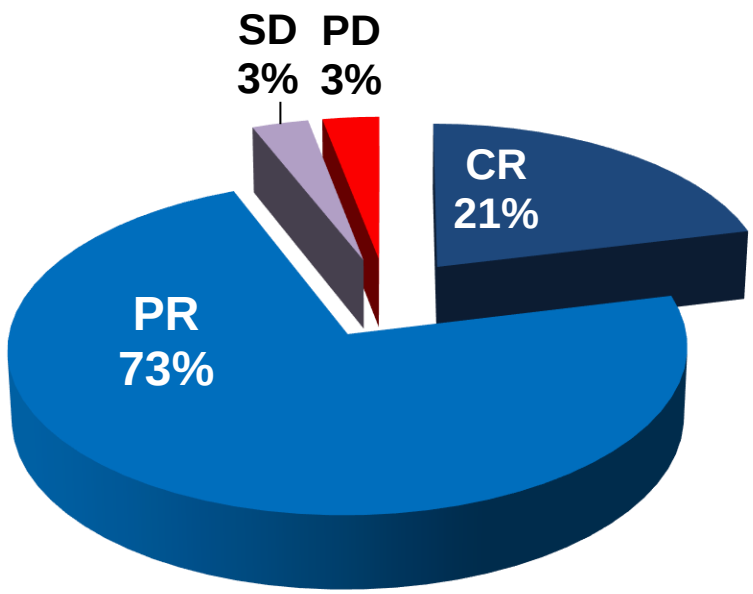
PFS on ibrutinib by IGHV mutation status



O'Brien et al. Blood 2018

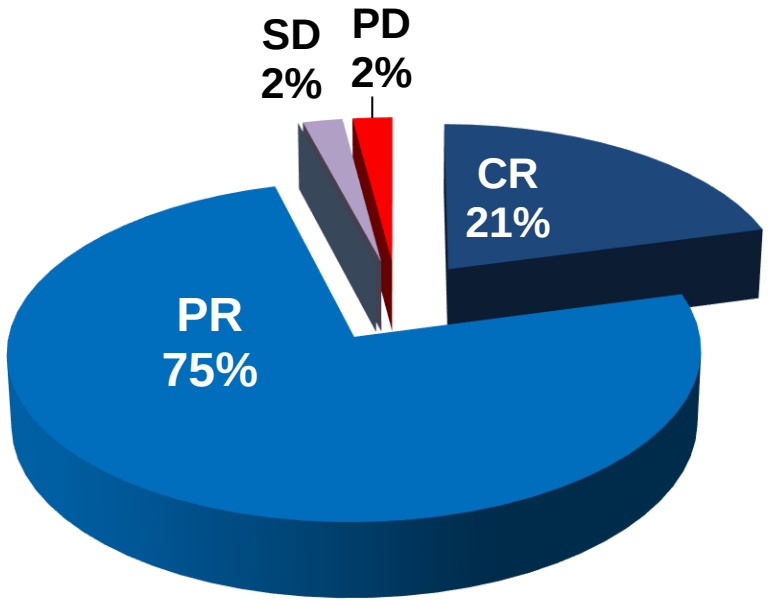
Ibrutinib for CLL with or without TP53 aberration (NHLBI IST)

No *TP53* aberration (n=33)



50% treatment-naive

With *TP53* aberration (n=48)



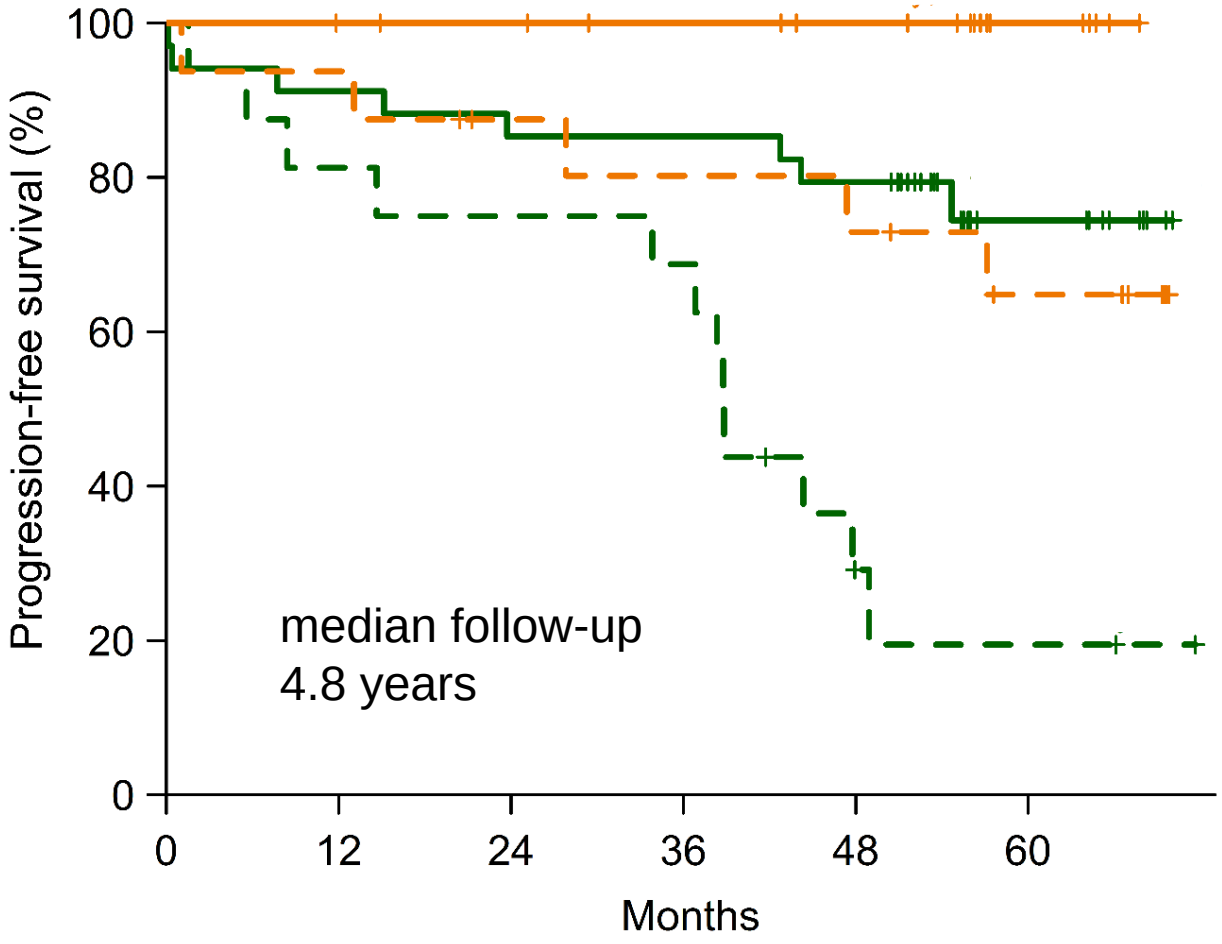
67% treatment-naive

Median to best response 24 months

TP53 aberration:
del17p or *TP53* mutation

Farooqui et al, Lancet Oncology 2015
Ahn et al, Blood 2018
Ahn, Tian, Wiestner. NEJM 2020

PFS on ibrutinib by treatment history and TP53 aberration



First line therapy, no *TP53* aberration

First line therapy, *TP53* aberration

Relapsed/refractory, no *TP53* aberration

Relapsed/refractory, *TP53* aberration

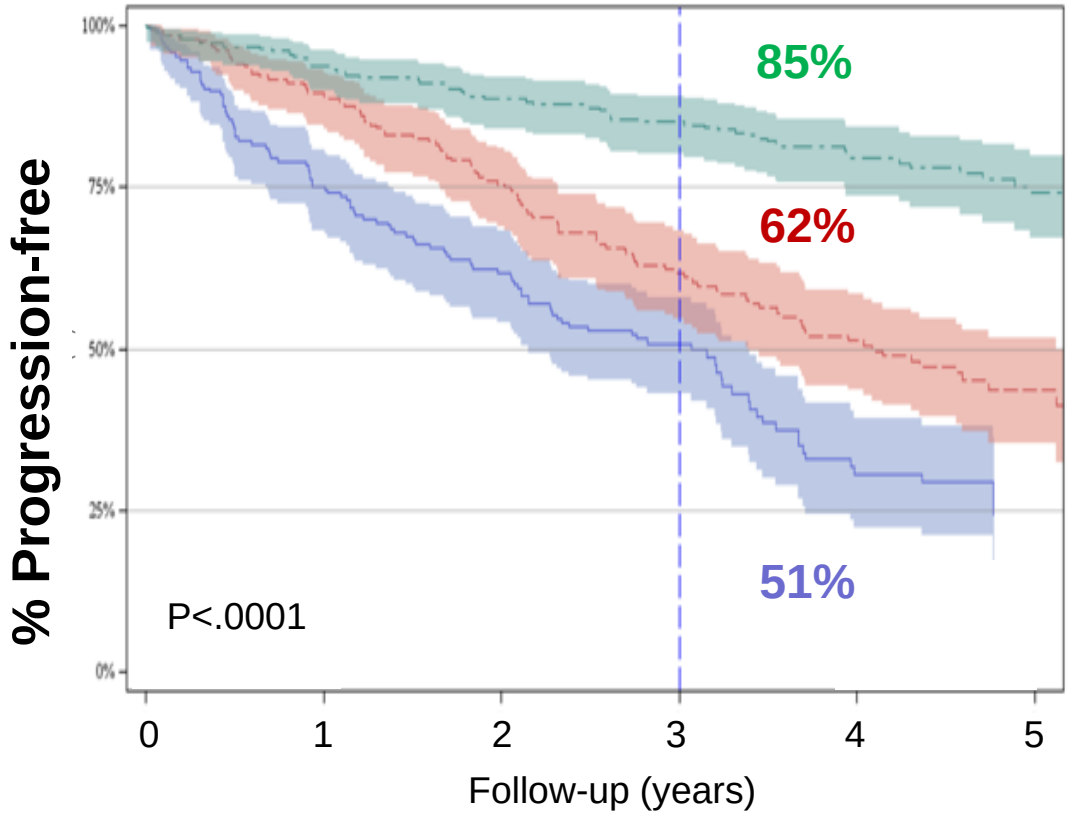
Ahn et al, Blood 2018

Prognostic model of PFS on ibrutinib across CLL populations

Variables	Adverse Factors
Prior treatment	Yes
TP53 aberration	present
B2M	> 4.0 mg/L

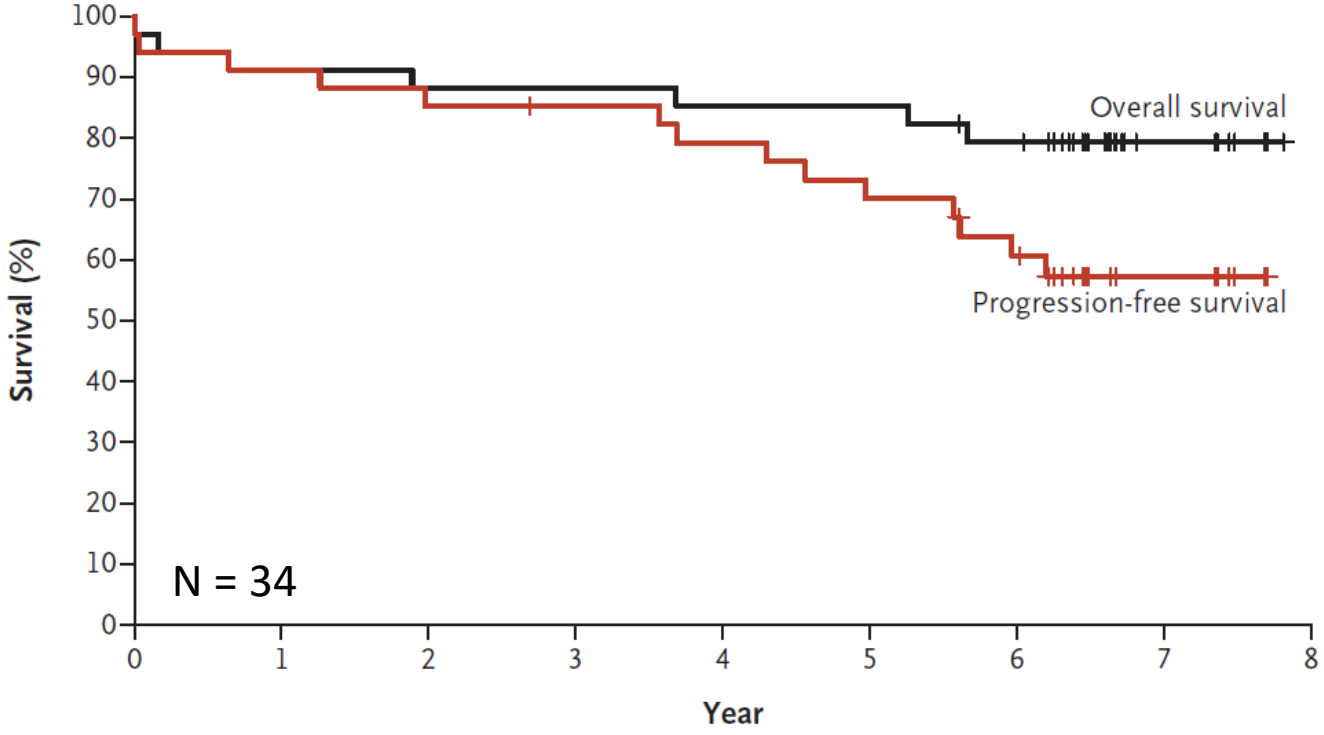
# of Adverse Factors	Risk Group
0-1	Low
2	Int
3	High

Ahn et al, ASH 2018
Ahn et al, JCO in press

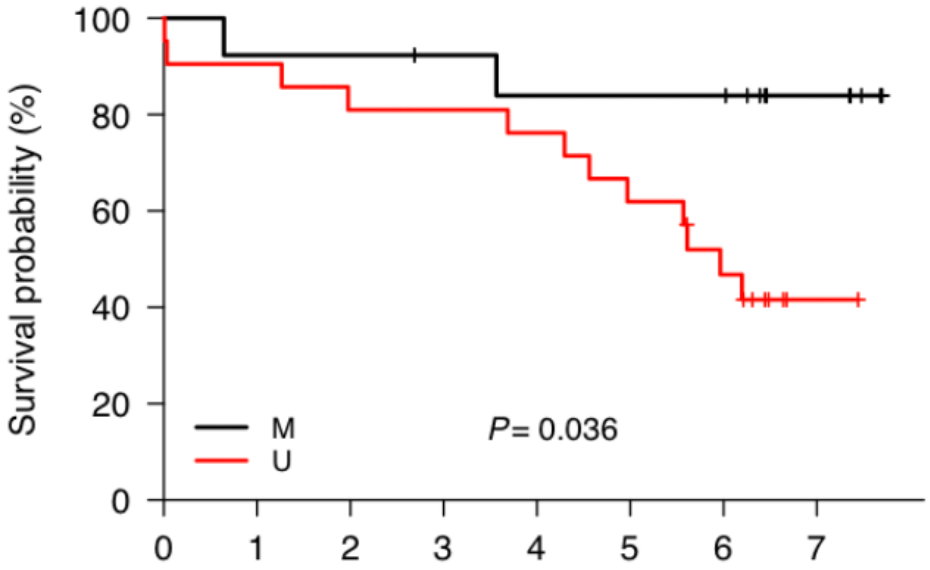


# at risk						
Low	260	229	209	194	137	70
Int	208	180	147	93	67	21
High	187	136	105	52	27	
Total	655					

Long-term disease control with ibrutinib as first line therapy of CLL with TP53 aberration



PFS by IGHV mutation status

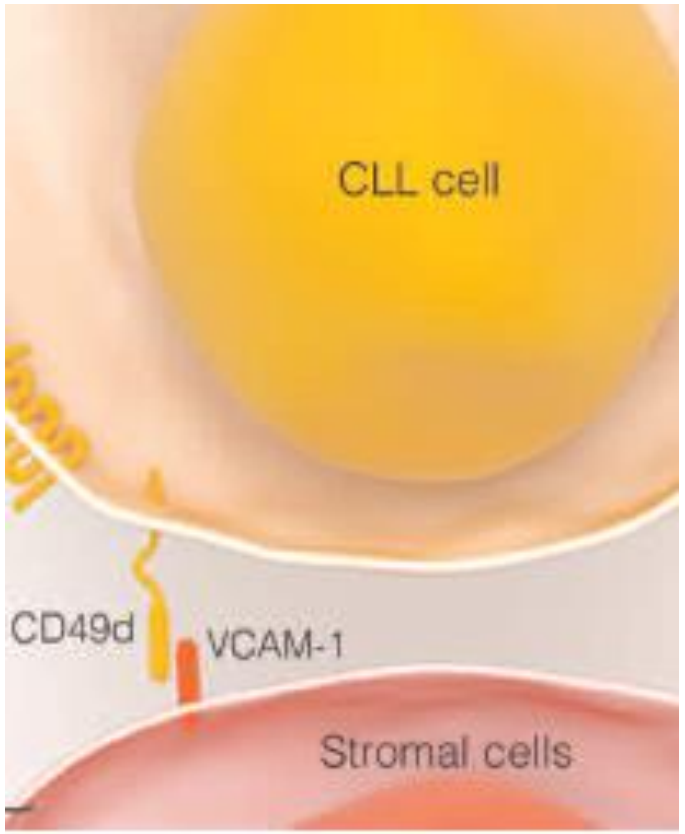


	2 Yr	3 Yr	4 Yr	5 Yr	6 Yr
			% (95% CI)		
Overall Survival	88 (78–100)	88 (78–100)	85 (74–98)	85 (74–98)	79 (67–94)
Progression-free Survival	85 (74–98)	85 (74–98)	79 (67–94)	70 (56–88)	61 (46–80)

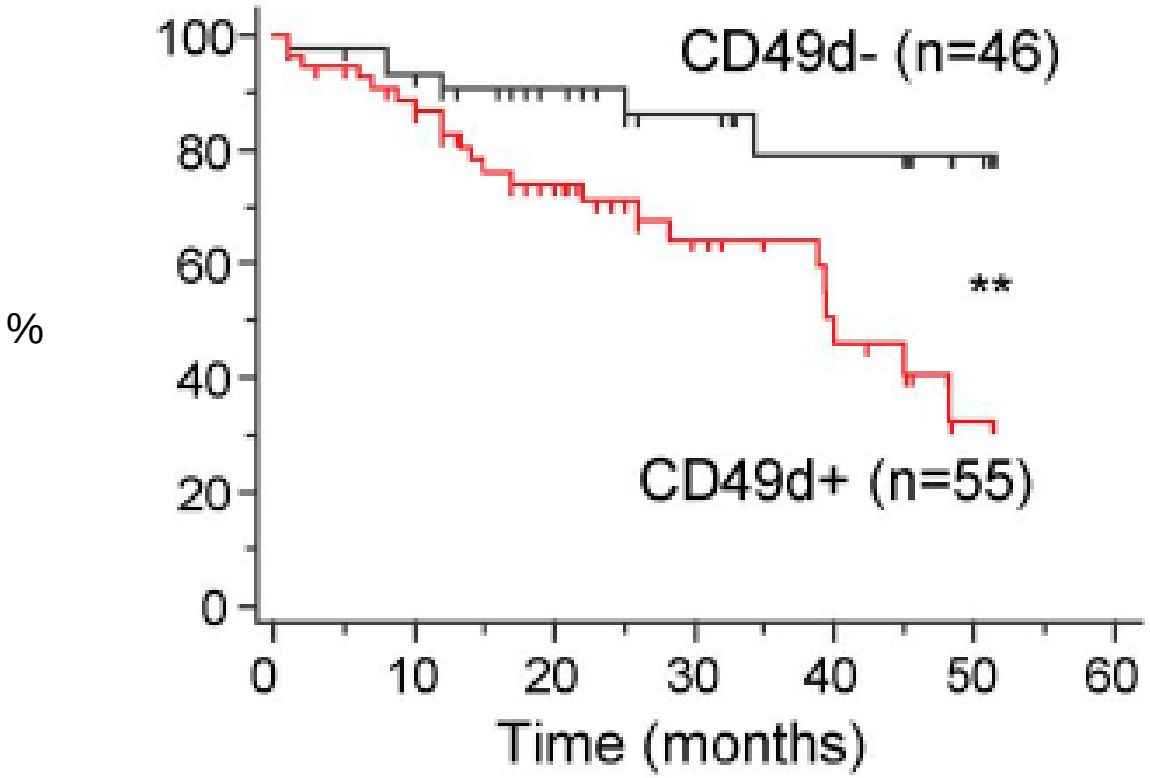
Ahn et al, NEJM 2020

CD49d expression is associated with inferior PFS with ibrutinib

CD49d (integrin α1)
mediates cell adhesion



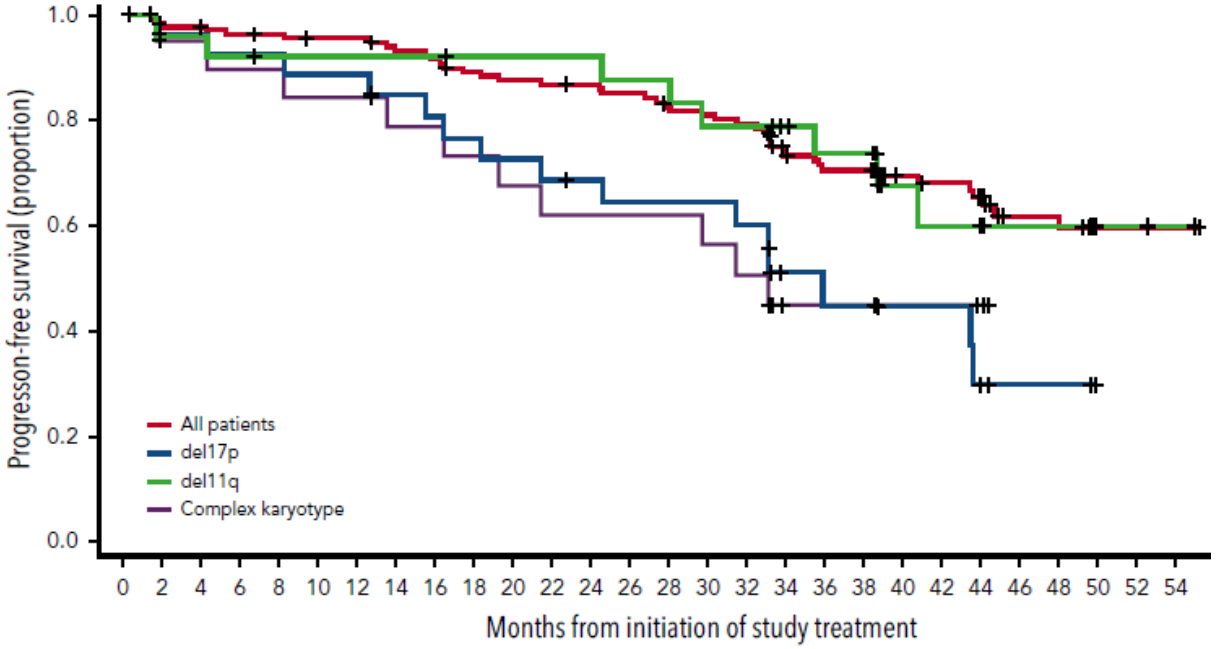
Progression-free survival



Tissino et al, JEM 2018

Acalabrutinib in relapsed/refractory CLL

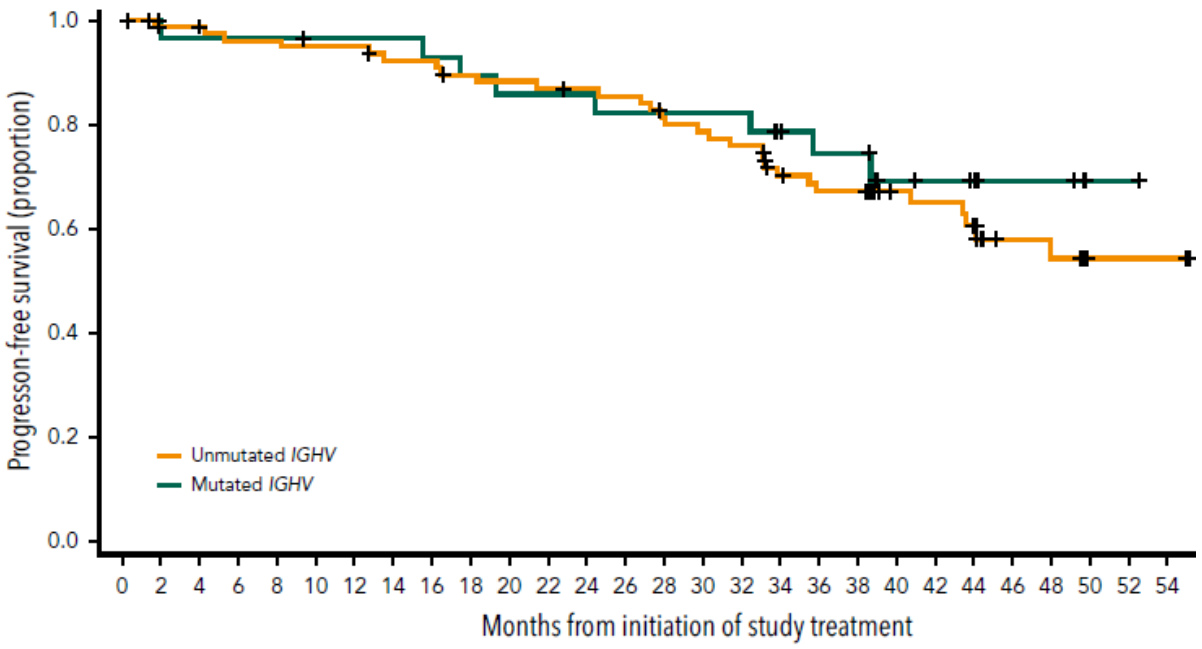
Progression-free survival by cytogenetics



Overall response rate by cytogenetics

All	94%
Del17p	93%
Del11q	95%
Complex	90%

Progression-free survival by IGHV status



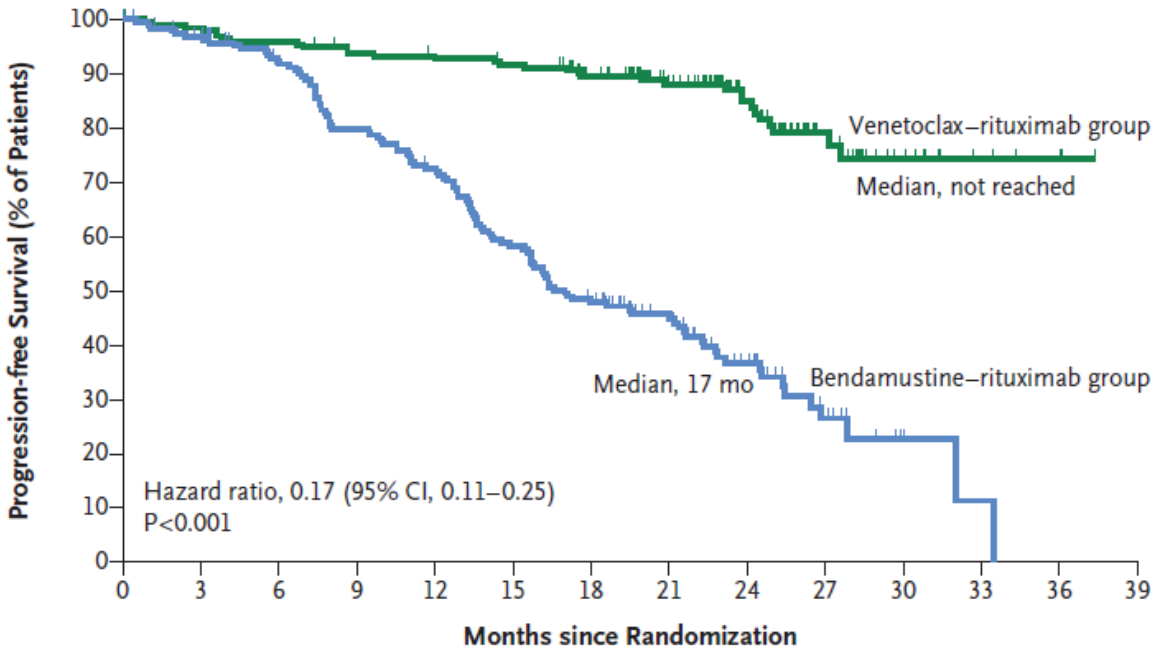
Overall response rate by IGHV

Unmutated	95%

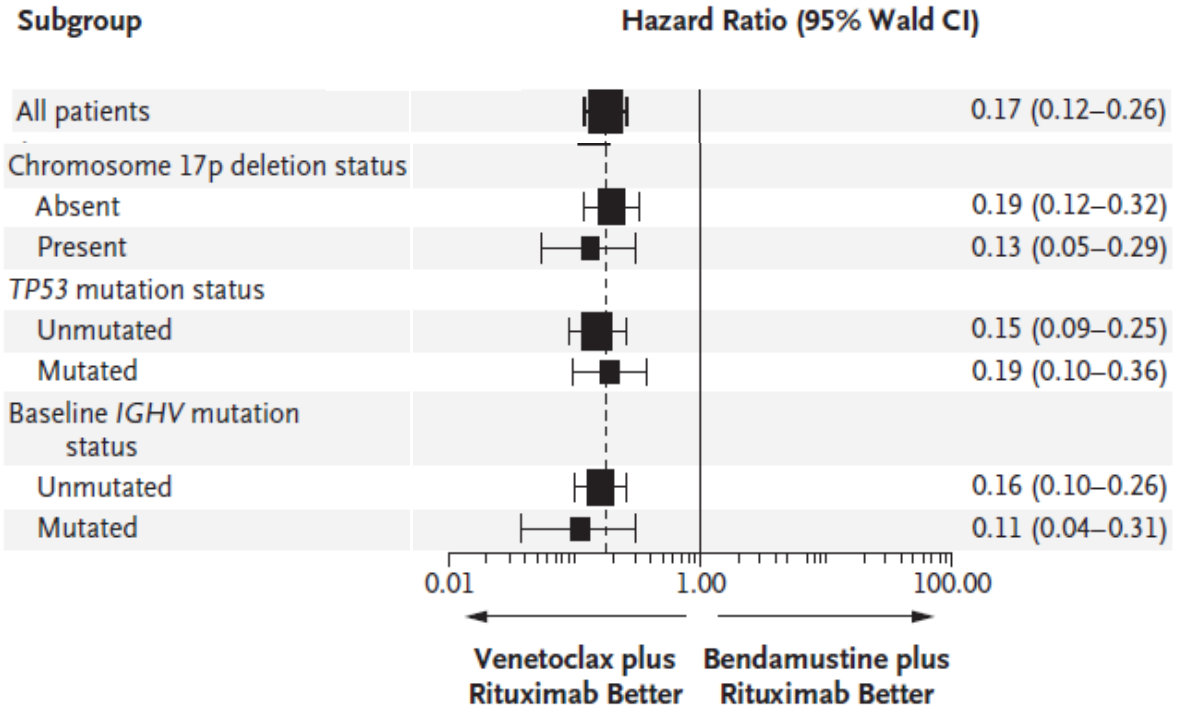
Byrd et al. Blood 2020

Venetoclax-rituximab for relapsed/refractory CLL: the Murano study

Progression-free survival by study arm



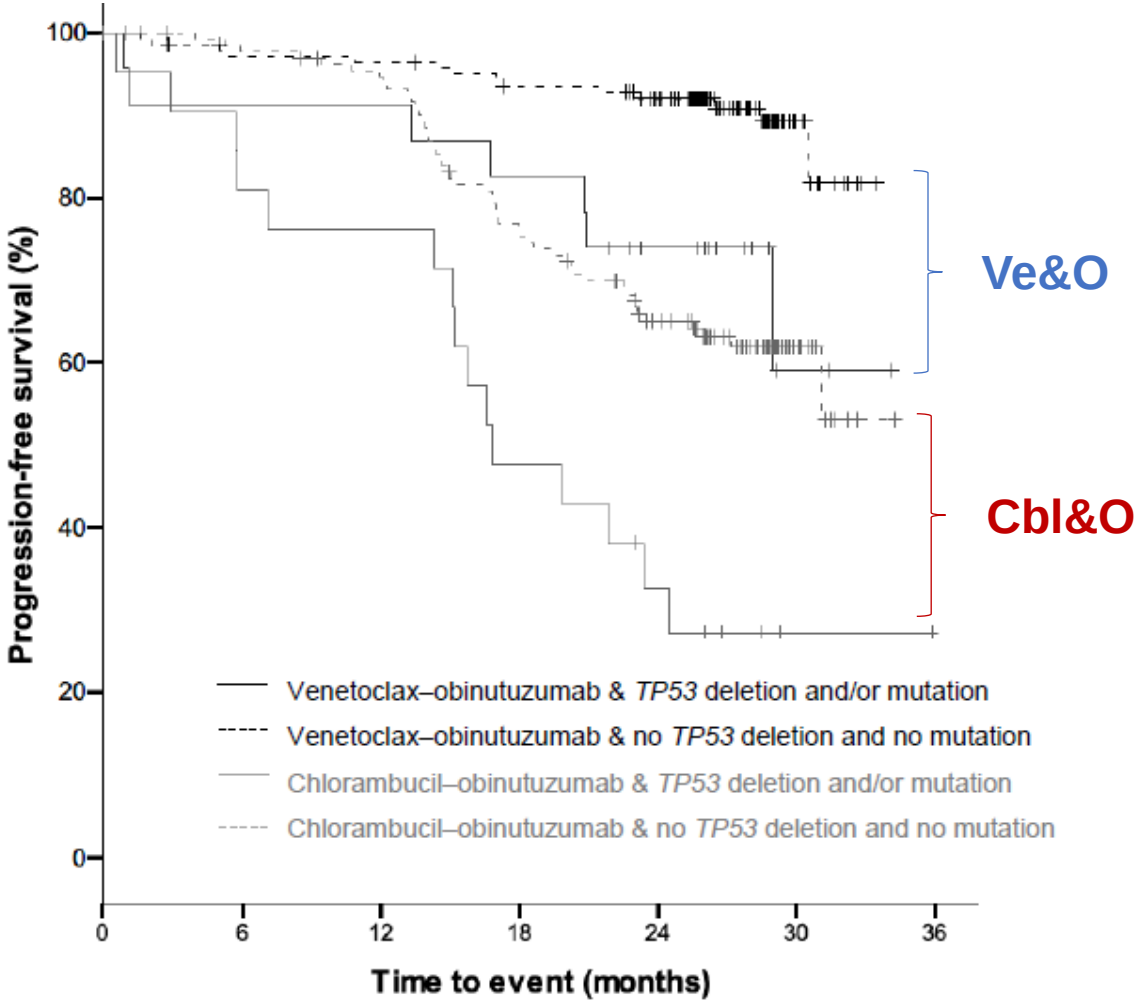
Superior activity across-risk groups



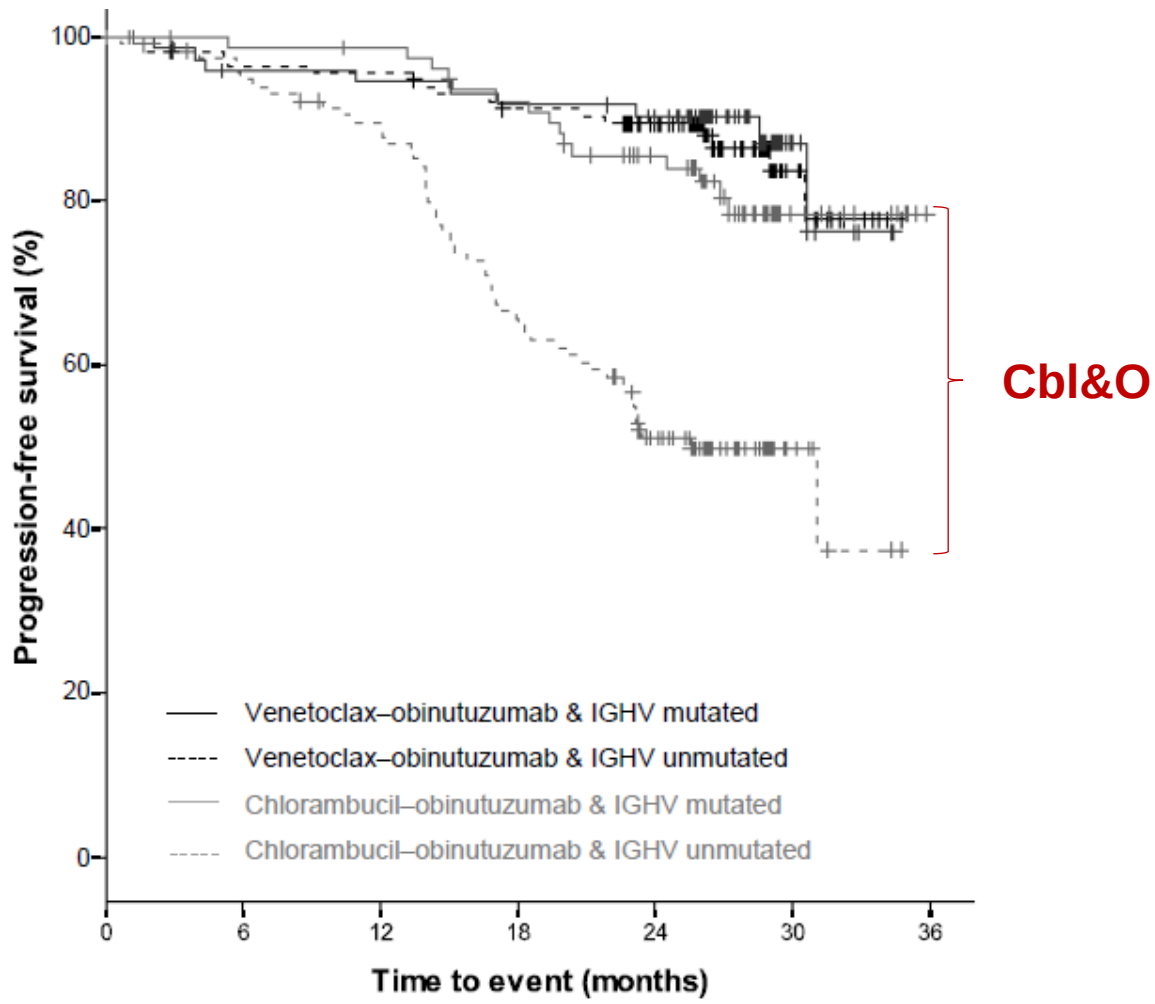
Seymour et al, NEJM 2018

PFS on venetoclax & obinutuzumab (CLL14 trial) by TP53 and IGHV

by *TP53* aberration



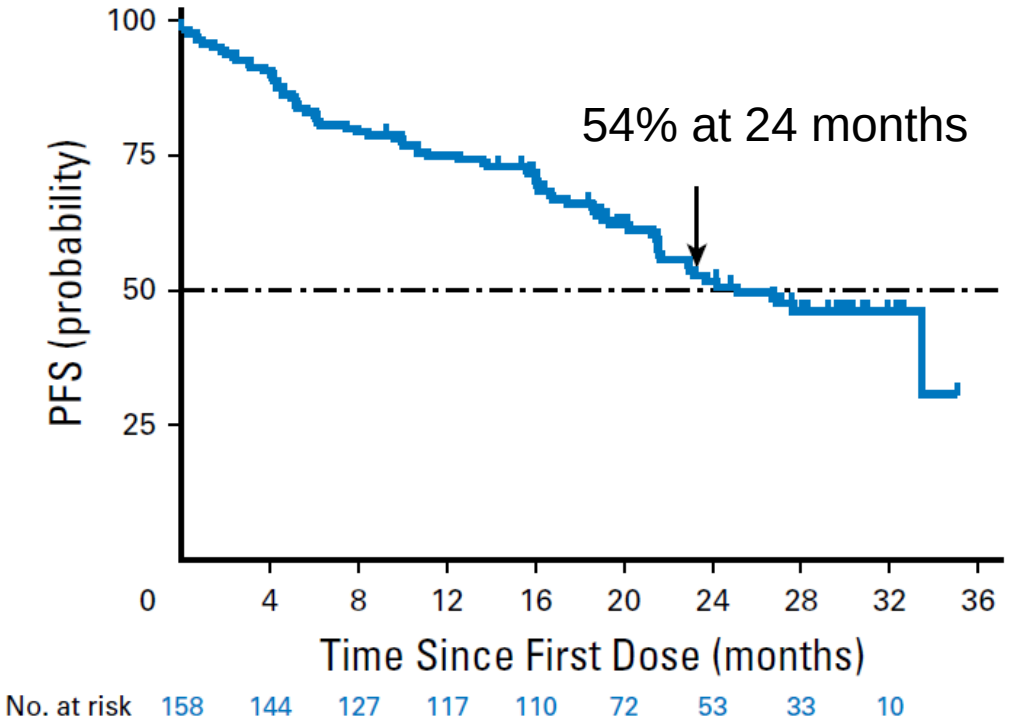
by IGHV status



Fischer et al, NEJM 2019

Targeted agents in relapsed/refractory CLL with TP53 aberration

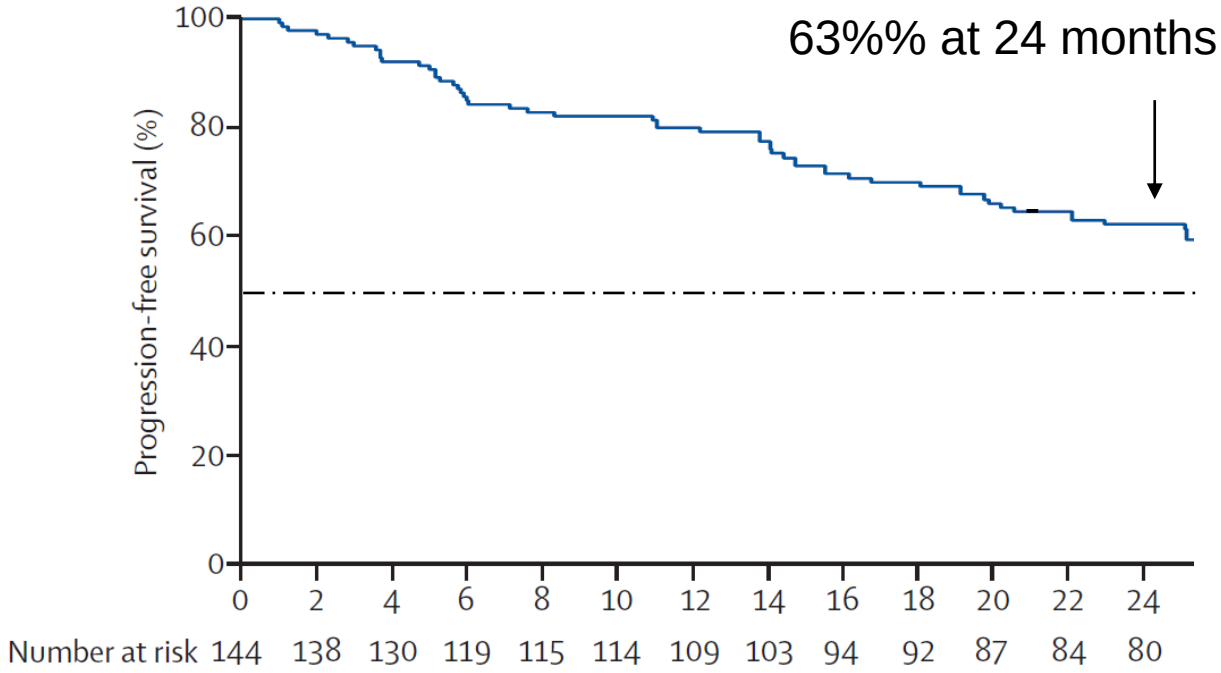
venetoclax



158 patients
Median prior therapies: 2 (0-10)

Stilgenbauer et al JCO 2018

ibrutinib

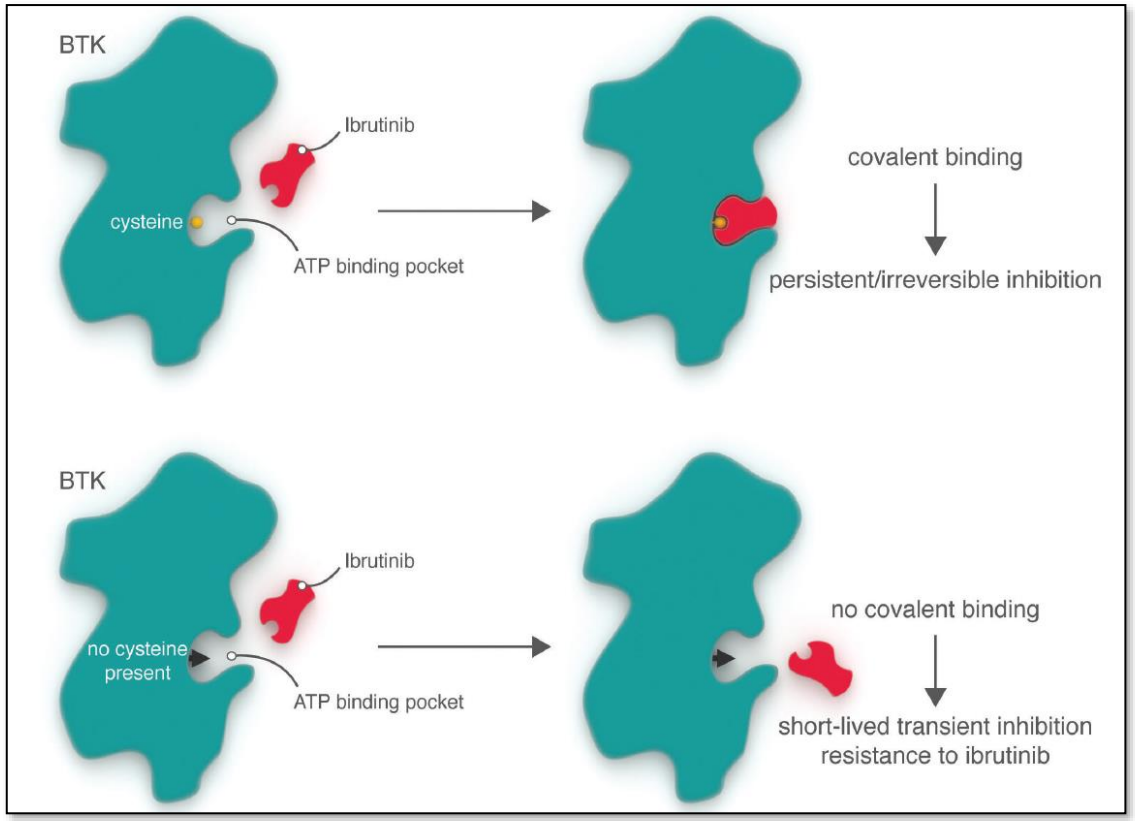


145 patients
Median prior therapies: 2 (1-3)

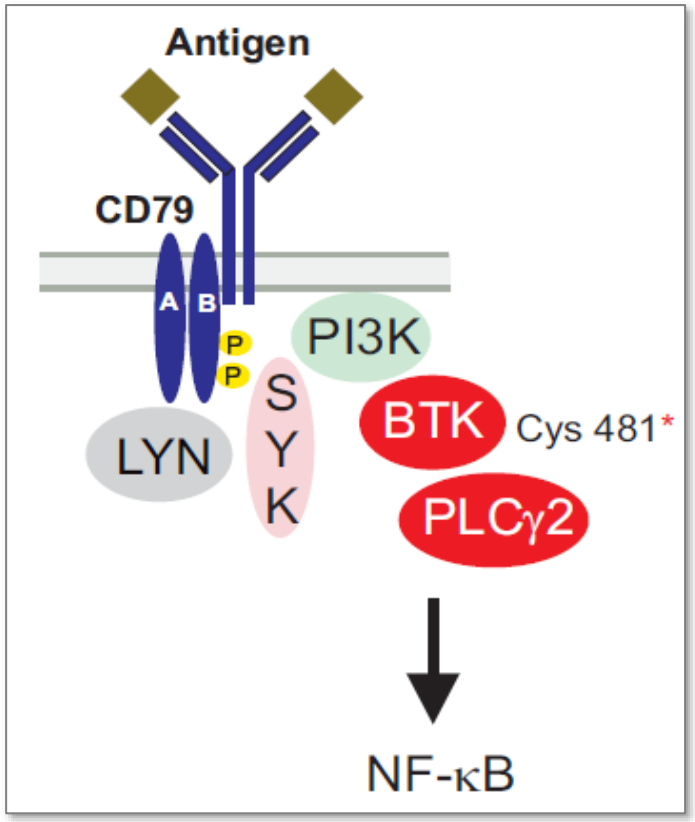
O'Brien et al Lancet Onc 2016

BTK inhibitor resistance and mutations in BTK & PLCG2

Mechanism of action and resistance to BTKi



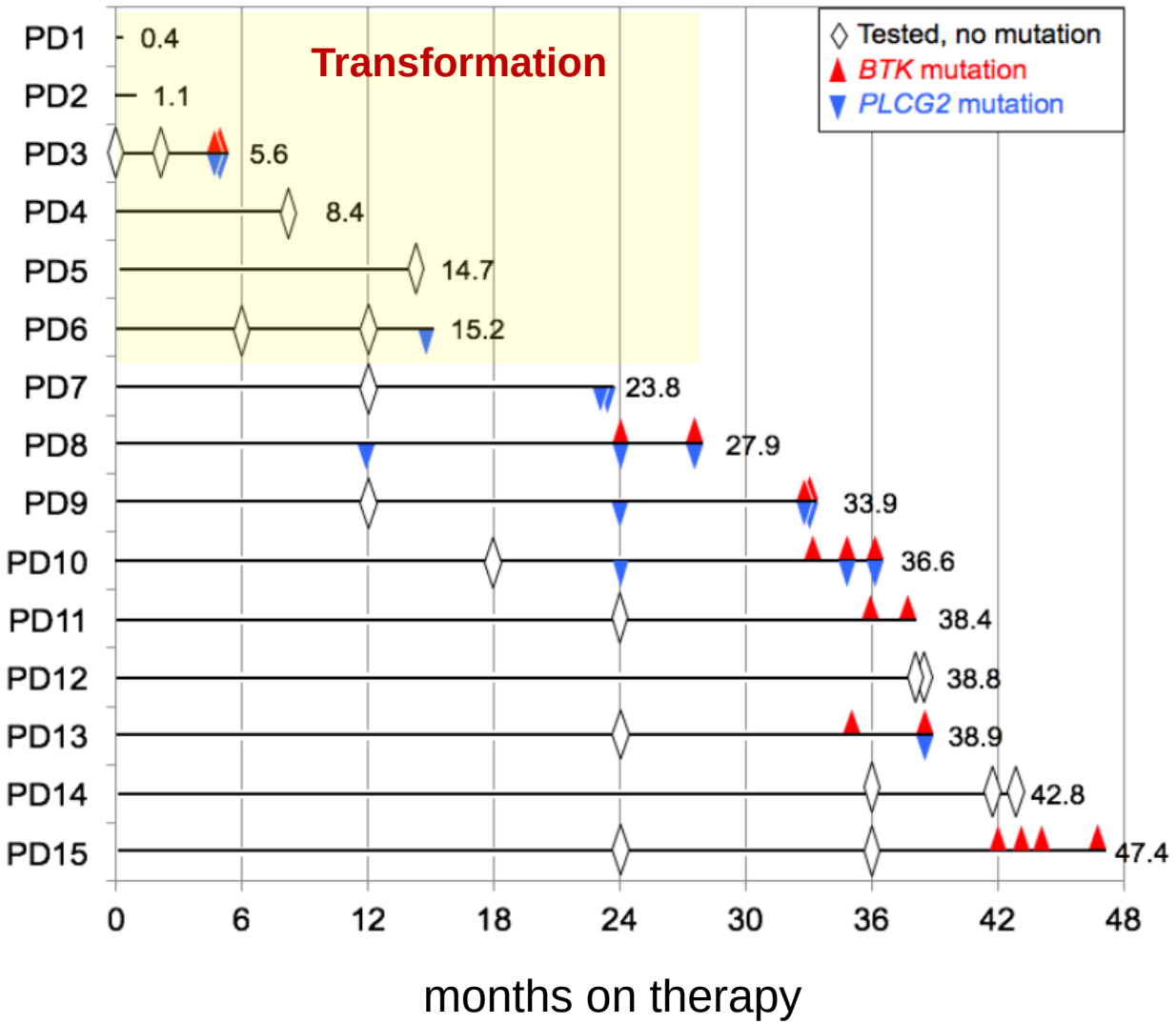
Restoration of B-cell receptor signaling



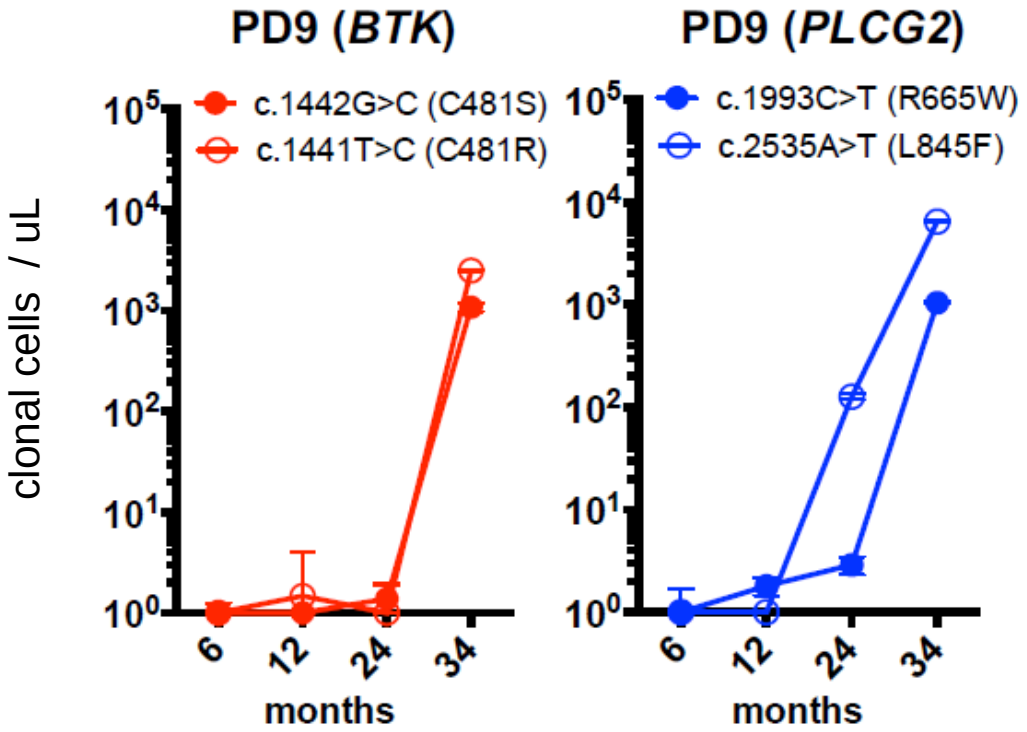
From Wiestner, Haematologica 2015

Chang, ASCO 2013; Woyach, NEJM 2014;
Furman, NEJM 2014

Emergence of multiple ibrutinib-resistant clones over time

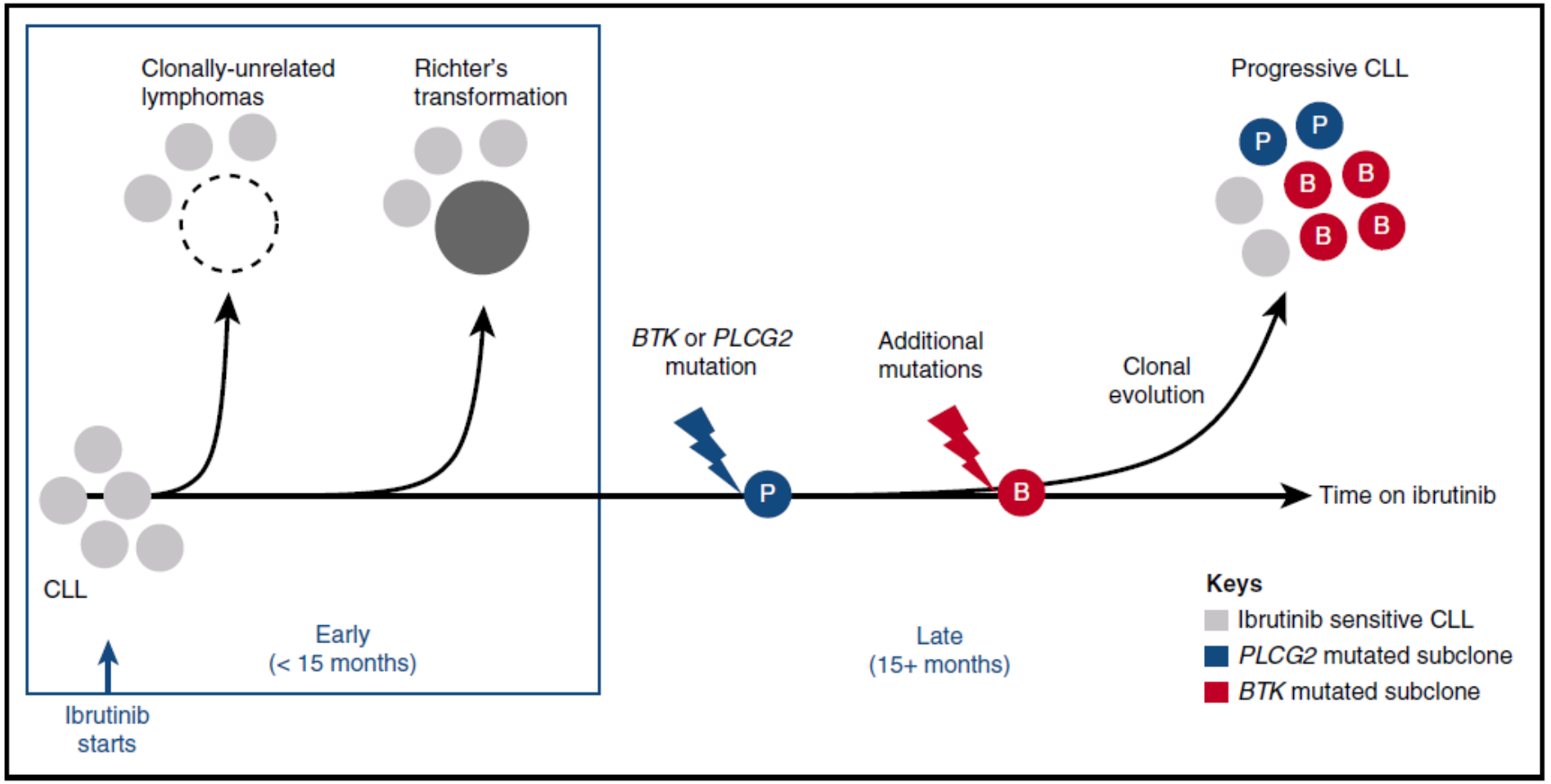


Concurrent expansion of multiple drug resistant subclones



Ahn, Underbayev et al, Blood 2017

Biology of progressive disease on ibrutinib (covalent BTK inhibitors)



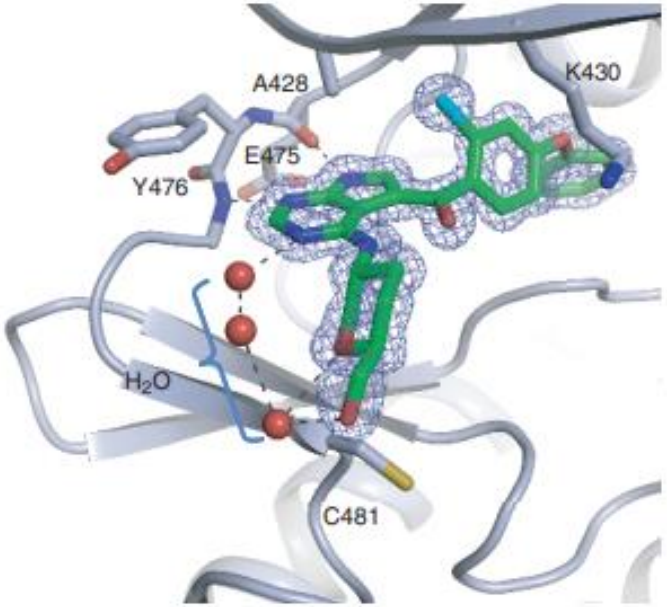
Ahn, Underbayev et al, Blood 2017

Specific mutations are found in ~ 60-70% of patients progressing with CLL.

Ahn, Blood 2017
Woyach, JCO 2017
Byrd, Blood 2020

Overcoming BTKi resistance due to C481 mutations

Reversible BTK inhibition independent of C481

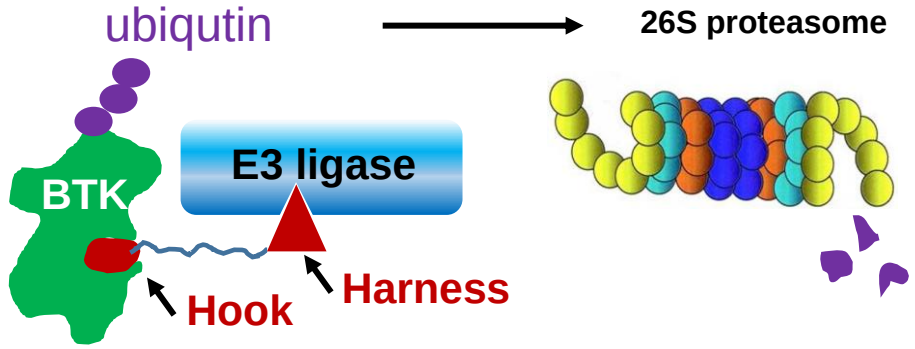


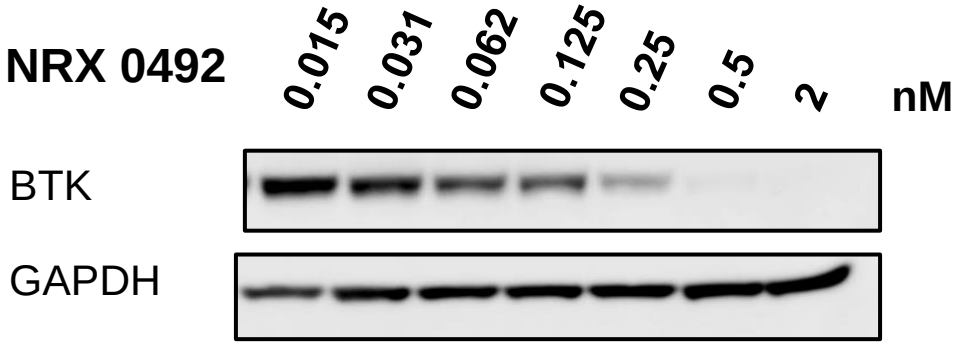
ARQ 531
Loxo 305
Vecabrutinib

www.clinicaltrials.gov

From Reiff et al, Cancer Discovery 2019

Inducing BTK degradation

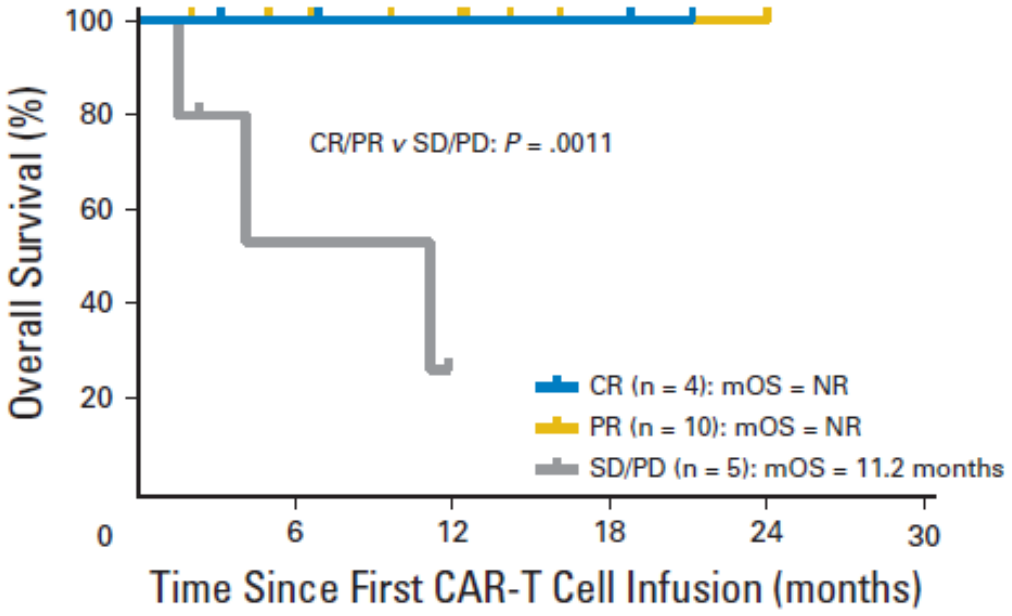




Zhang et al, ASH 2019

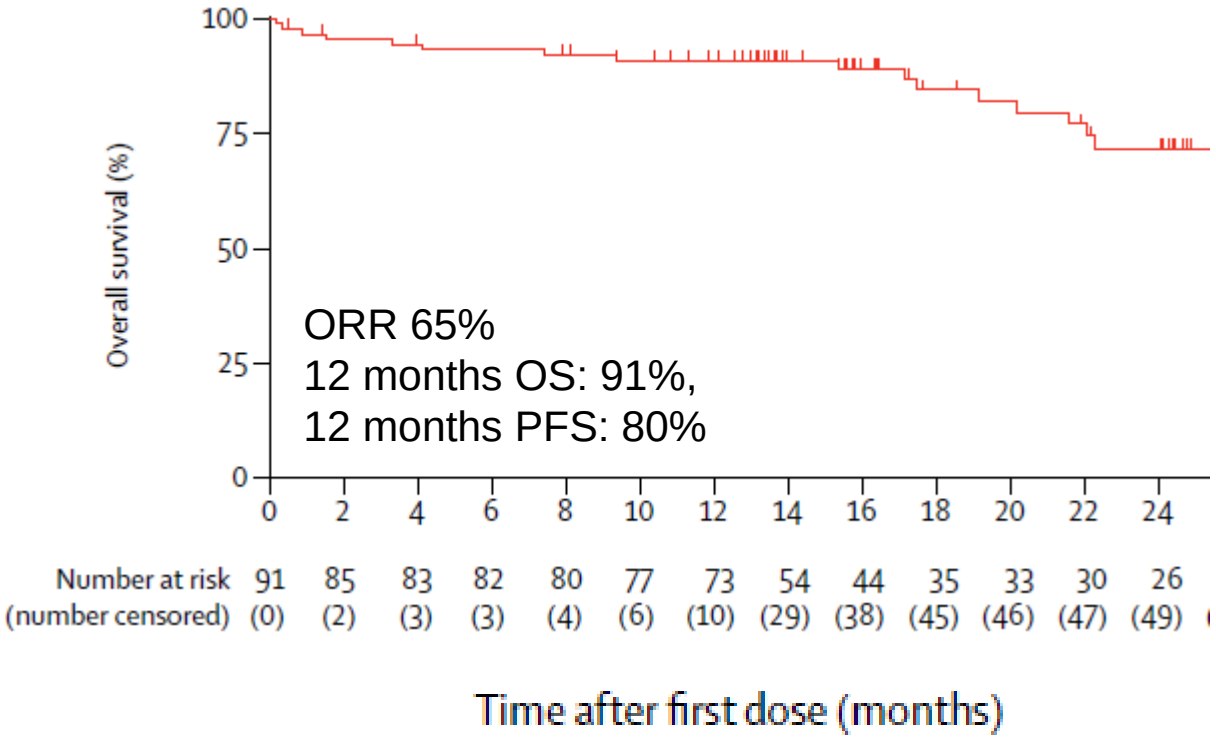
Prognosis after ibrutinib failure: improved with novel therapies

OS with CAR-T therapy



Turtle et al, JCO 2017

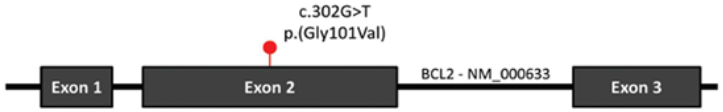
OS with venetoclax after ibrutinib
(68% ibrutinib refractory)

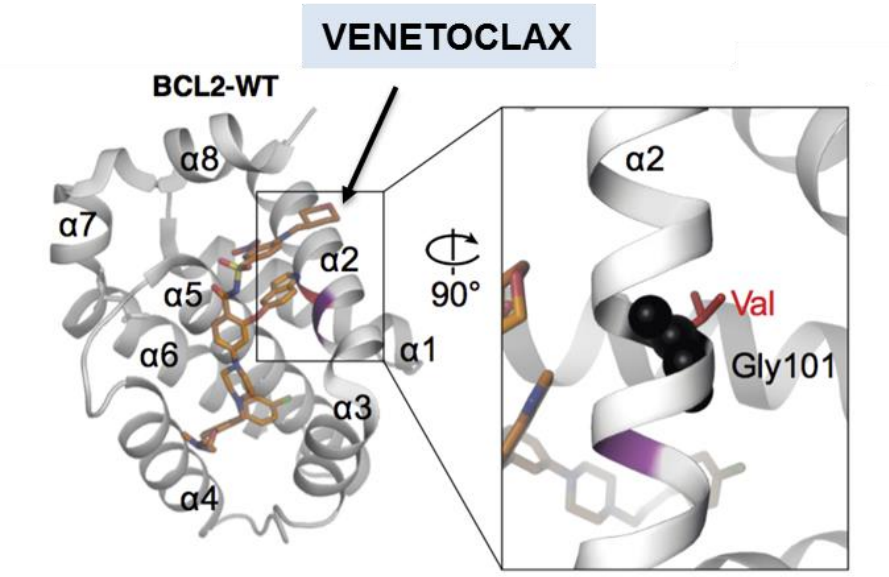


Jones et al, Lancet Oncol 2018

Genetic mechanisms of venetoclax resistance

BCL2 c.302G>T, p.(Gly101Val) detected in samples from 4 patients at CLL-type progression on venetoclax





Population	Number Assessed	BCL2 Gly101Val Detected (%)
Venetoclax-naïve CLL	96	0 (0%)
CLL-type progression on venetoclax	15	7 (46.7%)
Other B-cell malignancies		
- Follicular lymphoma	28	0 (0%)
- Mantle cell lymphoma	28	0 (0%)
- Diffuse large B-cell lymphoma	47	0 (0%)
- Lymphoplasmacytic lymphoma	95	0 (0%)
- Multiple Myeloma	103	0 (0%)
Cancer Database (COSMIC[a])	47, 628	0 (0%)
Population Database (gnomAD[b])	30, 836	0 (0%)

Blombery et al, Cancer Discovery 2019

CLL biology and treatment response

IGHV mutation status:

no difference in ORR, PFS, or OS with ibrutinib (BTK inhibitors) or venetoclax

in IGHV mutated CLL with no adverse cytogenetics chemoimmunotherapy can be equally effective in first line as targeted agents

TP53 aberration:

strongly favors use of ibrutinib (BTK inhibitors) or venetoclax over alternative agents

remains associated with shorter PFS with targeted agents

CD49d expression*:* possibly associated with inferior PFS with ibrutinib, awaiting independent confirmation

Complex karyotype*:* conflicting data, needs standardized methods and confirmation of independent prognostic value

Prior therapy: treatment history impacts PFS with targeted agents (BTKi)

B2M: appears important – at least with ibrutinib, variable cutoffs used

NIH National Heart, Lung, and Blood Institute