Sequential Therapy and Mechanisms of Resistance

Stephan Stilgenbauer

Homburg / Ulm

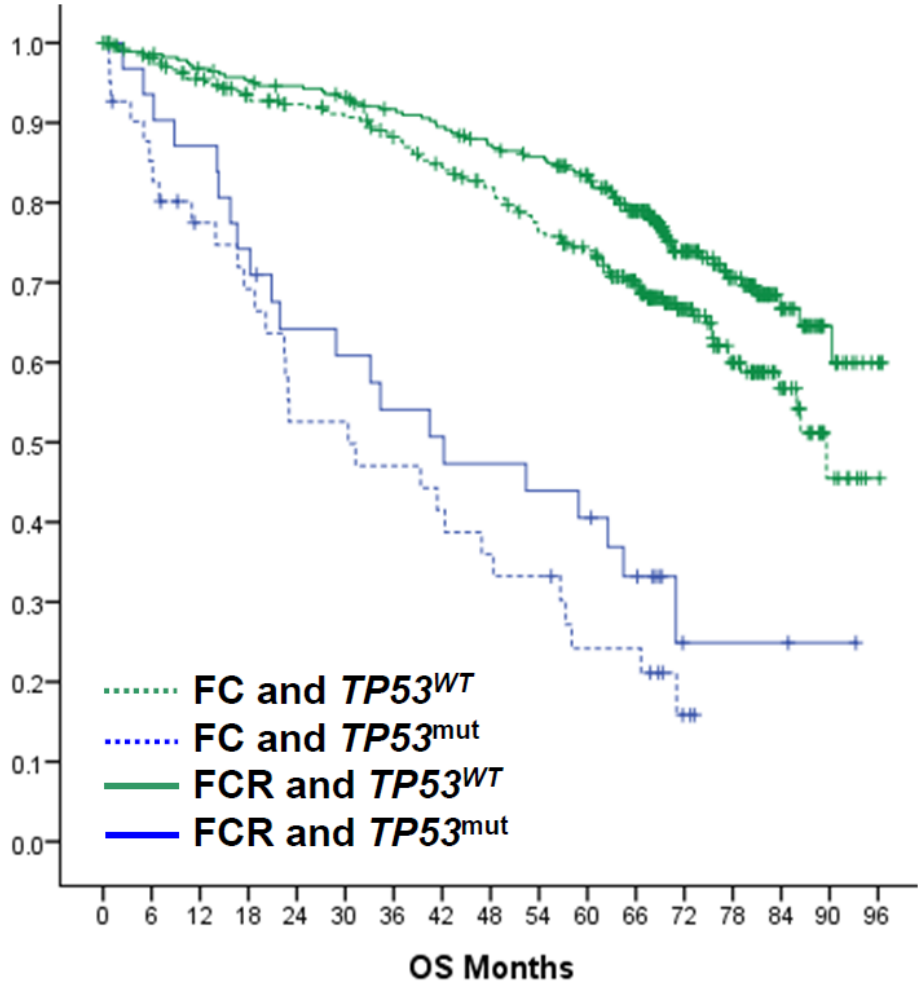
Disclosures Stephan Stilgenbauer:

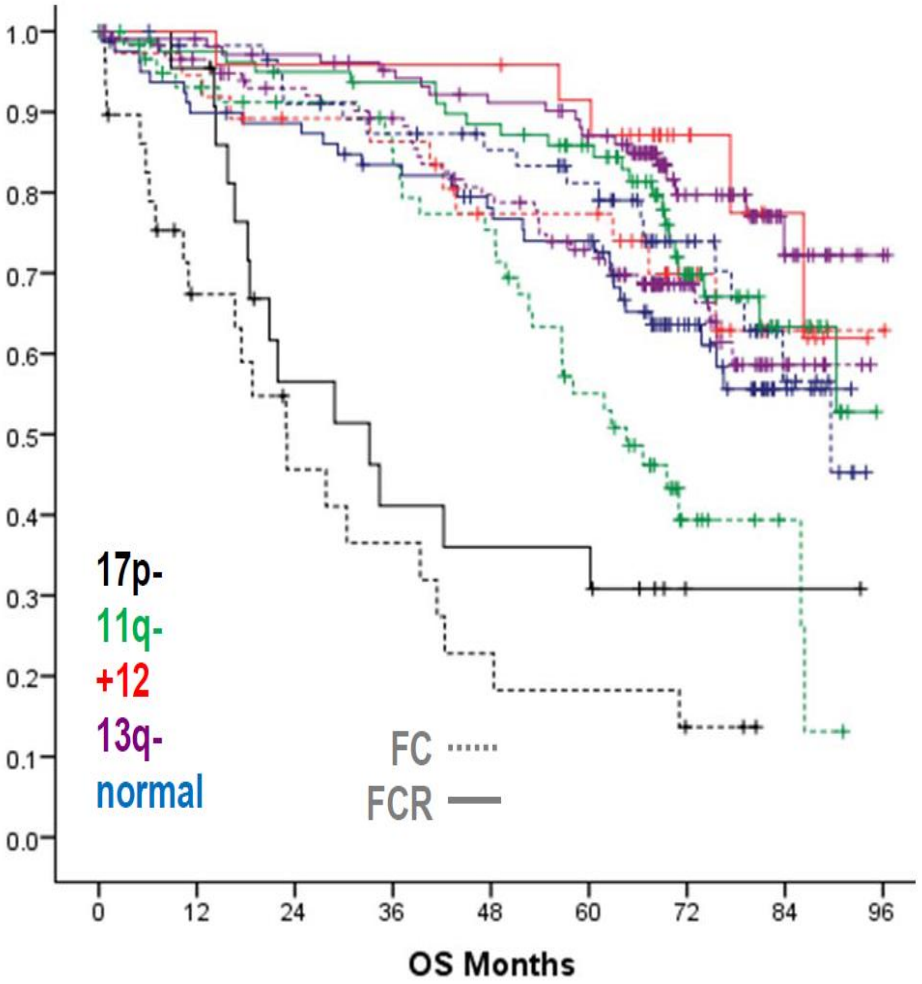
- Advisory board member
- Speaker honoraria
- Research grants
- Travel support

AbbVie, Amgen, Celgene, Gilead, GSK, Hoffmann-La Roche, Janssen, Novartis, Pharmacyclics, Sunesis

CLL8 Trial: Overall Survival by Genetic Subgroup and Treatment

Stilgenbauer et al. Blood 2014



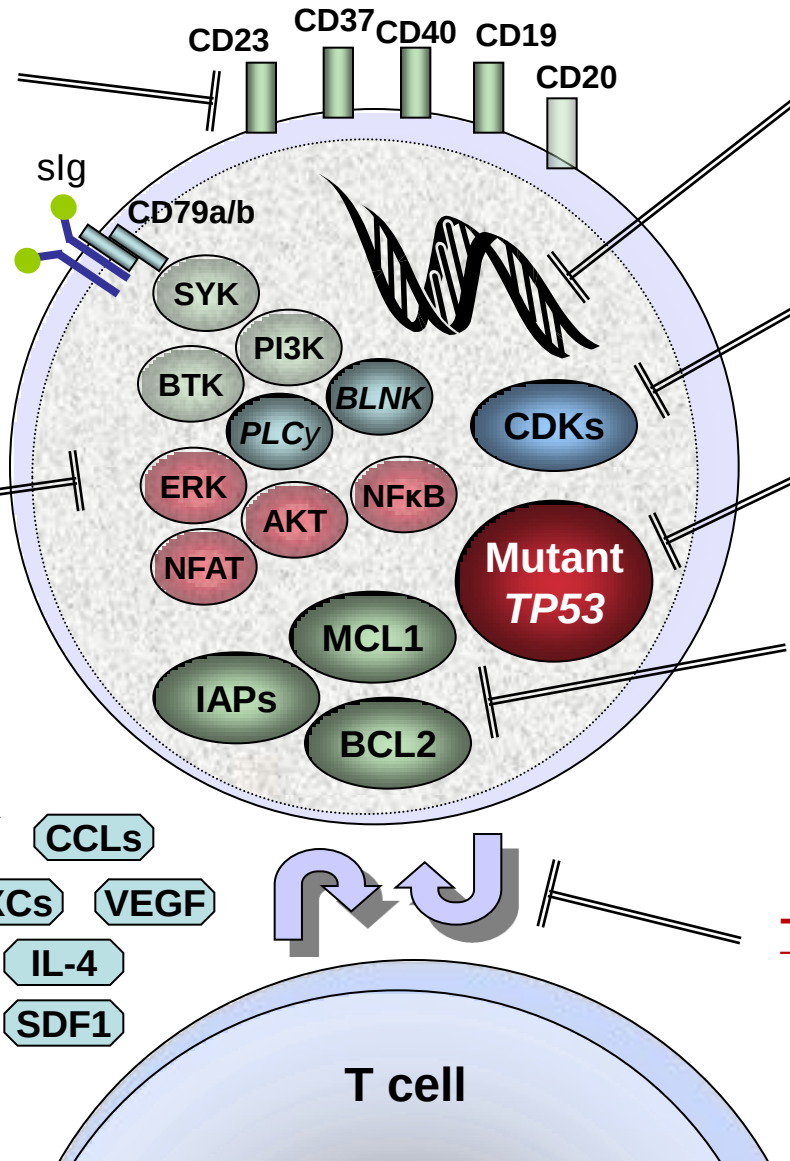


From Biology to Therapy: Model System CLL

Antibodies:
Rituximab (CD20)
Ofatumumab (CD20)
Blinatumomab (CD19/CD3)
XmAb5574 (CD19)
HCD122 (CD40)
Obinutuzumab (CD20)

Signal transduction inhibitors:
Idelalisib (PI3K)
Duvelisib (PI3K)
Ibrutinib (BTK)
Fostamatinib (Syk)
A-443654, GSK690693 (Akt)

Microenvironment modulation:
Lenalidomide (Imids)
CXCR4 antagonists



Classical treatment:
Chemotherapy

CDK inhibitors:
Flavopiridol
Dinaciclib

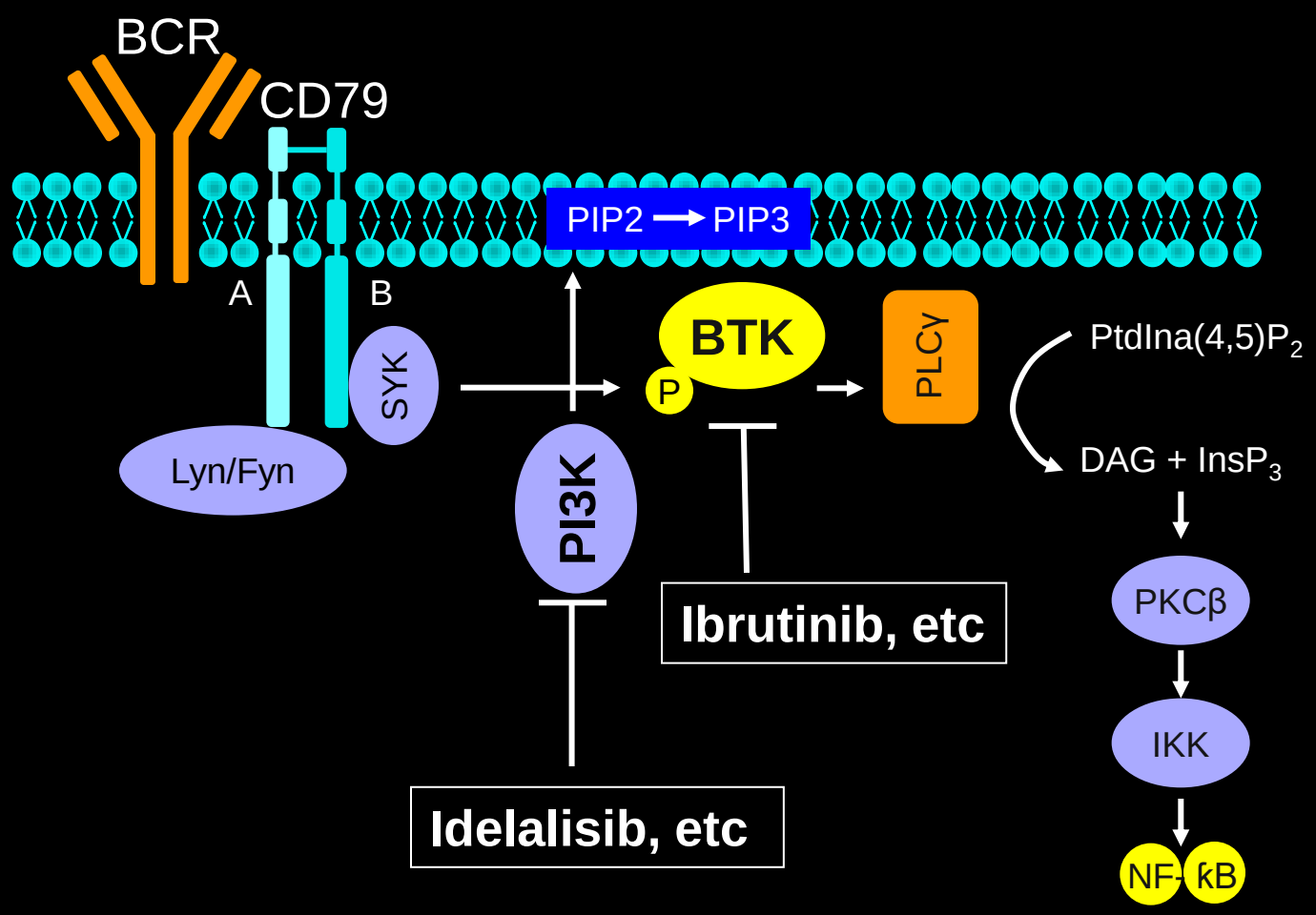
Aberrant p53:
PRIMA, RITA
HDAC inhibitors

Apoptosis machinery:
SMAC-mimetics
Obatoclax GX15-070
Venetoclax (BCL2)

T cell - CLL interaction:
Lenalidomide (Imids)
CAR T-cells (CD19)
Allo-SCT (GvL effect)

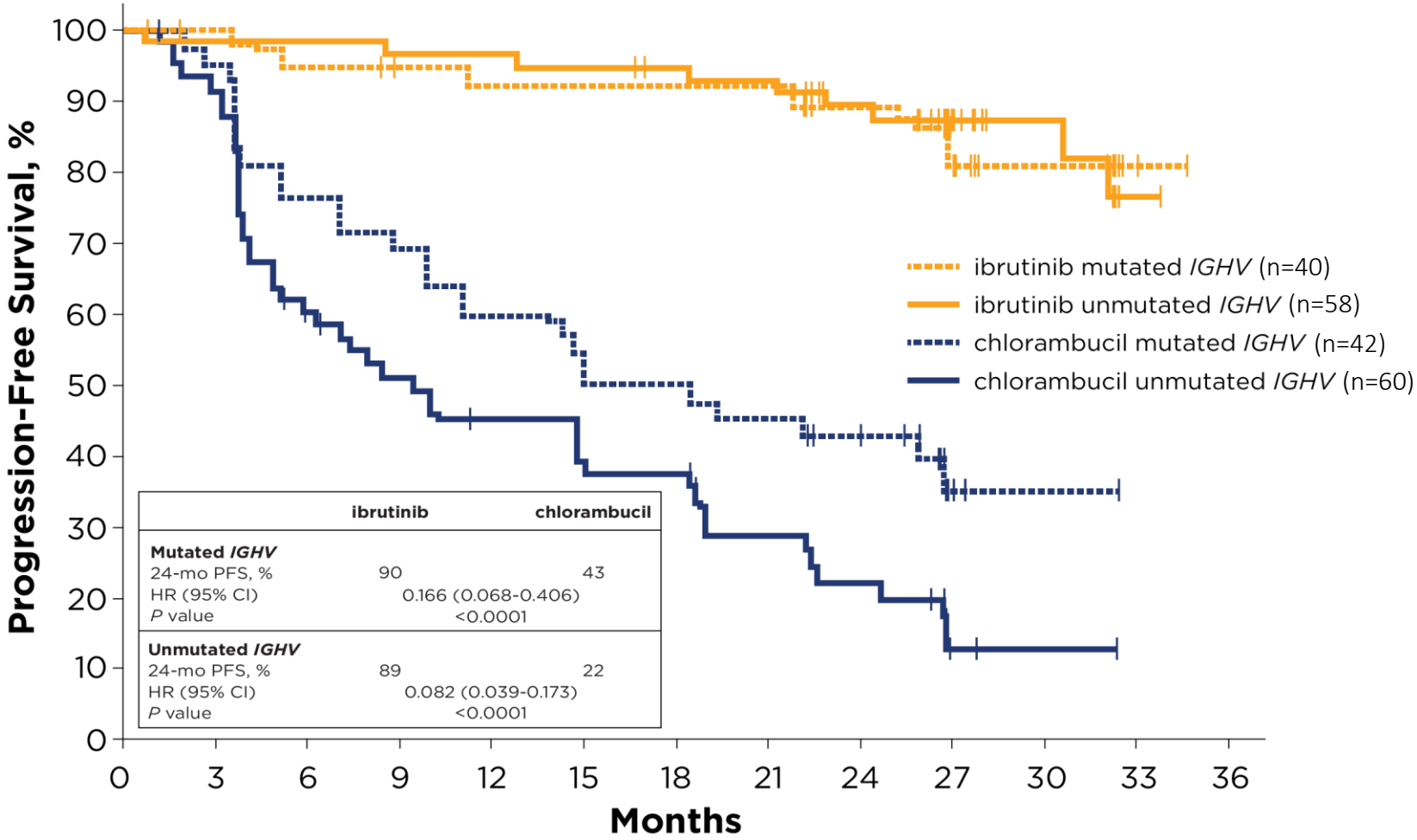
B Cell Receptor Signaling Inhibition as Therapeutic Principle in CLL

Wiestner A et al. ASH 2014



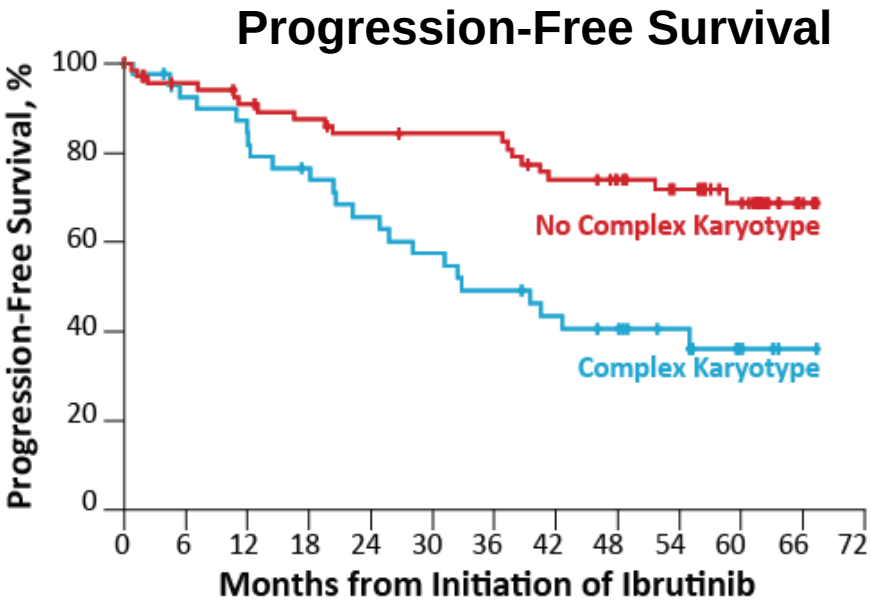
Frontline Ibrutinib vs. Chlorambucil in CLL Patients ≥65 Years CLL, no 17p- RESONATE-2 Trial (n=269)

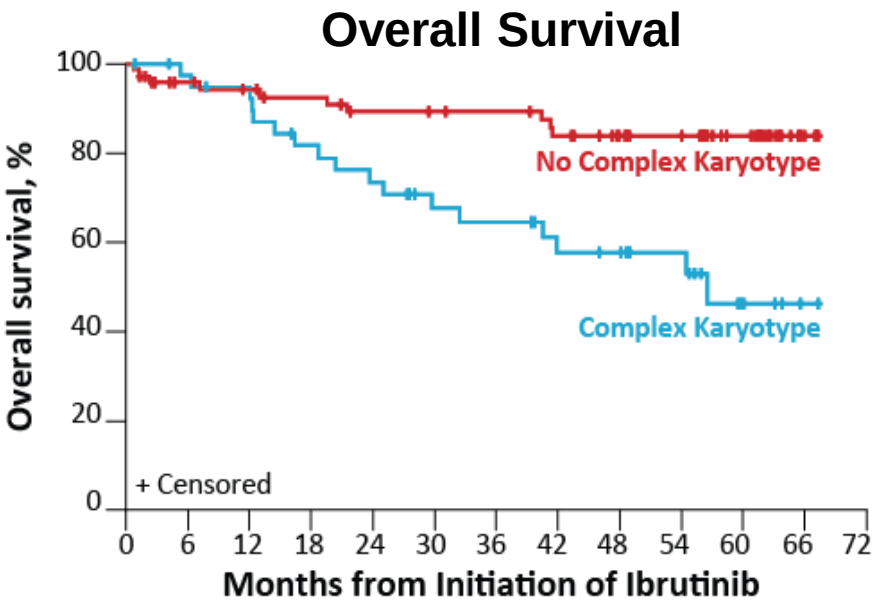
Burger et al. NEJM 2015; Barr et al., ASH 2016



Ibrutinib & Genomic Complexity (PCYC 1102/03)

O'Brien et al. ASH 2016; similar data from RESONATE: Moreno et al. EHA 2017





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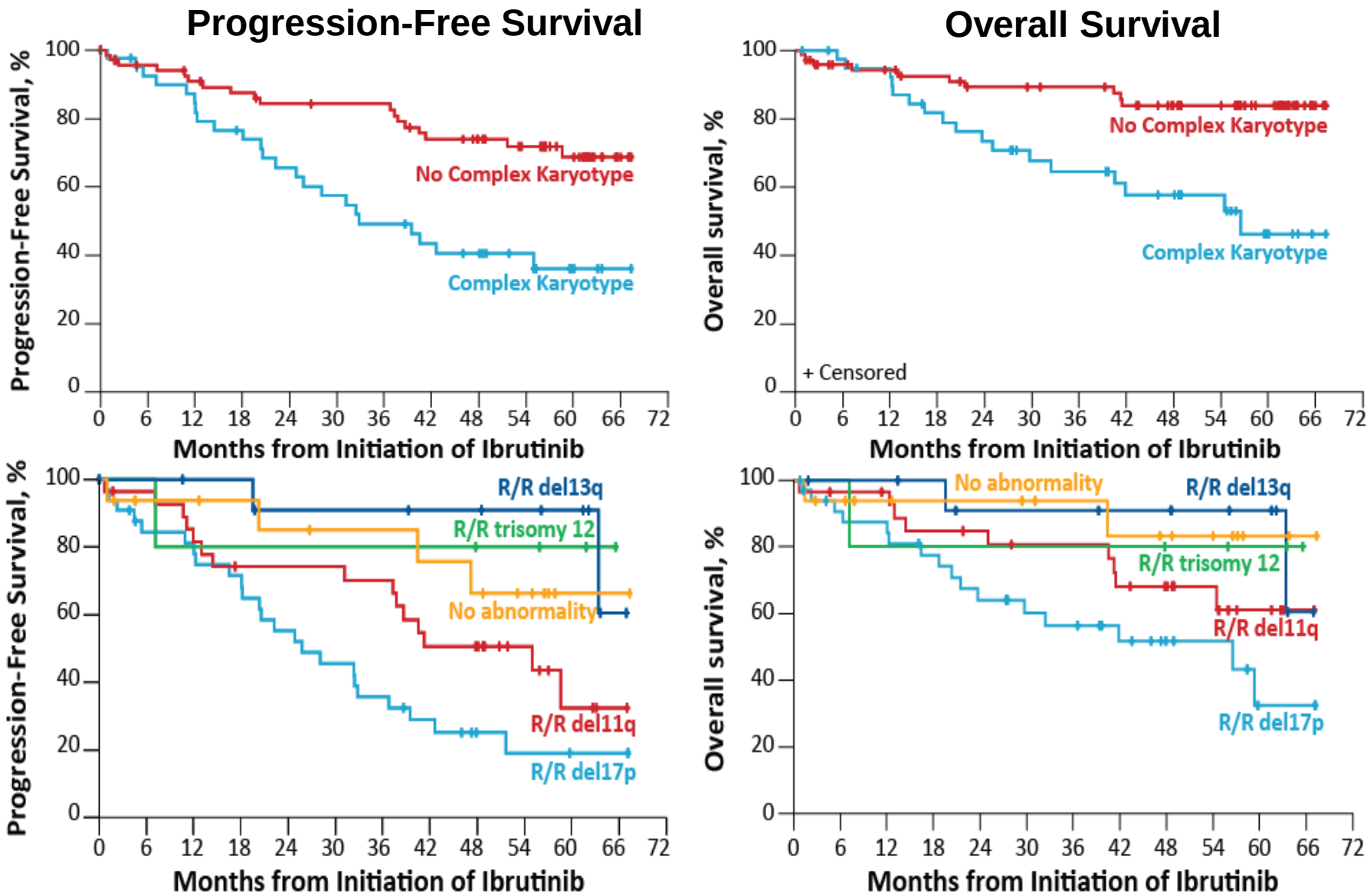
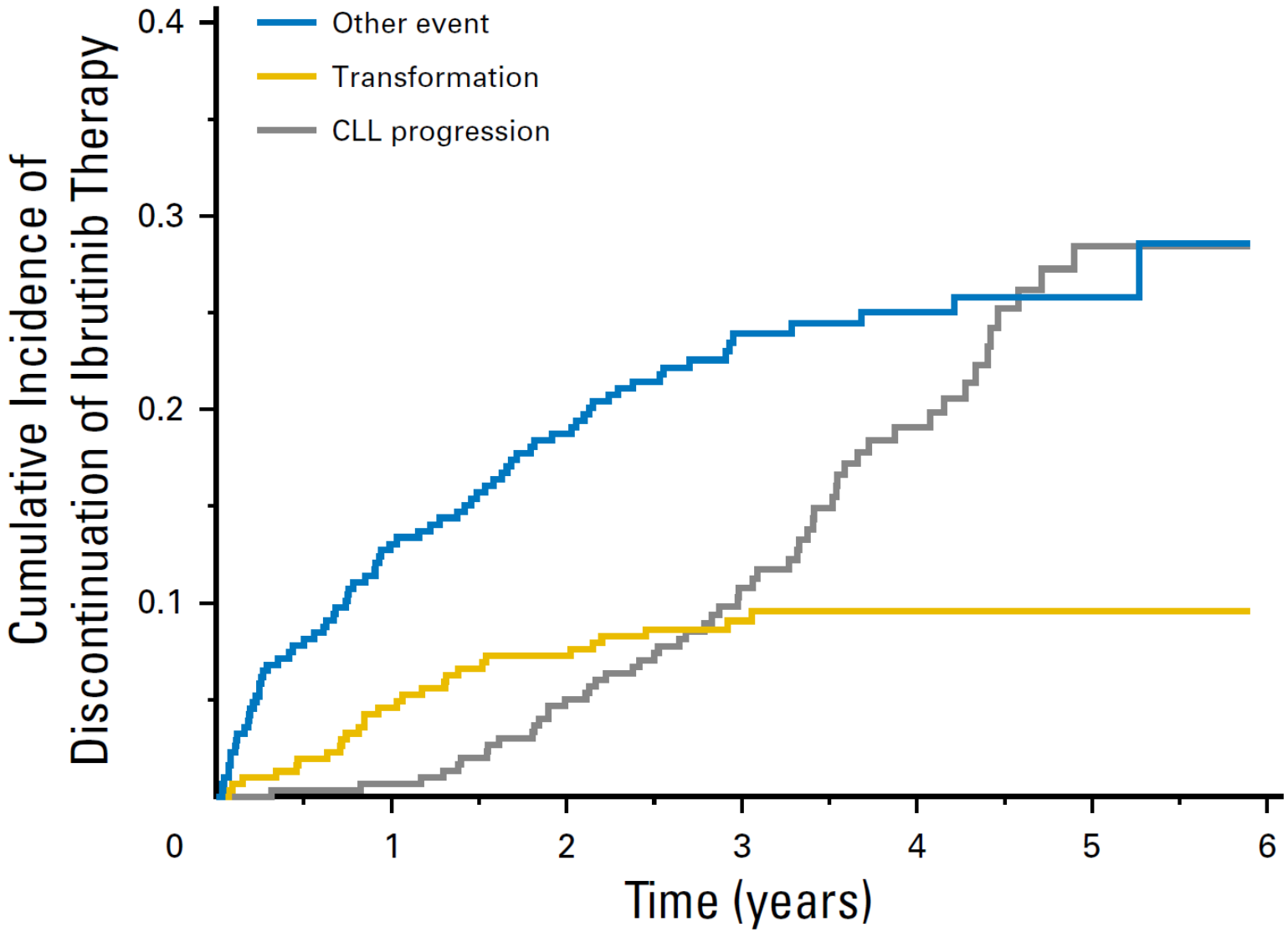


Rates of Ibrutinib Discontinuation

Woyach et al. JCO 2017



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EDITORIAL

Targeted Cancer Therapy: From Bench to Bedside to Patient

Walid F. Gellad, *Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System; University of Pittsburgh, Pittsburgh, PA*

See accompanying article on page 306

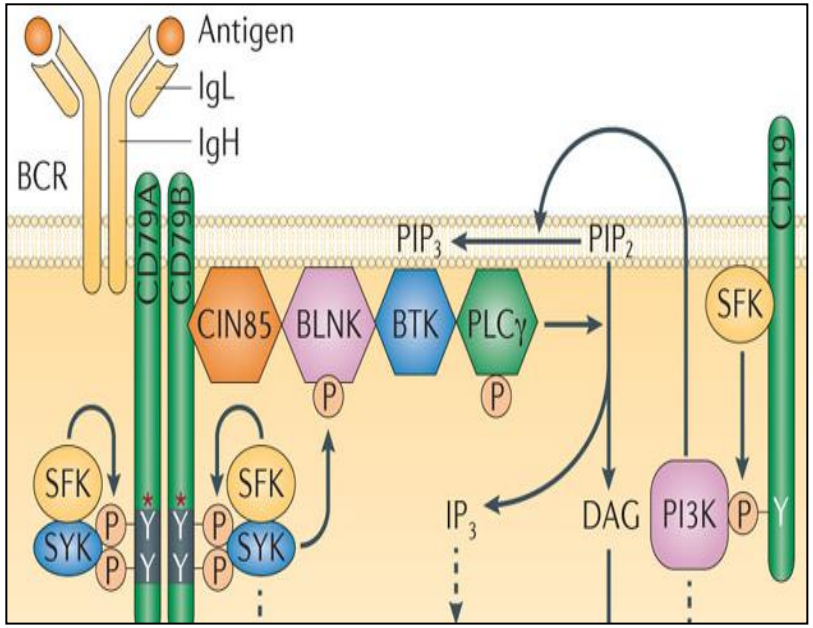
ing the market for advanced cancers to replace intravenous chemotherapy (eg, crizotinib in non–small-cell lung cancer).[28] Oncologists will not be able to rely on a visit to their office to ensure that treatment is taken. Drug development, as well, will need to pay more attention to the issue of adherence, to ensure that scientific discoveries actually reach patients and are used optimally.

Mechanisms of Resistance to Ibrutinib

Woyach et al., NEJM 2014; Maddocks et al. JAMA Oncol 2015; Woyach et al. JCO 2017

WES of samples at relapse vs. baseline:

Patient	Cytogenetics	Duration on Ibrutinib	Best Response	Identified Mutation
1	del(17p13.1), +12	621 d	PR	C481S BTK
2	del(17p13.1), complex karyotype	673 d	PR	R665W PLCγ2
3	del(11q22.3)	388 d	CR	C481S BTK
4	complex karyotype	674 d	CR	C481S BTK
5	del(17p13.1), complex karyotype	868 d	PR	C481S BTK
6	del(17p13.1), complex karyotype	505 d	PR	L845F PLCγ2, C481S BTK

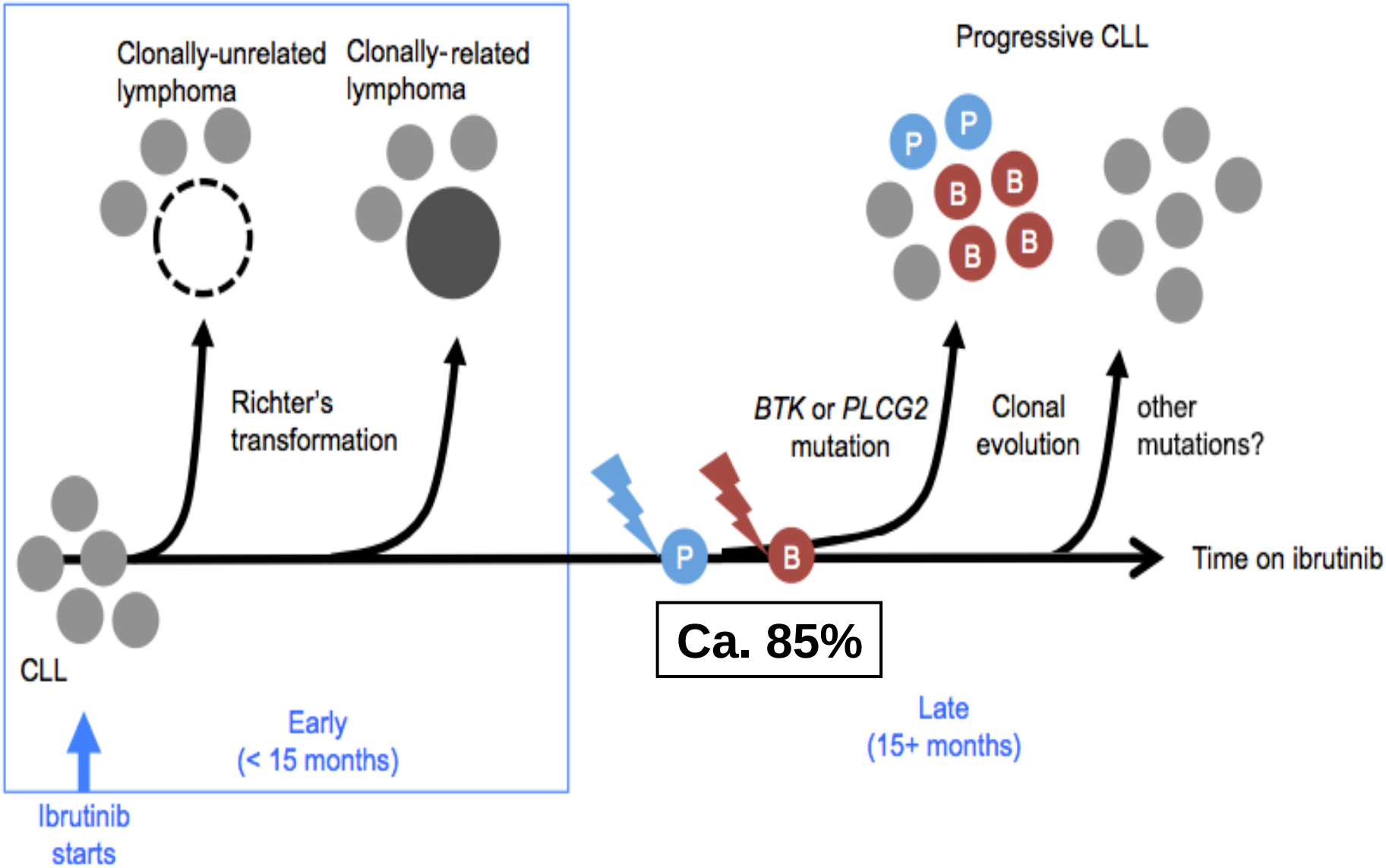


C481S *BTK* Mutation:
Prevents covalent binding but leaves BTK functional

***PLCg2* Mutation:**
Hypermorphic activation of downstream signaling

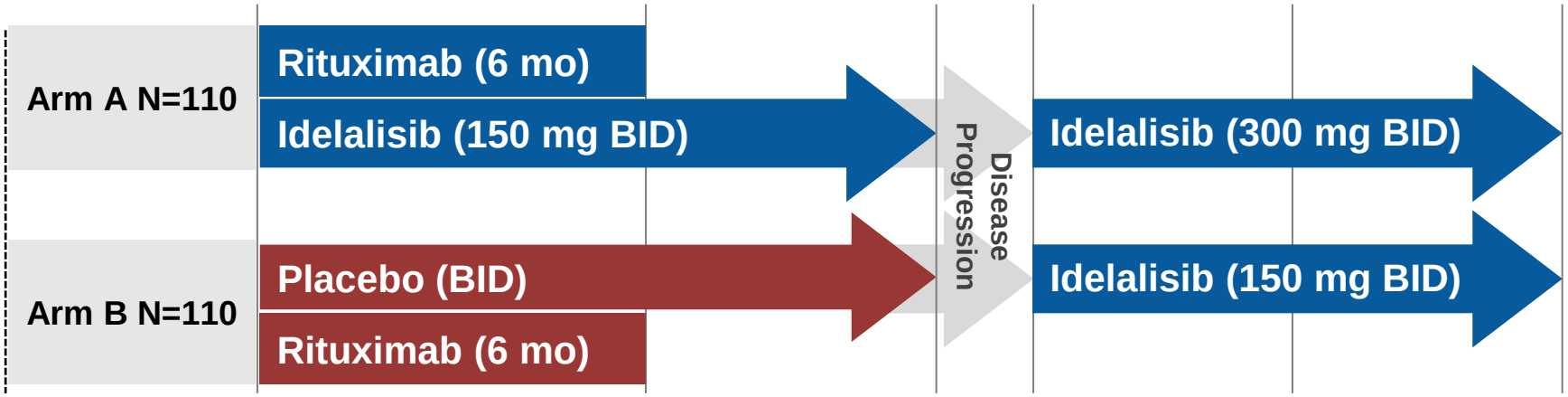
Mechanisms of Resistance to Ibrutinib

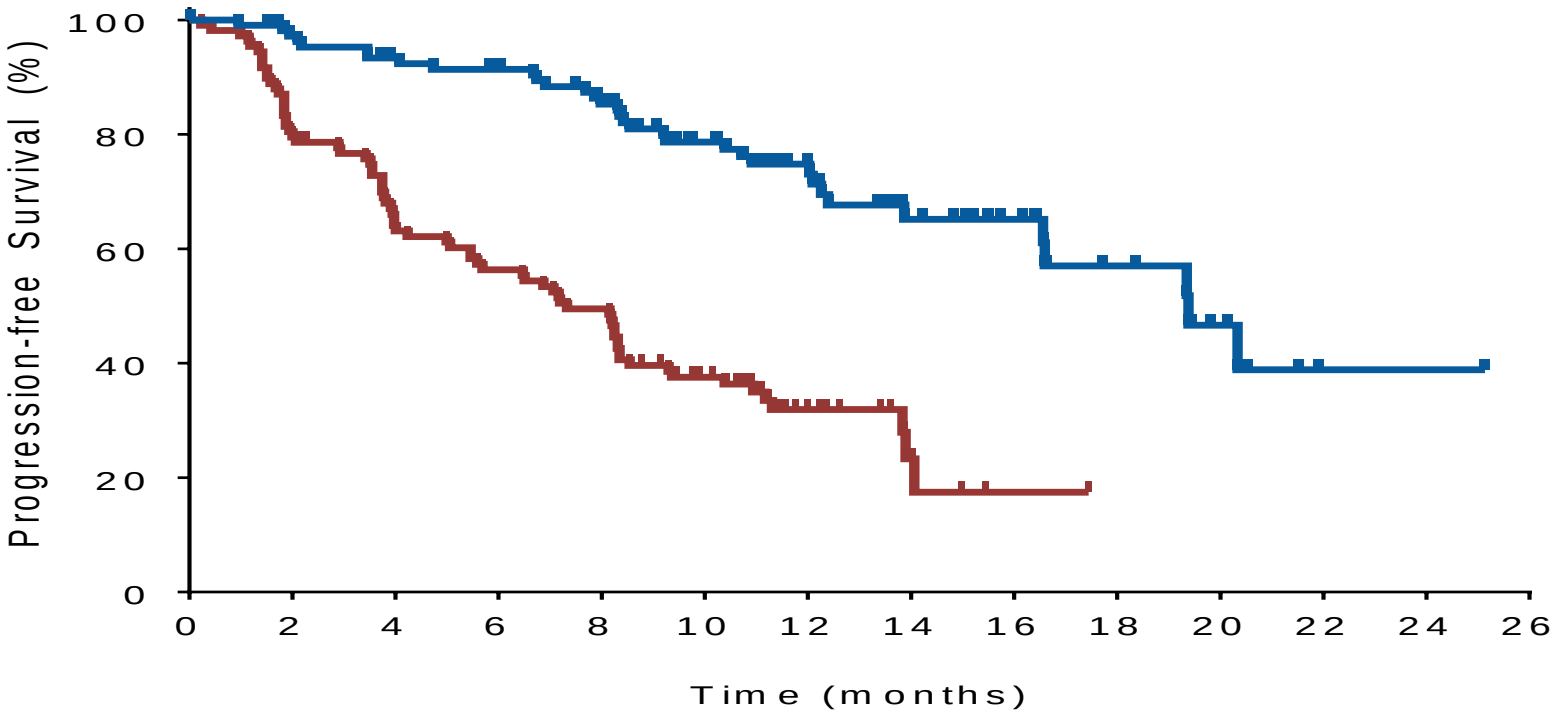
Woyach et al. JCO 2017; Ahn et al., Blood 2017 (modified)



Gilead 116: PI3K Inhibitor Idelalisib

Furman, Sharman, Coutre, et al. NEJM 2014; Sharman et al. In revision 2018





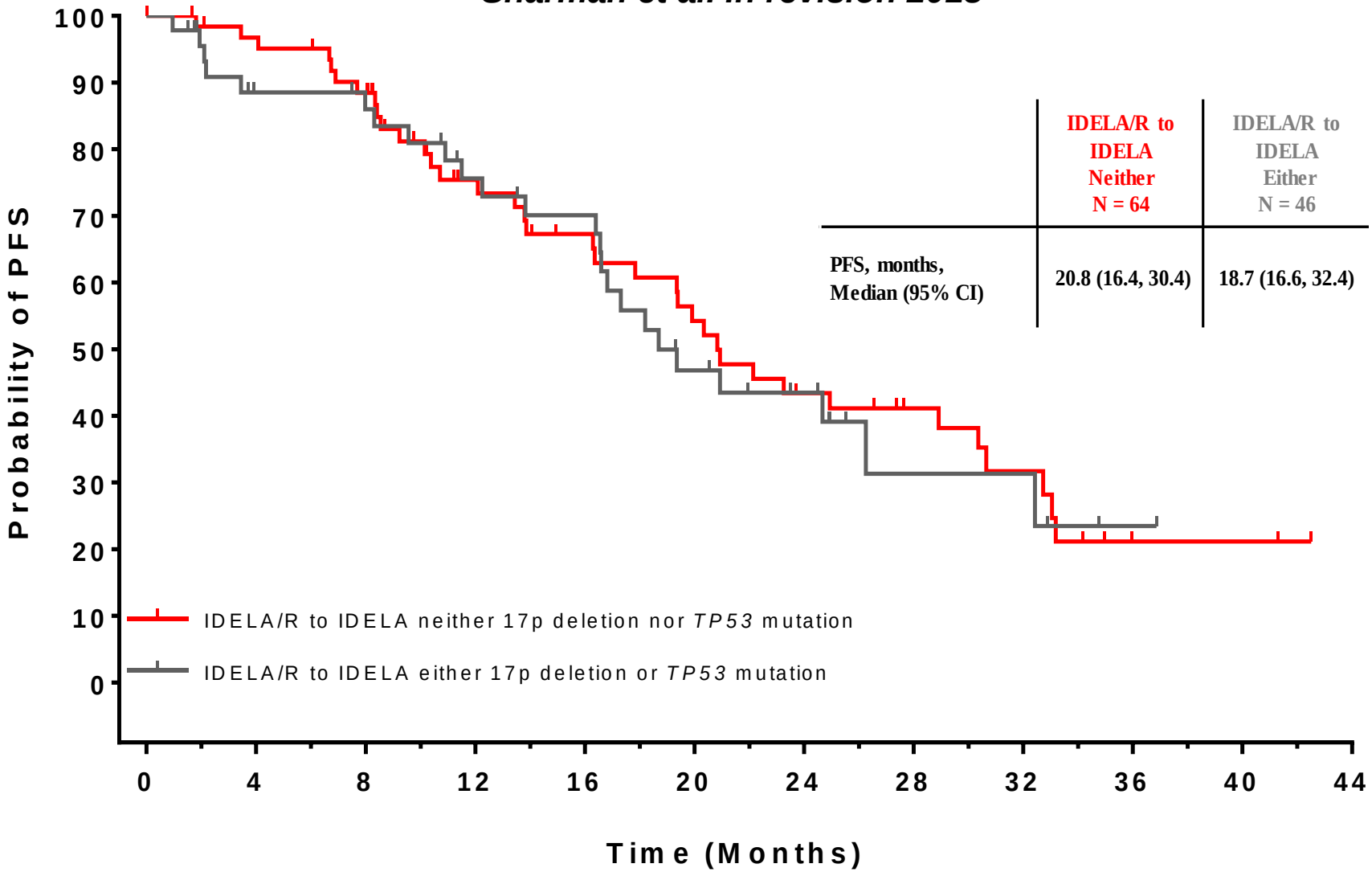
Gilead 116: AEs > 15% (incl. Cross-over)

Sharman et al. In revision, 2018

	IDELA + R (N=110)				PBO + R → IDELA (N=108)			
	Any Grade, %		Grade ≥3, %		Any Grade, %		Grade ≥3, %	
AE by Preferred Term	2nd IA	Update	2nd IA	Update	2nd IA	Update	2nd IA	Update
Any AE	96	98	64	80	98	100	52	78
Pyrexia	35	44	3	6	17	32	1	3
Diarrhea/colitis	21	42	6	16	16	44	–	13
Fatigue	26	36	5	5	28	43	3	5
Cough	17	34	1	2	28	44	2	2
Nausea	26	31	–	2	21	36	–	1
Chills	21	26	2	2	16	22	–	–
Infusion reaction	19	20	–	–	30	32	4	4
Constipation	13	19	–	–	11	21	–	1
Decreased appetite	12	19	–	2	10	17	2	3
Pneumonia	10	18	8	13	13	31	9	20
Dyspnea	13	17	3	6	19	25	3	5
Rash	10	17	1	3	5	12	–	1
Vomiting	13	17	–	–	8	21	–	1
Upper respiratory infection	7	15	2	1	11	24	2	2
Edema, peripheral	10	15	–	–	9	19	2	3
Night sweats	11	14	–	2	10	20	–	–
Asthenia	7	12	1	–	9	19	4	6
Abdominal pain	7	10	1	2	9	19	1	2

Gilead 116/117 R-Idelalisib Subgroup: Impact of *TP53* Mutation/Deletion

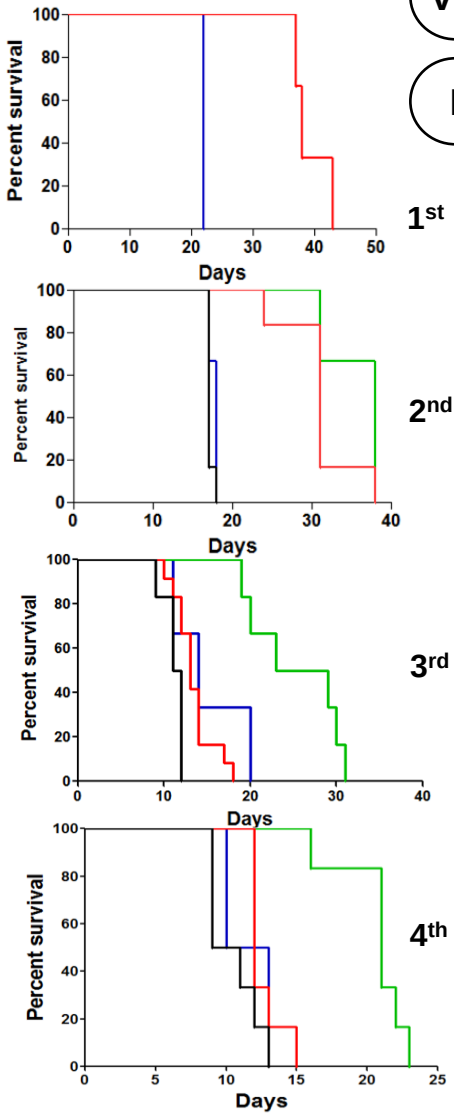
Sharman et al. In revision 2018

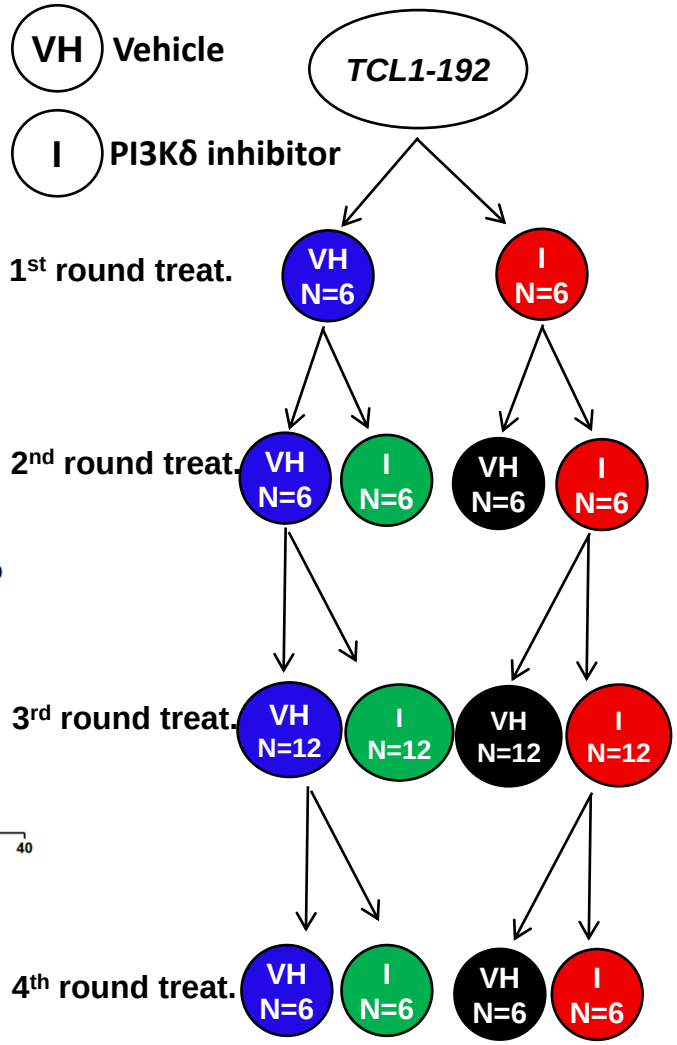


	IDELA/R to IDELA Neither N = 64	IDELA/R to IDELA Either N = 46
PFS, months, Median (95% CI)	20.8 (16.4, 30.4)	18.7 (16.6, 32.4)

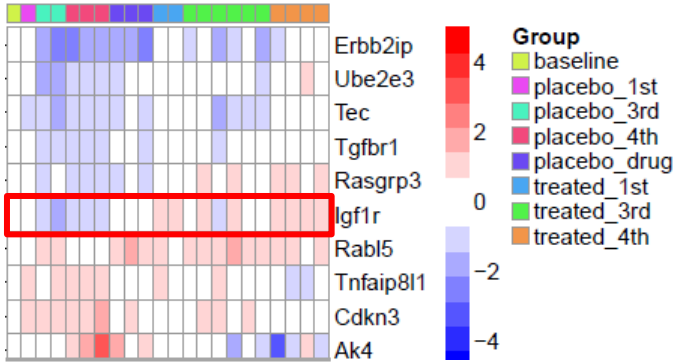
In-vivo Modeling of Resistance to PI3K Inhibitor Idelalisib: Towards the "Refractome"

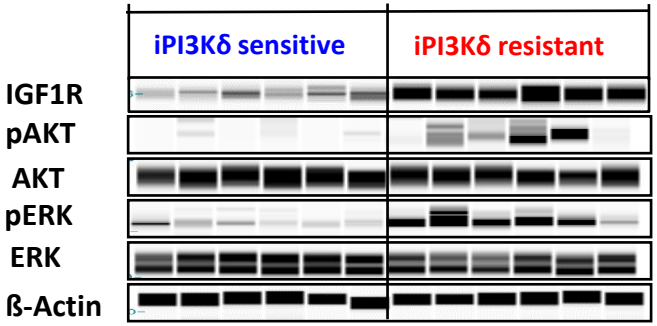
Scheffold et al. ASH 2016; similar data in human CLL: Ghia et al. ASH 2016



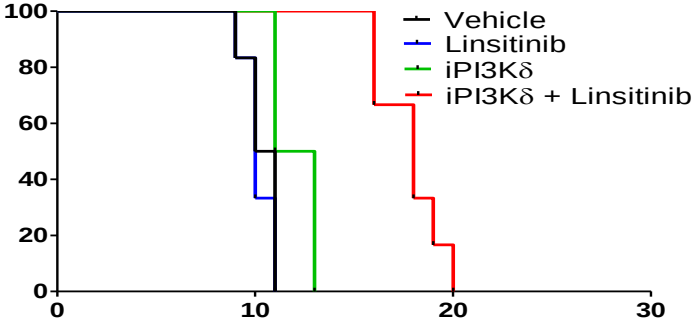


WES: no recurrent mutations



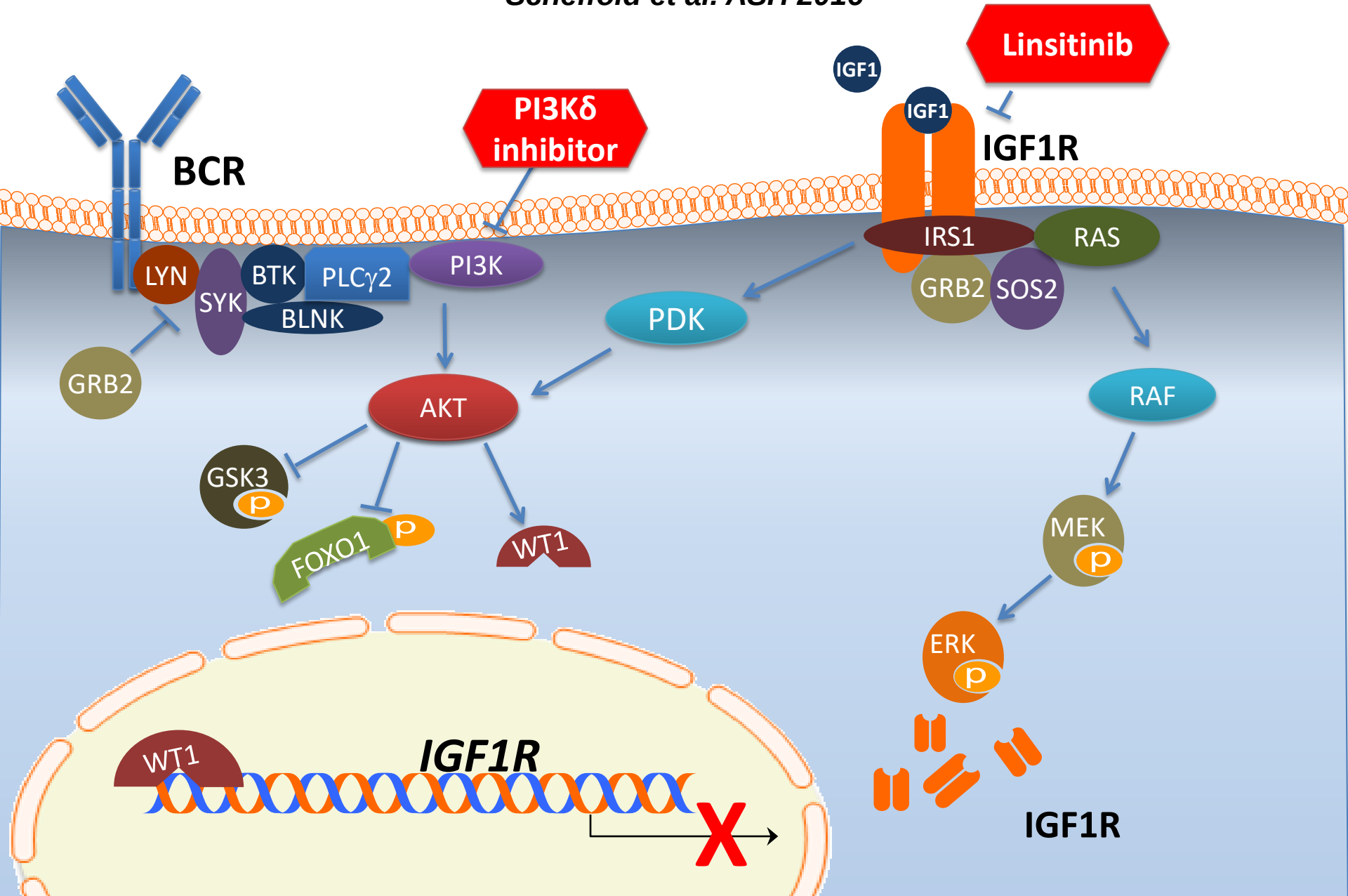


Treatment of PI3Kδ-I resistant tumors



PI3K-Inhibitor "Refractome" Model

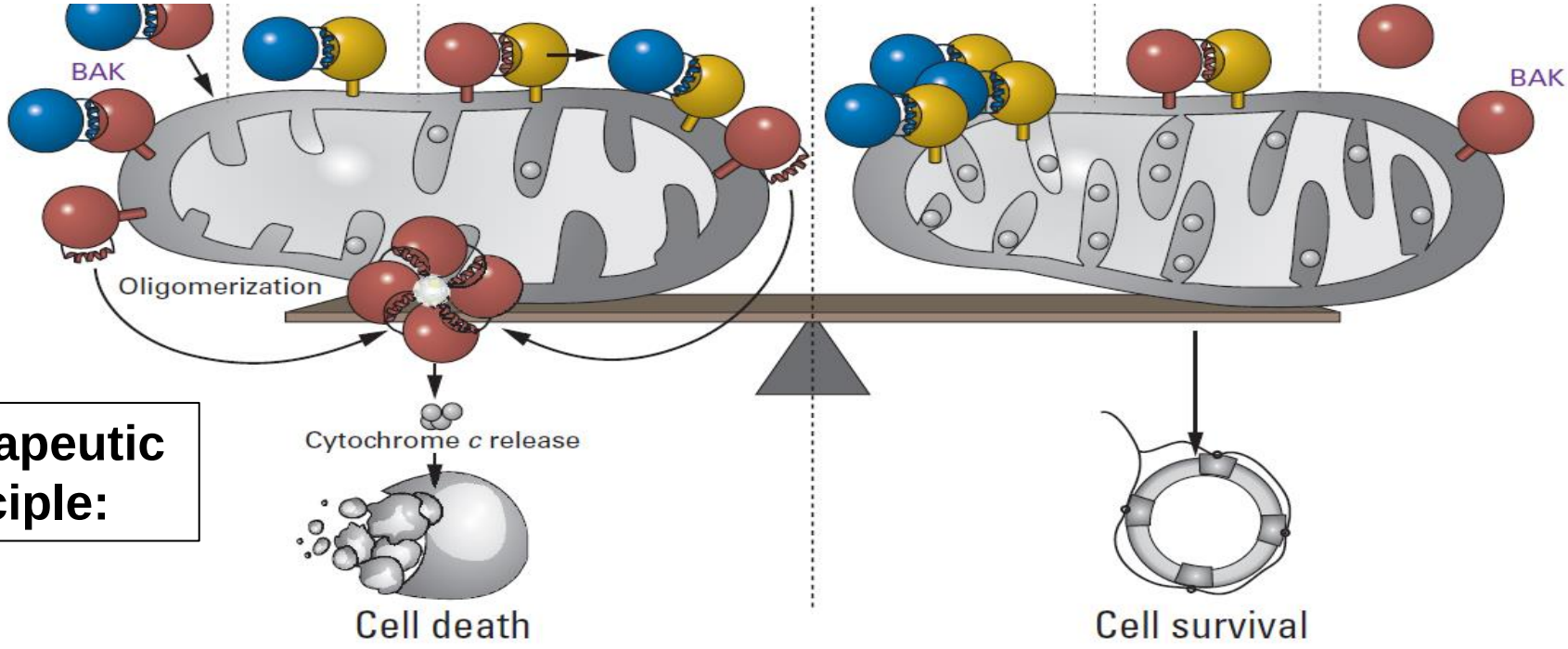
Scheffold et al. ASH 2016



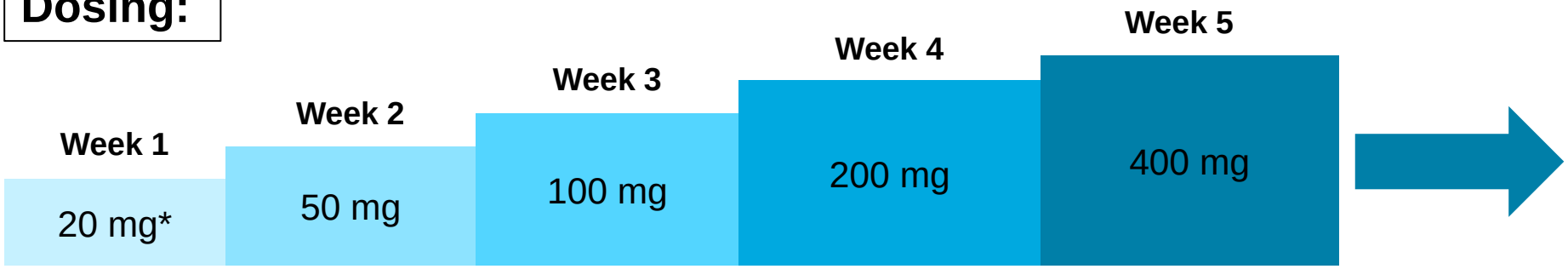
Venetoclax: BCL2 Antagonist

Walensky et al. J Clin Oncol 2012; Roberts et al. NEJM 2016; Seymour et al. NEJM 2018

Therapeutic Principle:

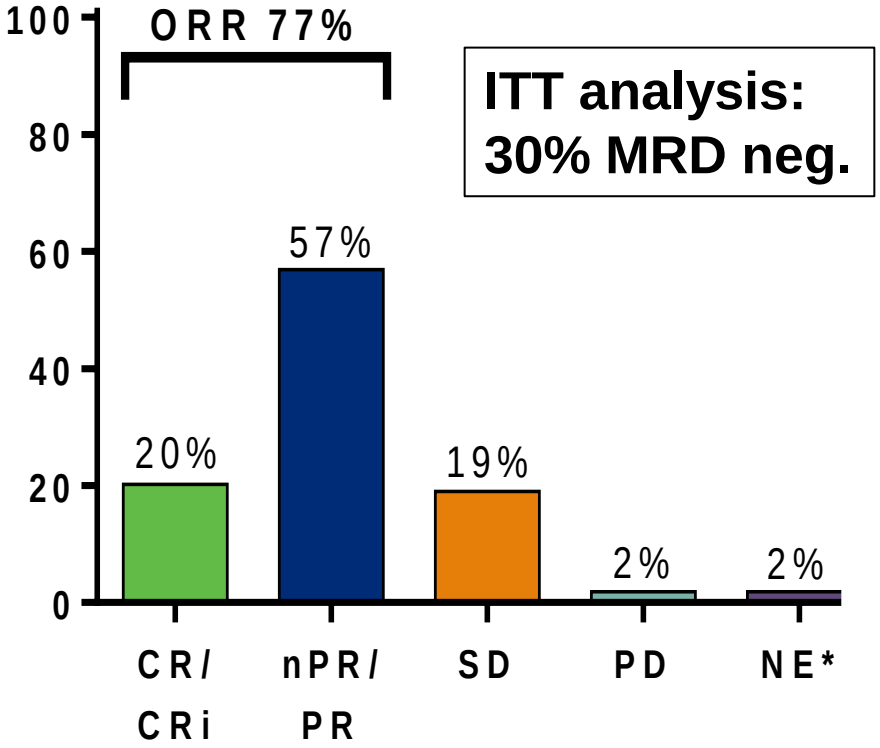


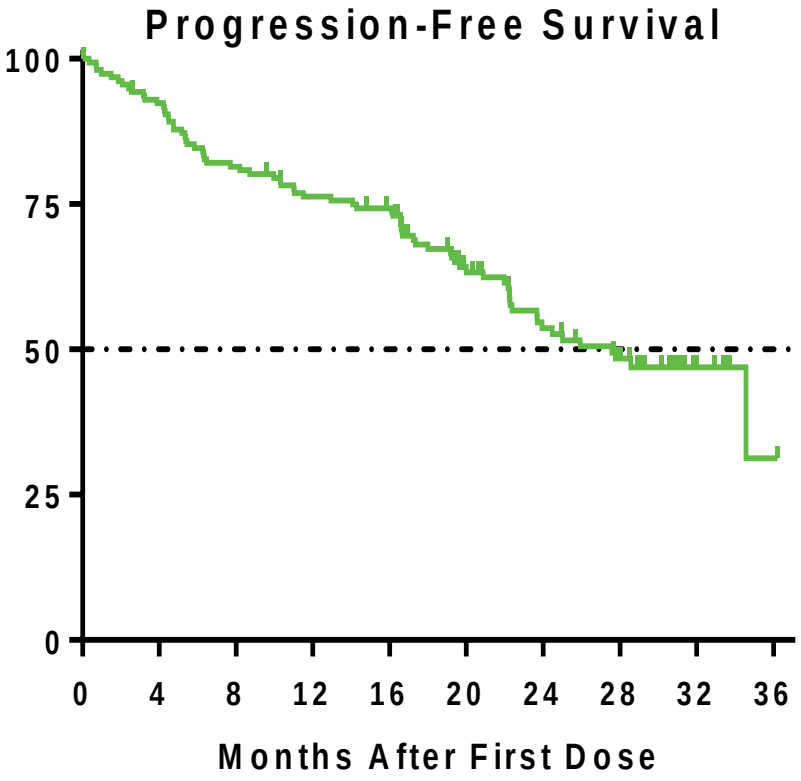
Dosing:



BCL2 Inhibitor Venetoclax (ABT-199): Pivotal Phase II Trial in 17p- CLL (n=158)

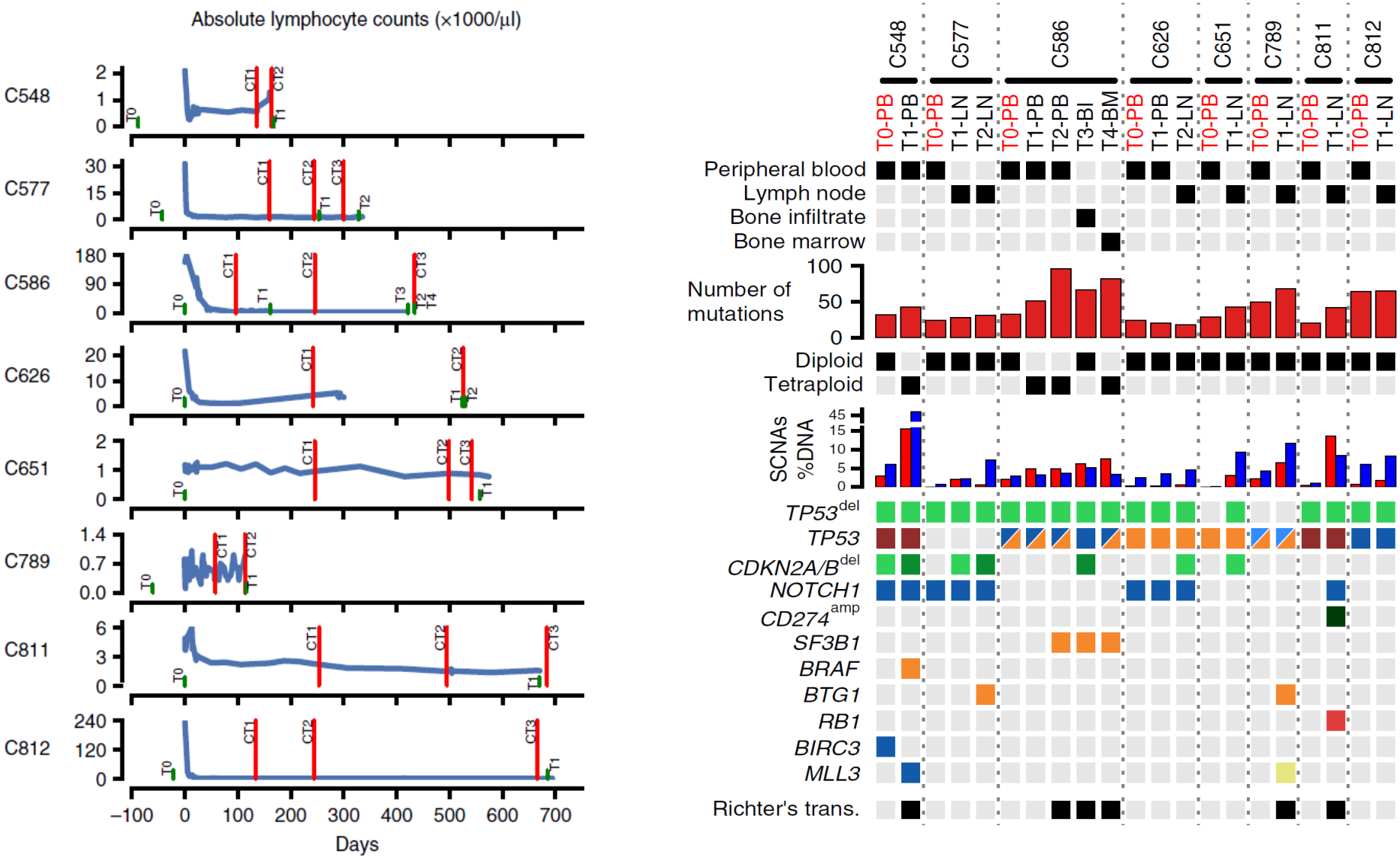
Stilgenbauer et al. Lancet Oncol 2016; Stilgenbauer et al. JCO 2018





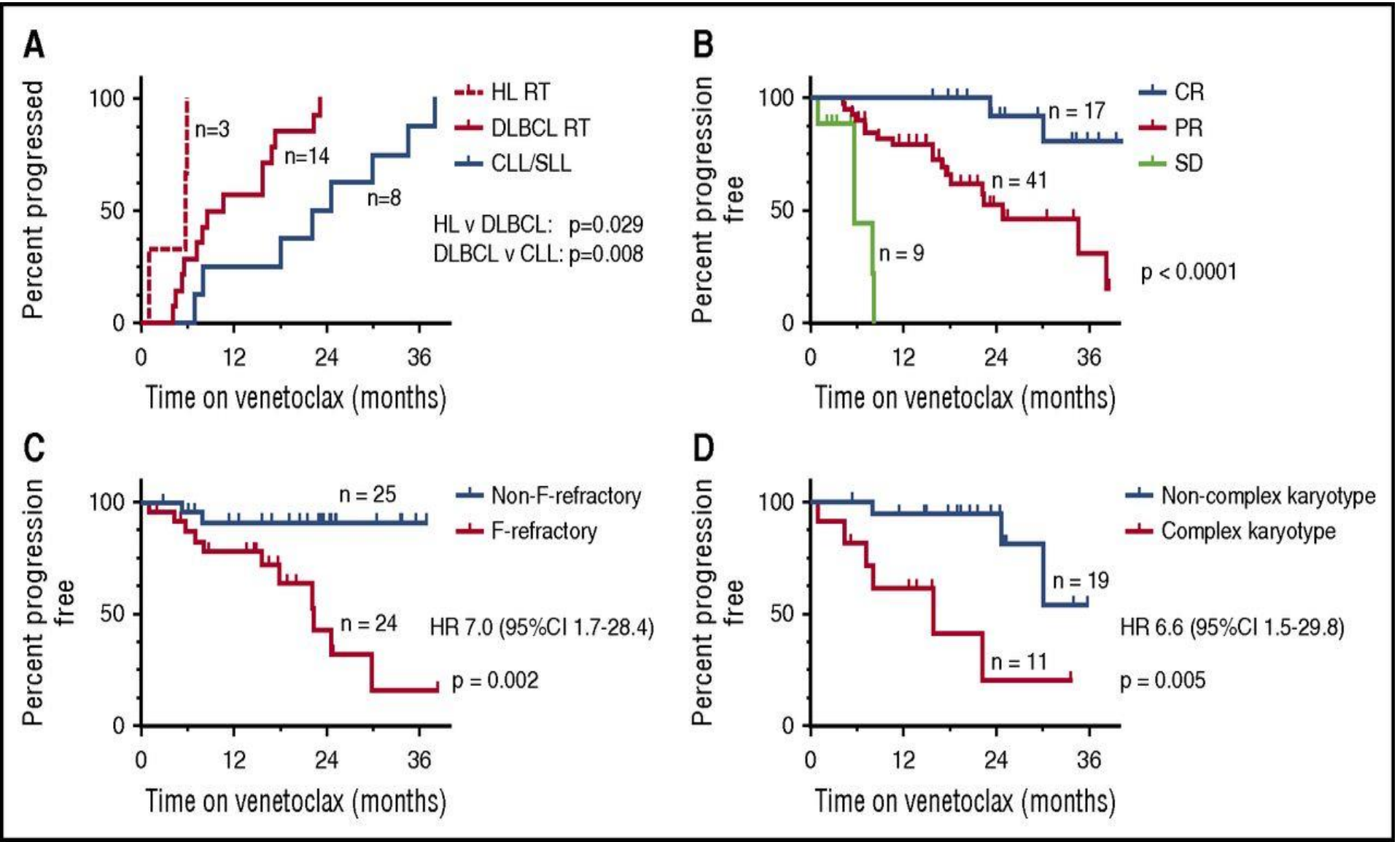
Clonal Dynamics towards the Development of Venetoclax Resistance

Herling et al. Nat Comm 2017



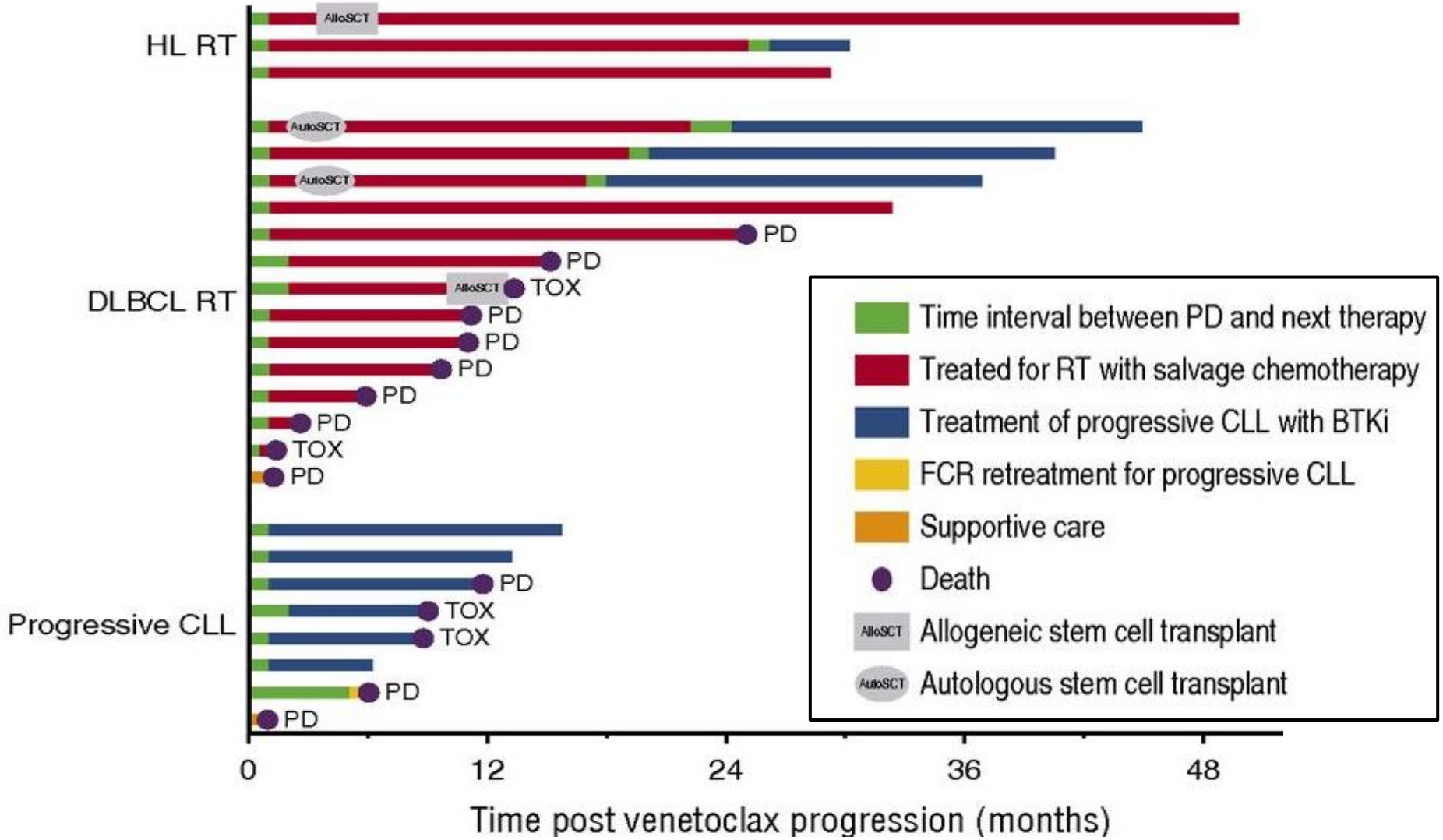
Clinico-pathological Features of Venetoclax Treatment Failure: Outcome

Anderson et al. Blood 2017



Clinico-pathological Features of Venetoclax Treatment Failure: Treatment

Anderson et al. Blood 2017



Retrospective Analysis of the Sequencing of Ibrutinib, Idelalisib, and Venetoclax in CLL

Adapted from Mato et al. Ann Oncol 2017

Response to subsequent therapy following kinase inhibitor

Response, %	BCR-I treatment	venetoclax	CIT
ORR	58.5	73.6	49.9
CR	4.1	31.5	2.1

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Response to subsequent therapy, %	ibrutinib → idelalisib	idelalisib → ibrutinib	BCR-I → venetoclax
			74
CR	0	5	32
SD	39	15	16

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			74
CR	0	5	32
SD	39	15	16

Patients who discontinued ibrutinib for any reason

%	idelalisib	venetoclax
ORR	46	79

M14-032: Venetoclax in CLL rel/refr to Ibrutinib or Idelalisib

Jones et al. Lancet Oncol 2017; Coutre et al. Blood 2017; Byrd et al. EHA 2018

- **Phase 2 study of venetoclax in CLL relapsed or are refractory to ibrutinib (Arm A) or idelalisib (Arm B)**
- **Objectives: ORR, safety, DoR, PFS, OS, MRD**

Inclusion criteria:

- **Treatment indication (iwCLL)**
- **ECOG 0 – 2**
- **ANC ≥1000/µL**
- **Hgb ≥8 g/dL**
- **Platelets ≥30,000/mm^3**
- **CrCl ≥50 mL/min**

Exclusion criteria:

- **Richter's transformation by PET and biopsy**
- **Active and uncontrolled autoimmune cytopenias**
- **Allogeneic SCT within 1 year**

M14-032: Venetoclax in CLL rel/refr to Ibrutinib or Idelalisib

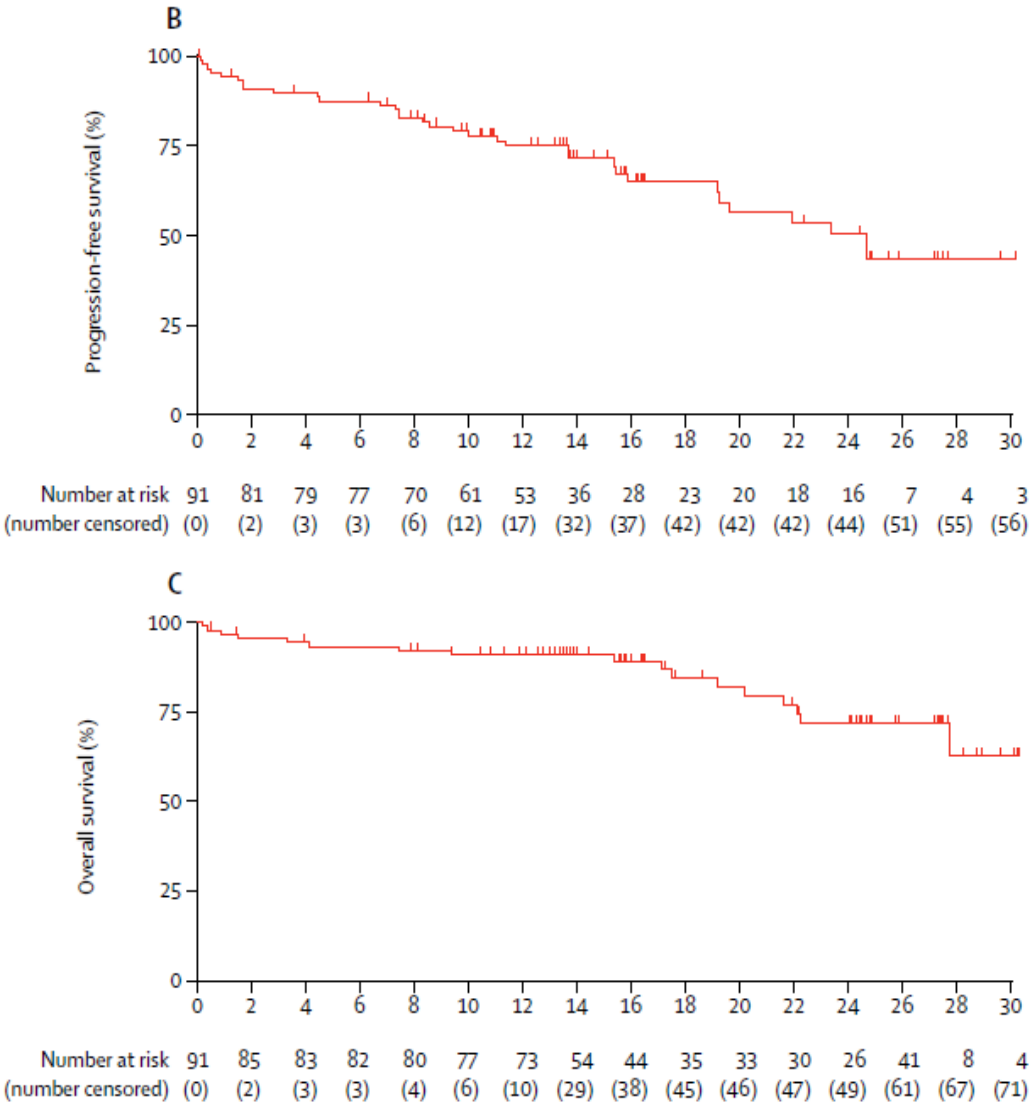
Jones et al. Lancet Oncol 2017; Coutre et al. Blood 2017; Byrd et al. EHA 2018

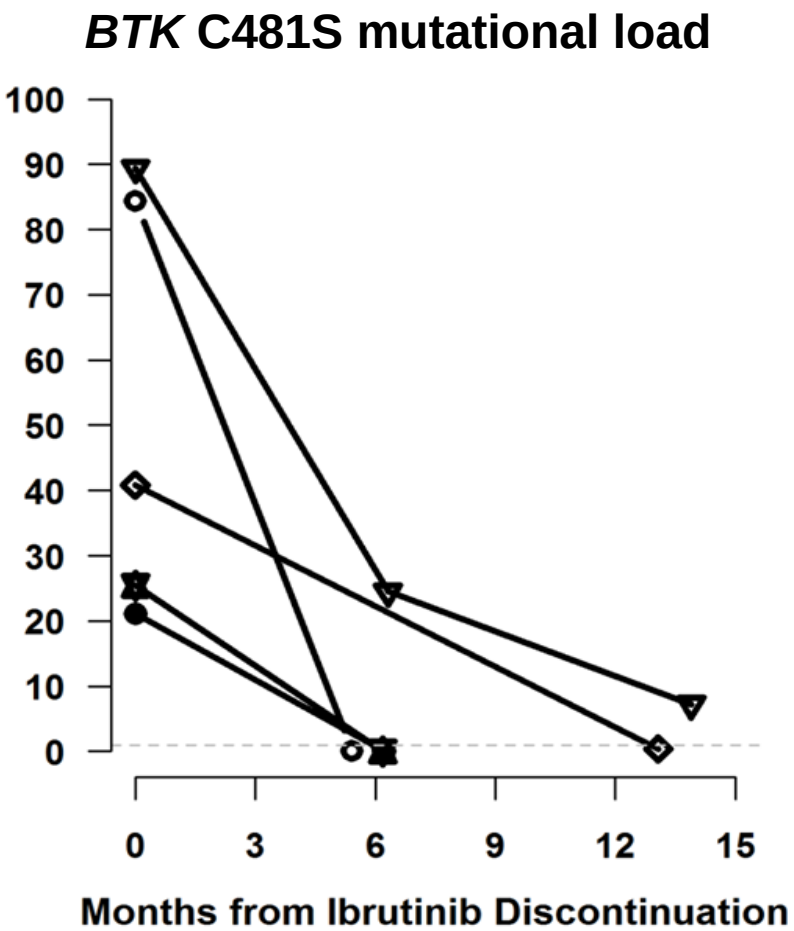
	Last prior BCR inhibitor					
	Ibrutinib (n=91)		Idelalisib (n=36)		Total (n=127)	
N (%)	INV	IRC	INV	IRC	INV	IRC
ORR	59 (65)	64 (70)	25 (69)	25 (69)	84 (66)	89 (70)
CR	5 (6)	0	2 (6)	0	7 (6)	0
CRi	4 (4)	1 (1)	2 (6)	0	6 (5)	1 (1)
nPR	3 (3)	0	0	0	3 (3)	0
PR	47 (52)	63 (69)	21 (58)	25 (69)	68 (54)	88 (69)

- **Patients had received a median of 4 prior therapies (1–15)**
- **Venetoclax monotherapy demonstrated good tolerability**

M14-032: Venetoclax in rel/refr CLL after Ibrutinib Failure

Jones et al. Lancet Oncol 2017; Woyach et al. ASH 2016





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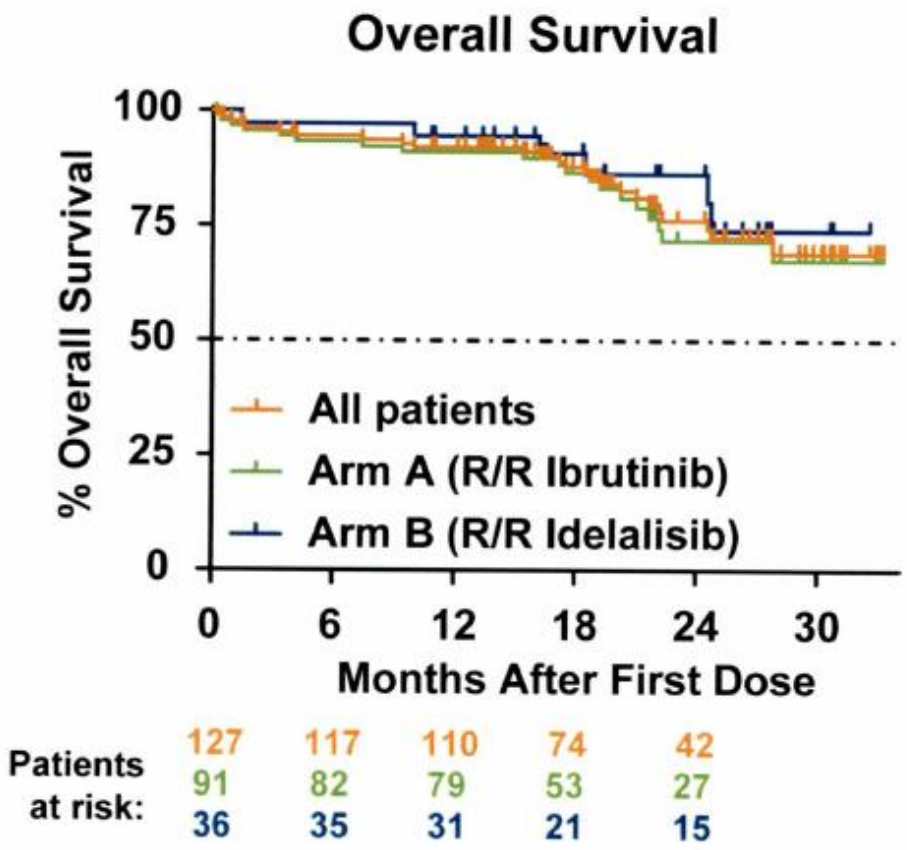
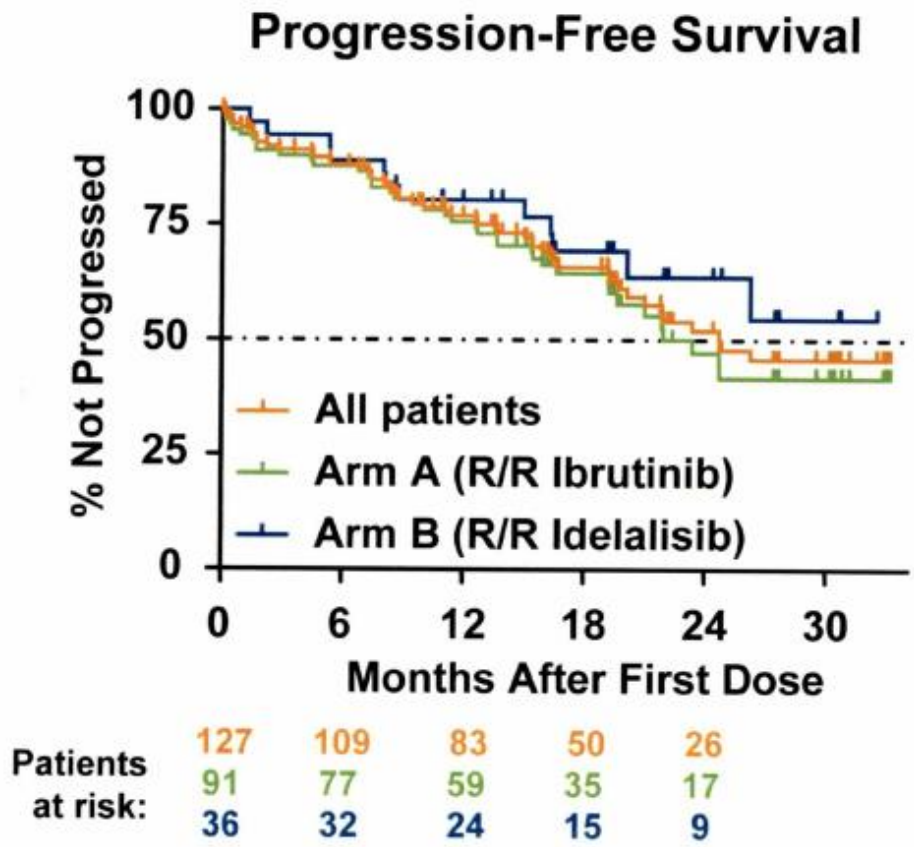
Byrd et al. EHA 2018

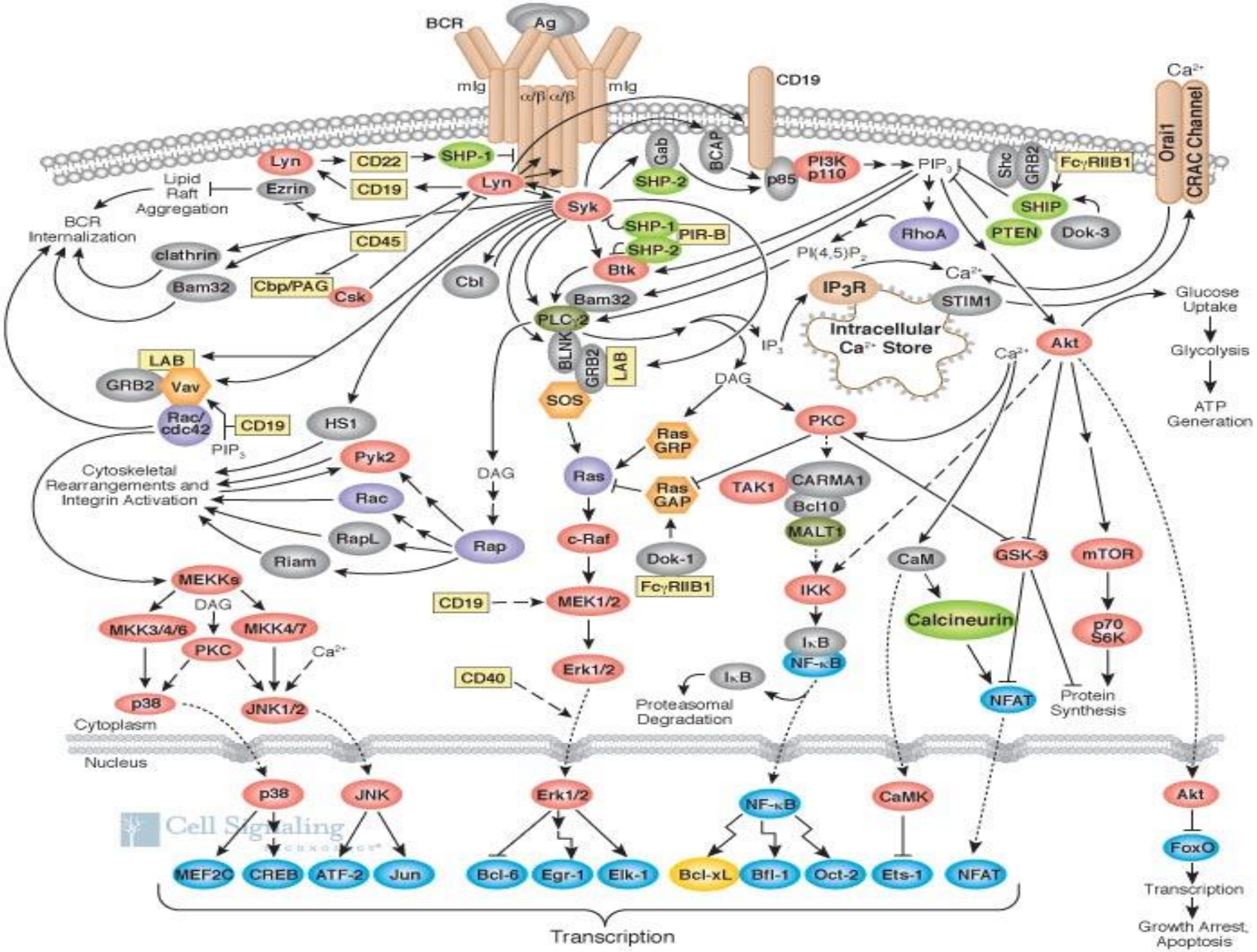




Targeted Therapies:

Bright Perspectives!

iwCLL 2019


BCR
Ag
mIg
α/β α/β
mIg
CD19
Ca2+
Orai1
CRAC Channel
Lyn
CD22
SHP-1
Lyn
Gab
BCAP
SHP-2
p85
PI3K p110
PIP3
Shc
GRB2
FcγRIIB1
Lipid Raft Aggregation
Ezrin
CD19
Syk
SHIP
BCR Internalization
SHP-1
PIR-B
SHP-2
RhoA
PTEN
Dok-3
CD45
clathrin
Btk
PI(4,5)P2
Ca2+
Bam32
Cbp/PAG
Csk
Cbl
Bam32
IP3R
STIM1
Glucose Uptake
PLCγ2
Intracellular Ca2+ Store
Glycolysis
LAB
BLNK
GRB2
LAB
IP3
Akt
GRB2
Vav
SOS
DAG
Ca2+
ATP Generation
Rac/cdc42
CD19
HS1
PKC
PIP3
Pyk2
Ras GRP
Cytoskeletal Rearrangements and Integrin Activation
DAG
Ras
Ras GAP
TAK1
CARMA1
Rac
Bcl10
MALT1
RapL
Rap
c-Raf
Riam
Dok-1
CaM
GSK-3
mTOR
MEKKs
FcγRIIB1
IKK
CD19
MEK1/2
DAG
Calcineurin
p70 S6K
MKK3/4/6
MKK4/7
PKC
Ca2+
IκB
NF-κB
Erk1/2
CD40
IκB
Proteasomal Degradation
NFAT
Protein Synthesis
p38
JNK1/2
Cytoplasm
Nucleus
p38
JNK
Erk1/2
NF-κB
CaMK
Akt
Cell Signaling
FoxO
MEF2C
CREB
ATF-2
Jun
Bcl-6
Egr-1
Elk-1
Bcl-xL
Bfl-1
Oct-2
Ets-1
NFAT
Transcription
Transcription
Growth Arrest, Apoptosis

Phase 2 Study of Idelalisib plus Rituximab in Treatment Naïve CLL with del(17p): Non-Laboratory Adverse Events

Hillmen et al. EHA 2017

	Idelalisib + Rituximab			
	Age <65 y n=41	Age ≥65 y n=61	Total N=102	
	Grade ≥3	Grade ≥3	Any Grade	Grade ≥3
Rash*	6 (15)	9 (15)	42 (41)	15 (15)
Diarrhea	7 (17)	8 (13)	38 (37)	15 (15)
Pyrexia	0	3 (5)	30 (29)	3 (3)
Cough	0	0	19 (19)	0
Nausea	0	0	19 (19)	0
Vomiting	0	0	17 (17)	0
Fatigue	0	1 (2)	16 (16)	1 (1)
Asthenia	0	2 (3)	15 (15)	2 (2)
Constipation	0	1 (2)	15 (15)	1 (1)