4th POSTGRADUATE
CLL
Conference

Novel approaches of treatment in Richter's syndrome

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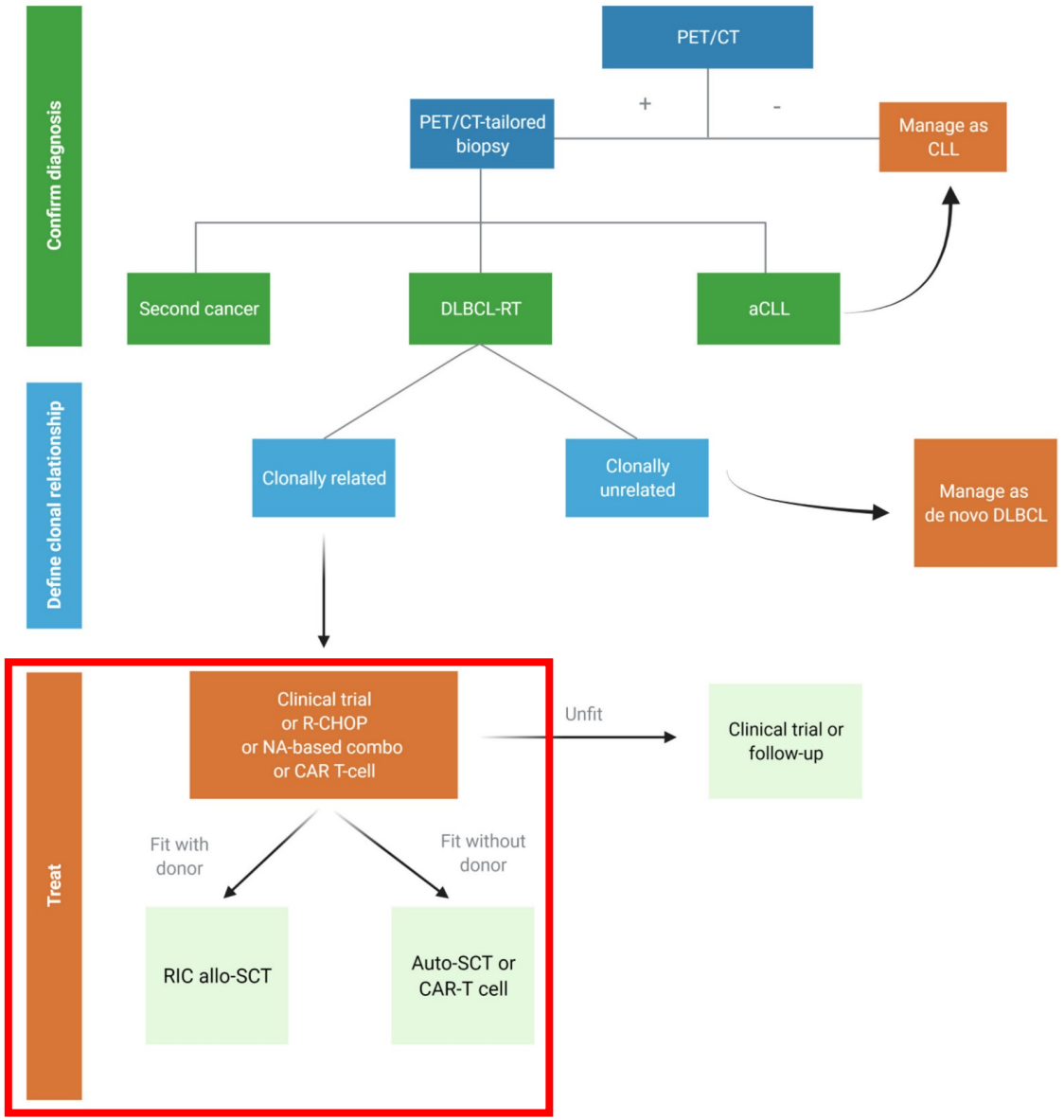
Treatment algorithm for RS patients



- ✓ RS represents the greatest **unmet clinical need** in the CLL field
- ✓ Current therapeutic approaches are limited and do not significantly reduce disease progression
- ✓ No drug or combination is currently approved for RS

Condoluci and Rossi, Front Oncol 2022

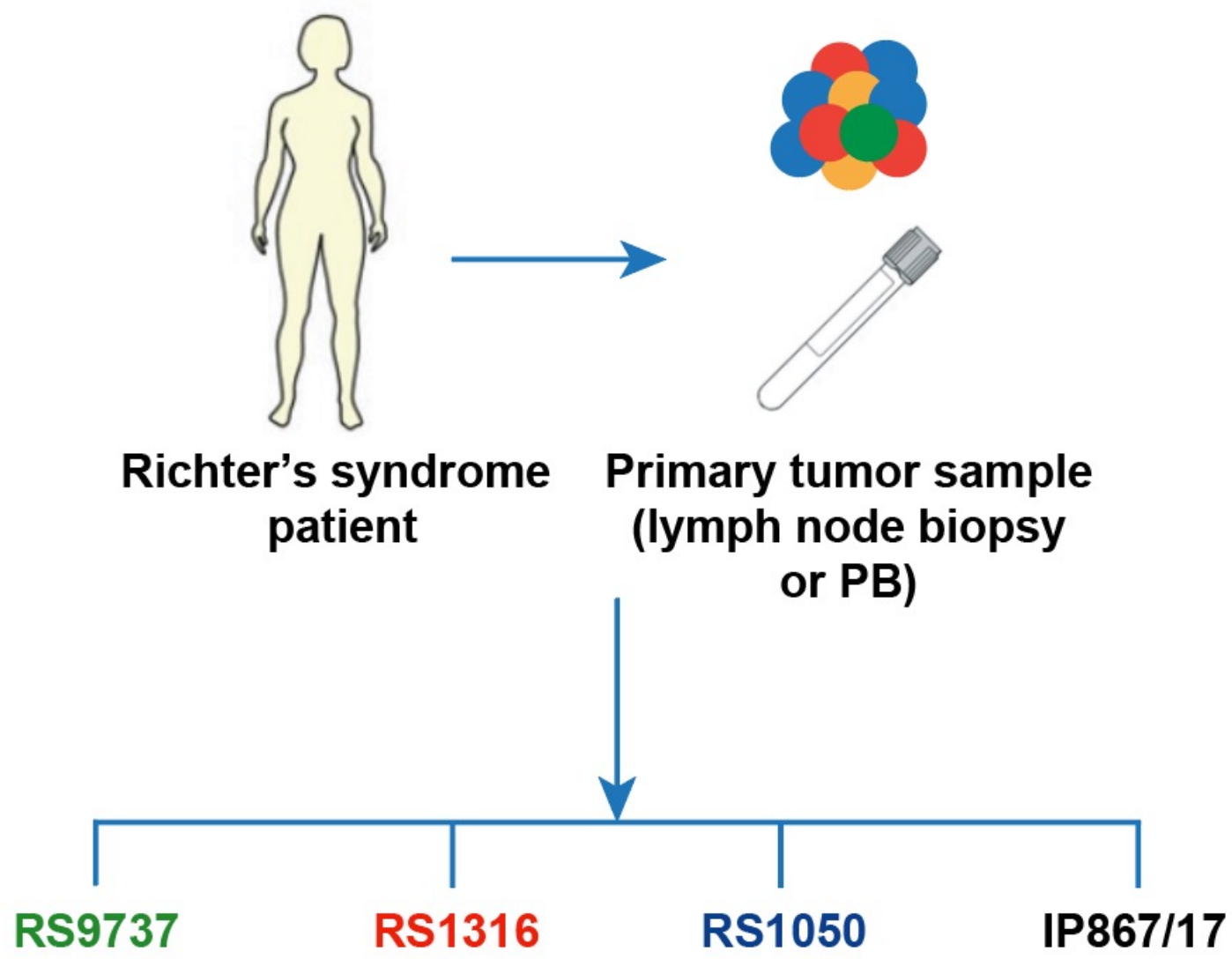
What novel agent combinations can be used?

Combination Regimen	CIT		Mono-clonal Ab	Small-Molecule Inhibitors							Immunotherapy				ADC
				BTKi				BCL2i	PI3Ki		Immune Checkpoint Blockade			CAR-T	
	R-EPOCH	R-CHOP	OBIN	IBR	ACALA	ZANU	PIRTO	VEN	DUV	COPA	*Anti-*PD-1	*Anti-*PD-L1	*Anti-*CTLA-4	*Anti-*CD19	POLA
IBR + NIVO *NCT02329847, NCT02420912*				■							■				
IBR + NIVO + IPI *NCT04781855*				■							■		■		
IBR + NIVO + Liso-Cel *NCT05672173*				■							■			■	
ACALA + R-CHOP *NCT03899337*		■			■										
ACALA + VEN + DURVA *NCT05388006*					■			■				■			
ZANU + TISLE *NCT04271956*						■					■				
PIRTO + VEN + OBIN *NCT05536349*			■				■	■							
VEN + R-EPOCH/ VEN + R-CHOP *NCT03054896*	■	■						■							
VEN + OBIN + ATEZO *NCT02846623, NCT04082897*			■					■				■			
VEN + DUV *NCT03534323*								■	■						
COPA + NIVO *NCT03884998*										■	■				
POLA + R-EPOCH *NCT04679012*	■														■

Ryan CE and Davids MS, *Am Soc Clin Oncol Educational Book* 2023

✓ Pre-clinical models are needed to determine the best combination

Patient-derived xenografts can be used to study mechanisms and therapies



- ✓ Grow reproducibly
- ✓ **Are genetically related to the primary**
- ✓ Have a stable mutational landscape

Vaisitti T. et al., Cancer Research 2018

RS-PDXs are genetically different, but related to their primary tumor

RS1316

Chromosomal abnormalities	Relevant genes
Deletion 6p22-p25	
Gain 8q22-qter	
Trisomy 12	
Gain 15q11	
Deletion 16p13.3	
Deletion 20q13.13	

RS1050

Chromosomal abnormalities	Relevant genes
Deletion 2p25.3-p16.3	
Amplification 2p16.3-p16.1	
Deletion 2p16.1	
Amplification 2p16.1-p14	*REL, XPO1*
Gain 6p25.3-p23	
Deletion 6p23-p21.32	
Gain 10 p15.3-q26.3	
Deletion 11p15.5-q25	
Deletion 13q14.11	
Deletion 13q14.2-q14.3	*MIRN15A-MIRN16-1*
Deletion 17p13.3-p11.2	*TP53*
Gain 18q21.2-q23	*MALT1, TNFRSF11A*

RS9737

Gene ID and mutation	IP867/17	RS1316	RS1050	RS9737
TP53 (c.673-2A>G; SAV)			•	
TP53 (c.254delC; fs)	•			
TP53 (p.H214fs)				•
NOTCH1 (p.2514fs4)				•
NOTCH2 (p.N1516S)		•		
BTK (p.E96G)				•
BTK (p.C481S)		•		
MYC (p.P60T)		•		
PIK3C2G (c.3263delA; fs)		•		
KRAS (p.G13C)		•		
KRAS (p.L19F)				•
KRAS (p.T58I)				•
EGR2 (p.H384N)			•	•
EGR2 (p.D411Y)				•
SETD2 (p.G889V)				•
TRAF3 (c.1230_1231delGA; fs)	•			
TRAF3 (p.T411S)	•			
MED12 (p.G44R)		•		
TBL1XR1 (p.E127D)				
ERBB3 (p.Y606H)			•	
CYLD (p.L475F)				
SMAD5 (p.S351T)			•	
PTPRK (p.W1055L)				
PAX5 (p.K196M)				
VCAM1 (p.P254A)				
STAT3 (p.K283T)				
NFKBIZ (p.L399P)				

Deletion 1p34-p36
Deletion 1q21.3
Gain 1q23.1-q25.1
Deletion 1q25.1
Gain 1q25.1-q31.1
Deletion 1q31.2
Gain 1q31.2-q31.3
Deletion 1q31.3
Gain 1q32.1
Deletion 1q32.2
Deletion 1q42-qter
Deletion 3p21
Gain 7q21-q22
Deletion 7q22-qter
Deletion 9p22-pter
Biallelic deletion 9p21 *CDKN2A*
Deletion 11q22 *ATM*
Deletion 11p11.2
Deletion 13q14
Gain 16q22-qter
Deletion 17p *TP53*
Gain 19p13.12

TNFSF18 TNF

0 ≤ VAF ≤ 0.30
0.31 ≤ VAF ≤ 0.60
0.61 ≤ VAF ≤ 1.00

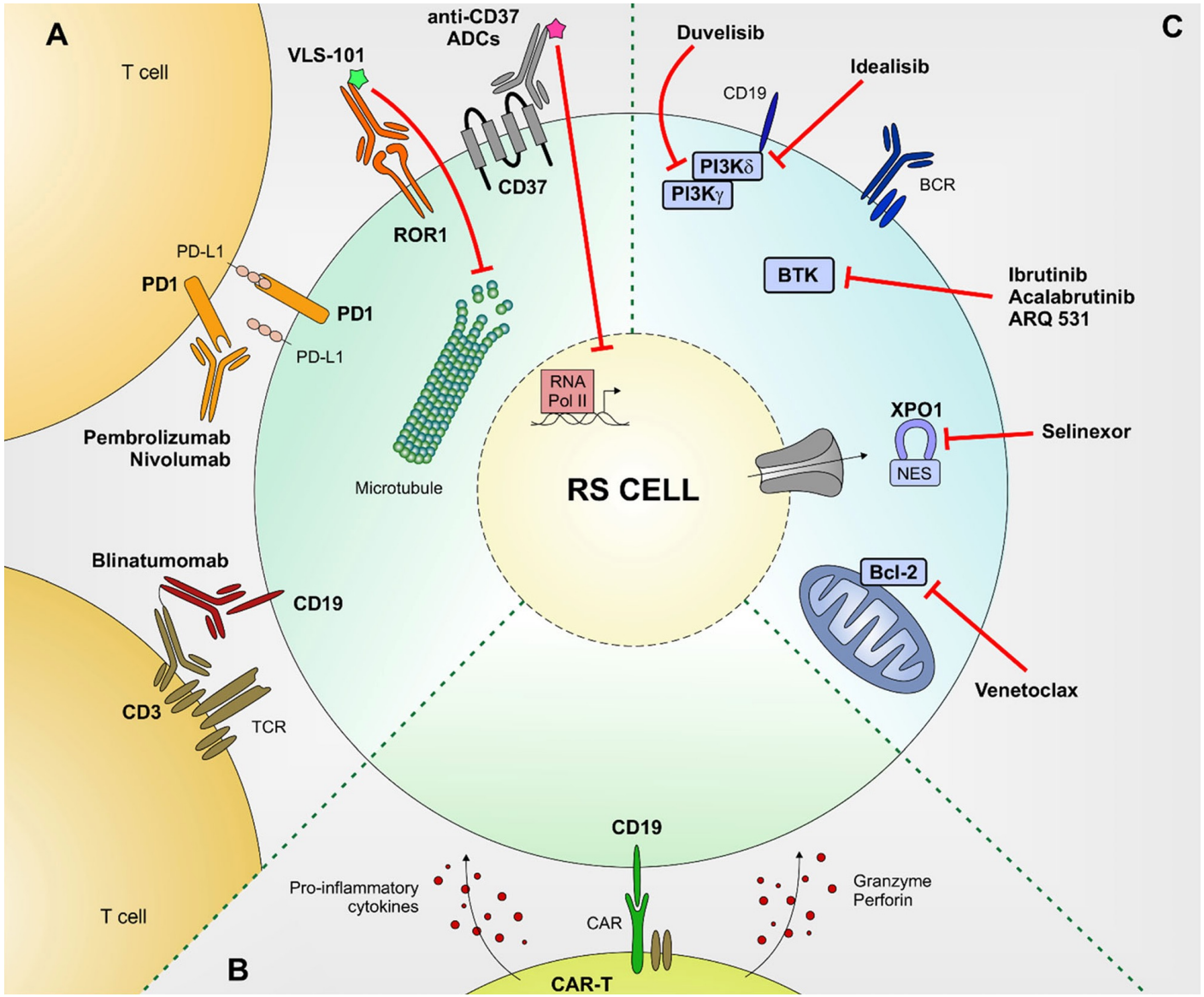
Variants already present in the primary sample

IP867/17

Chromosomal abnormalities	Relevant genes
Deletion 3p25.3-p14.2	
Deletion 4p16.3-q35.2	
Deletion 8p23.3-q21.13	
Deletion 8q21.13-q21.3	
Deletion 8q23.2-q23.3	
Deletion 8q24.12-q24.13	
Amplification 8q24.13	
Deletion 8q24.13-q24.21	
Amplification 8q24.21	*MYC*
Deletion 8q24.21-q24.22	
Deletion 9p11.q34.3	
Deletion 11q23.3-q25	
Deletion 12p13.33-q24.33	
Deletion 13q12.3-q14.11	
Deletion 13q14.3-q31.3	
Deletion 13q33.1-q33.3	
Deletion 14q11.2-q32.33	
Deletion 15q11.1-q26.3	
Deltion 17p13.3-p11.2	*TP53*

Vaisitti T. et al., Blood 2021

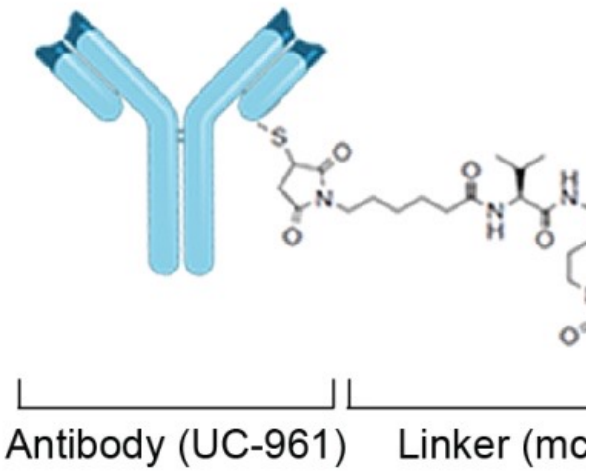
RS-PDX are good models to test tumor-targeting experimental therapies



- ✓ Antibody-drug conjugates
- ✓ Novel tumor-targenting agents
- ✓ Novel combinations

Iannello, Curr Treat Options in Oncology, 2022

Antibody-drug conjugates



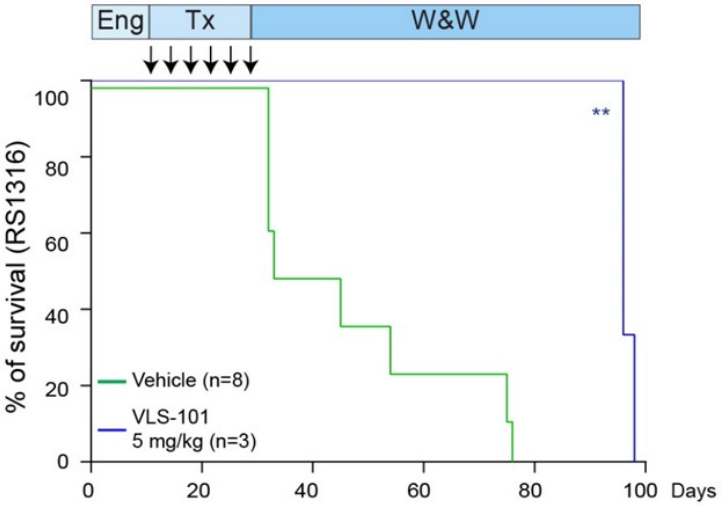
MMAE: monomethyl aurosta

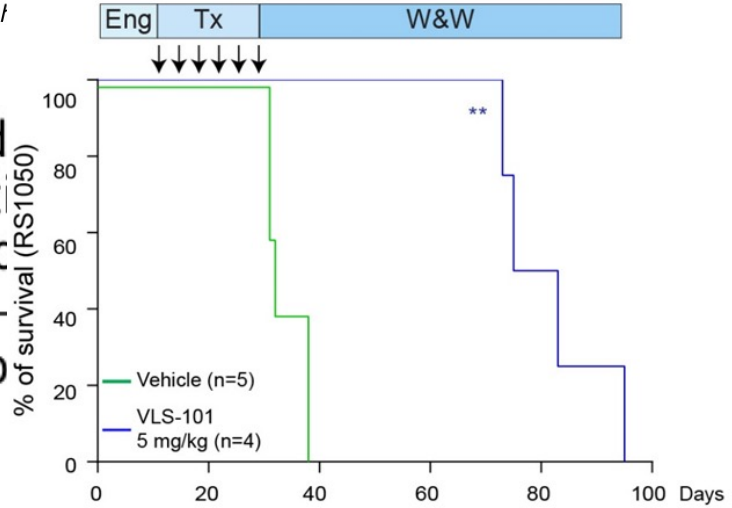
HEMATOLOGIC MALIGNANCIES—LYMPHOMA AND CHRONIC LYMPHOCY

7531

Zilovertamab vedotin (MK 2140) in relapsed/refractory (R/R) diffuse phoma (DLBCL): Early results from the phase 2 waveLINE-004 study.

Muhit Ozcan, Seung Tae Lee, Felix Mensah, Dipenkumar Modi, Alexander Fos Ewa Paszkiewicz-Kozik, Yazeed Sawalha, Ömür Gökmen Sevindik, La Armando Santoro, Kumudu Pathiraja, Samhita Chakraborty, Patricia Marinello, University School of Medicine, Ankara, Turkey; University of Maryland Marlene ebaum Comprehensive Cancer Center, Baltimore, MD; Indiana Blood and & Mari Franciscan Health, Indianapolis, IN; Karmanos Cancer Institute, Detroit, MI; Oslo Oslo, Norway; Sungkyunkwan University School of Medicine, Samsung Medical C Korea; Maria Sklodowska-Curie National Institute of Oncology, Warsaw, Poland Hospital and Solove Research Institute, The Ohio State University, Columbus, O University, International School of Medicine, Istanbul, Turkey; Faculty of Me University, Chiang Mai, Thailand; Humanitas University, Pieve Emanuele, and Research Hospital, Humanitas Cancer Center, Milan, Italy; Merck & Co., Inc., Rah Medical Center, Jerusalem, Israel



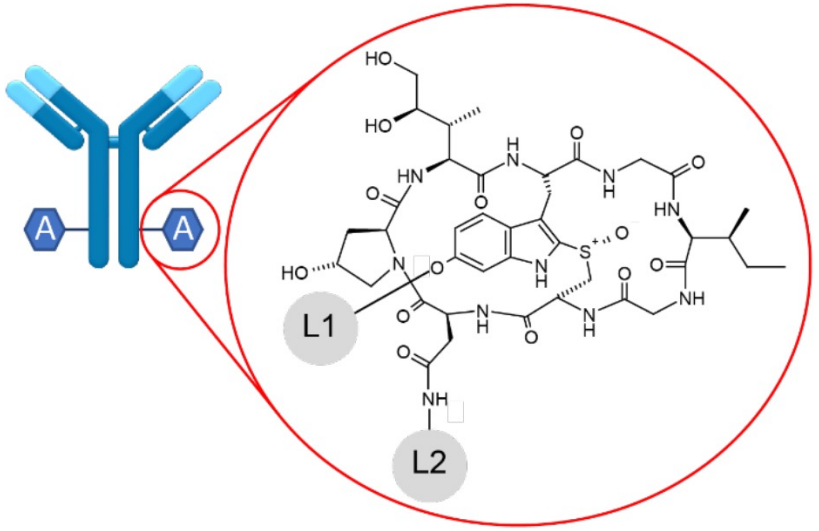


or tumor lysis syndrome due to treatment occurred and no pts died
Early results show that ZV had clinically meaningful antitumor acti
progressed after or have been ineligible for ASCT and/or CAR-T. Ac
manageable and consistent with other monomethyl auristatin E–
information: NCT05144841. Research Sponsor: Merck Sharp & Do
& Co., Inc., Rahway, NJ, USA.

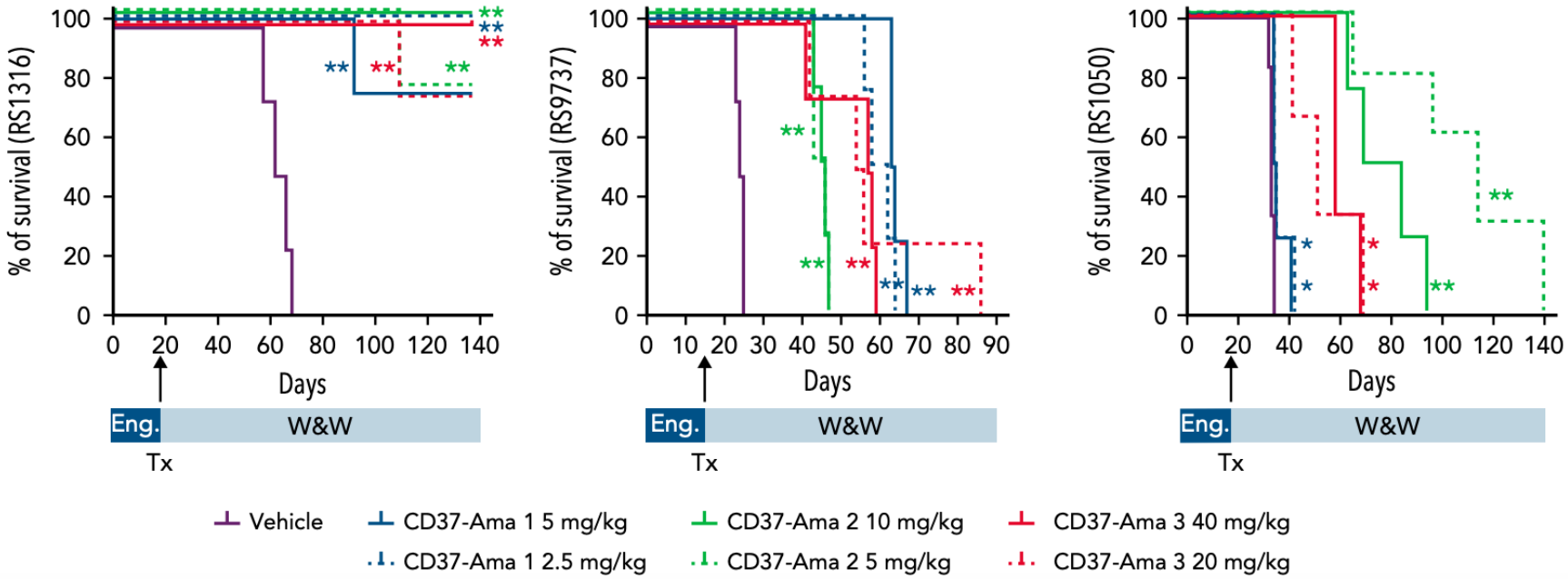
2023 ASCO annual meeting

Vaisitti, Blood 2021

Antibody-drug conjugates



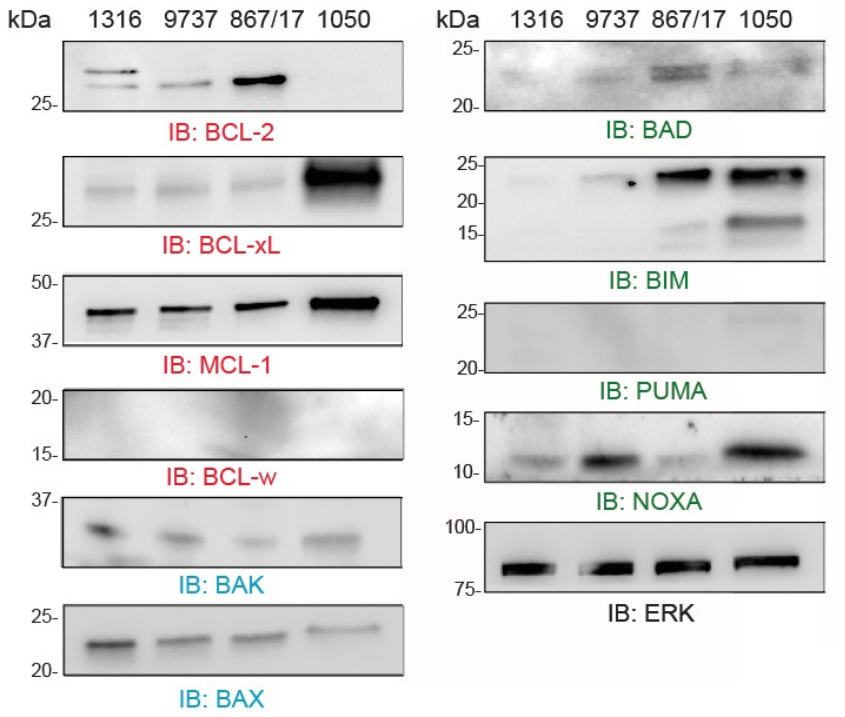
Anti-CD37-ADC



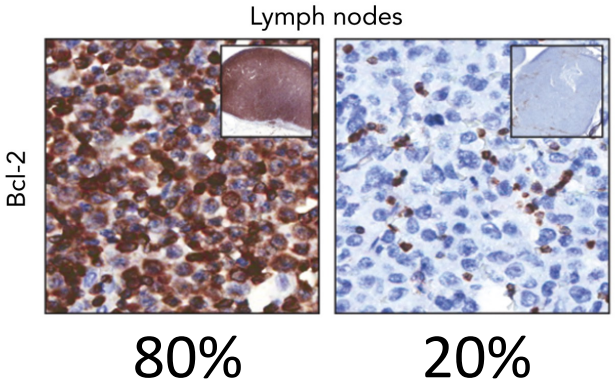
Vaisitti, Blood 2022

Targeting the apoptotic process

- ✓ RS show limited responses to bcl2 inhibitors
- ✓ RS show a different profile of expression of pro- and anti- apoptotic molecules compared to CLL
- ✓ RS cells show decreased apoptotic priming compared to CLL cells



Group	Members
Anti-apoptotic ●	•BCL2, •BCL-XL •MCL1 • Bfl-1
Pro-apoptotic ●	•BAX •BAK
Sensors ●	•BAD •BIM, •BID •Puma, Noxa



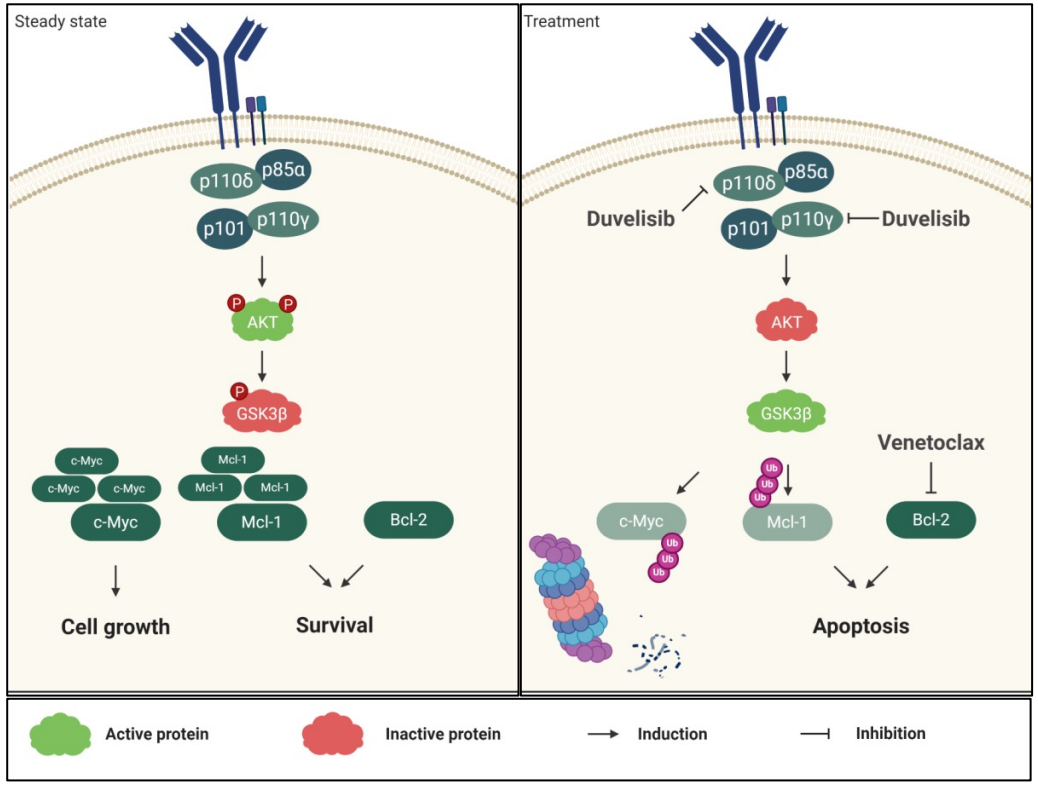
Iannello A, et al. Blood 2021

Unpublished, in collaboration with I. Ferrarini and C. Laudanna

Rationale for combining drugs that target multiple anti-apoptotic molecules

- ✓ BCR signaling prevents Mcl-1 ubiquitination

Active BCR signaling
No Mcl-1 degradation



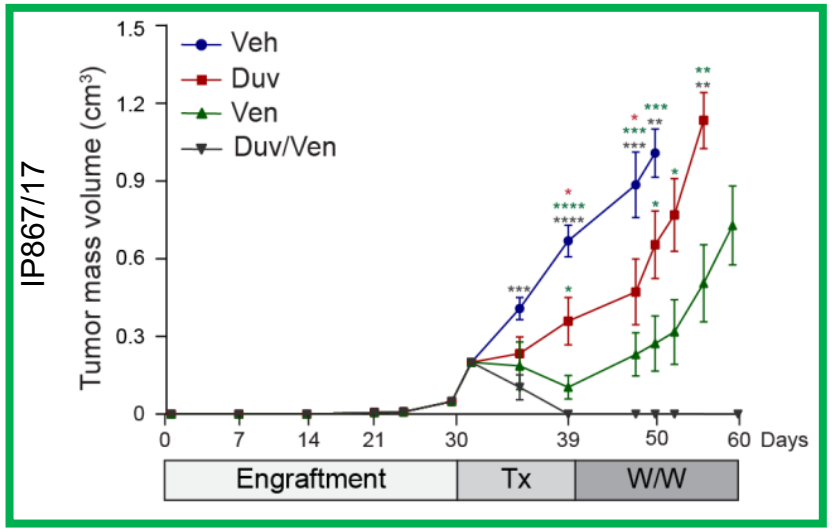
Blocked BCR signaling
Mcl-1 degradation

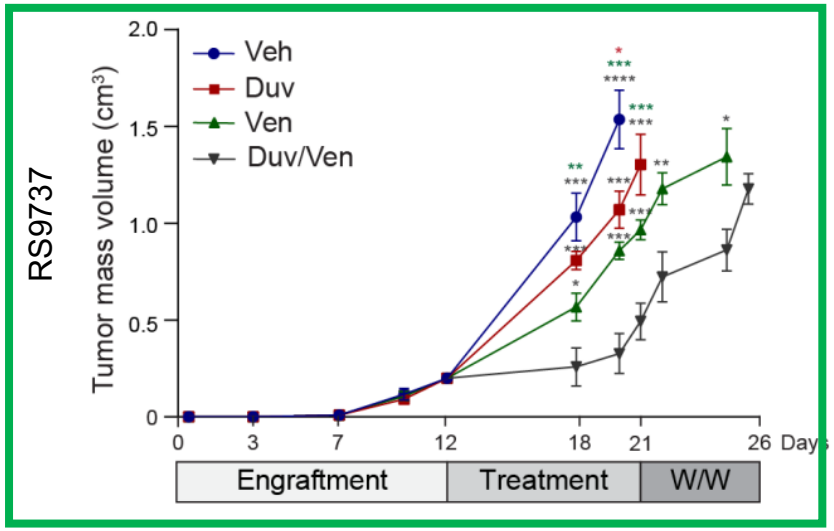
- ✓ Inhibition of PI3K signaling results in GSK3β activation, leading to ubiquitination and subsequent degradation of Mcl-1, making RS cells more sensitive to Bcl-2 inhibition by Ven.

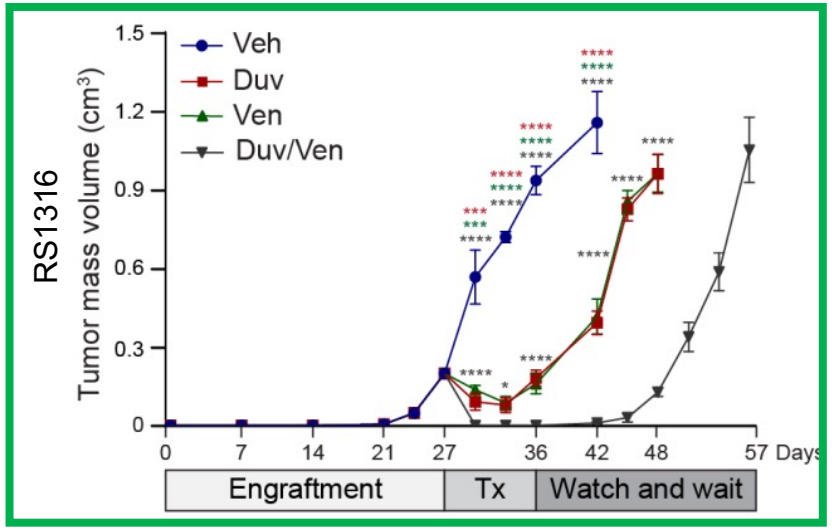
Iannello A, et al. Blood 2021

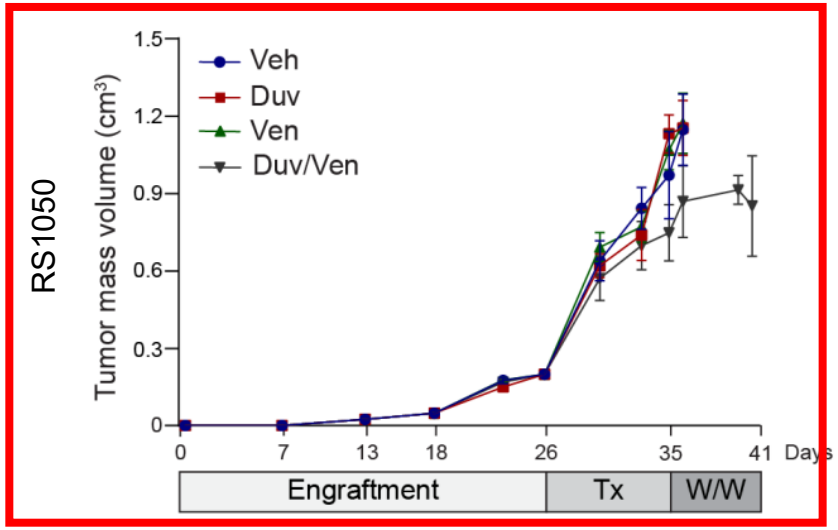
Effects of PI3Ki and BCL2i

✓ In vivo combination of Duv and Ven significantly blocks tumor growth in sub-cutaneous RS-PDX models that express BCL2



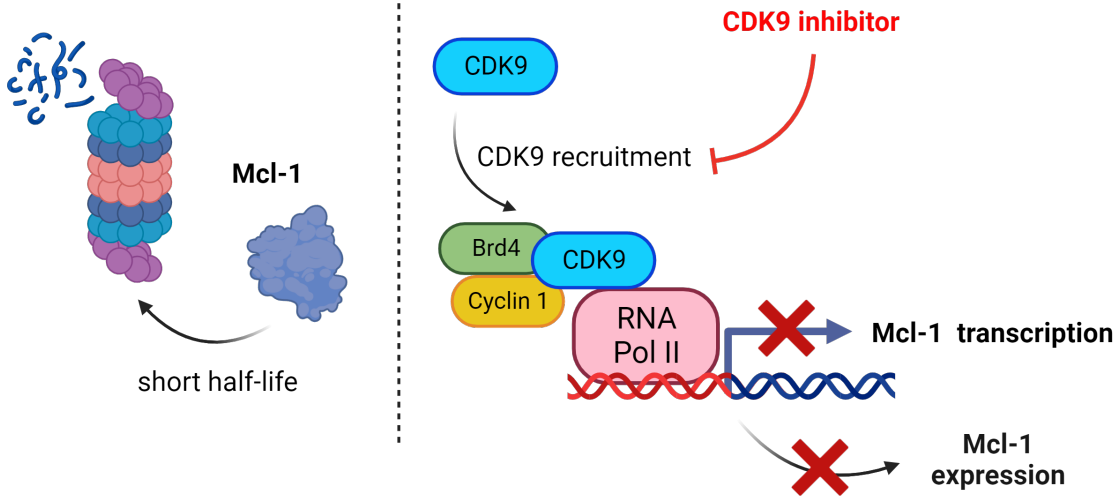


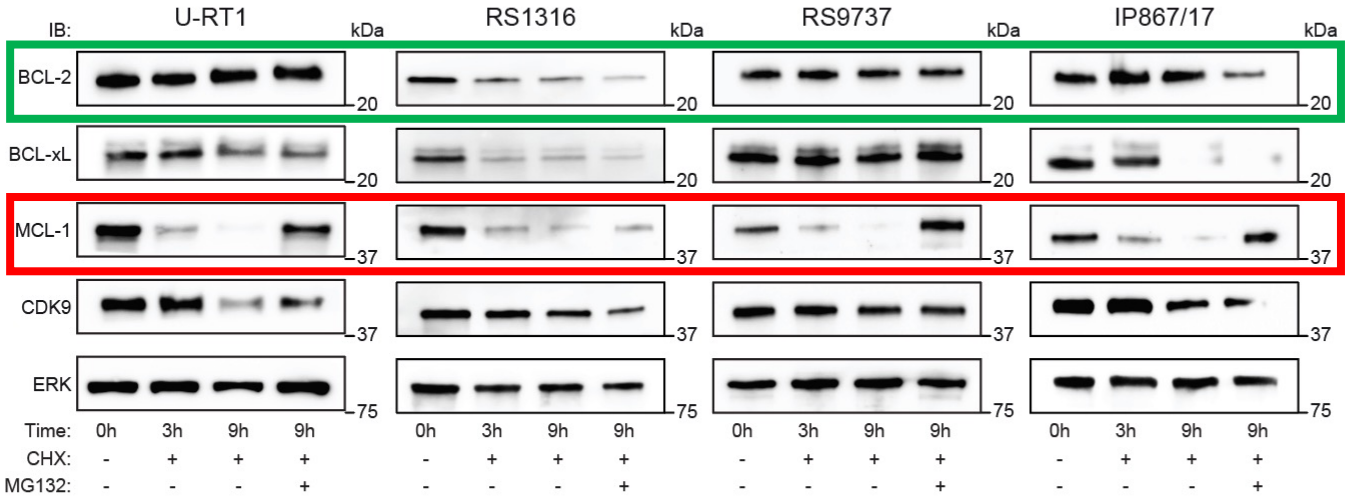


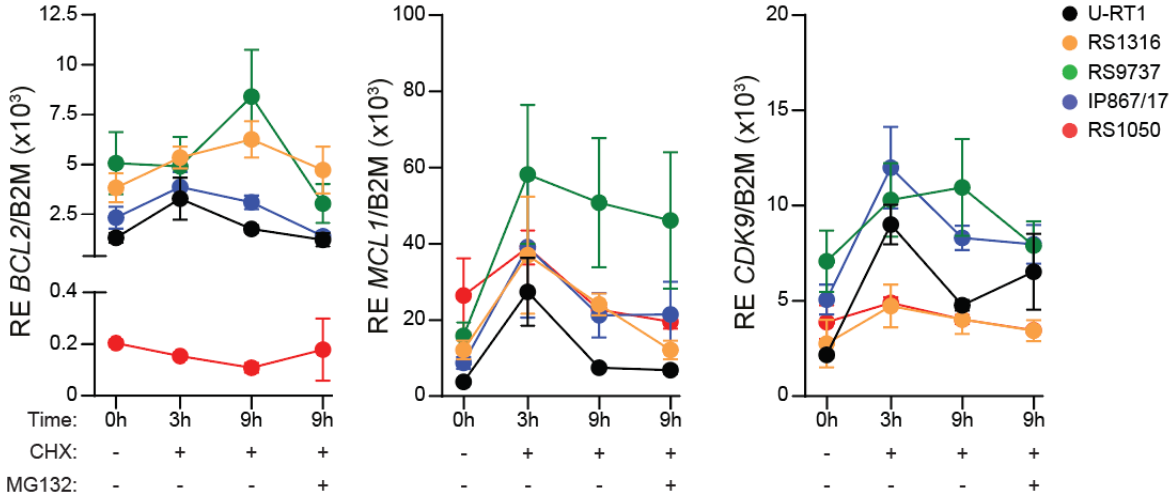


Iannello A, et al. Blood 2021

Alternative strategies for inducing apoptosis

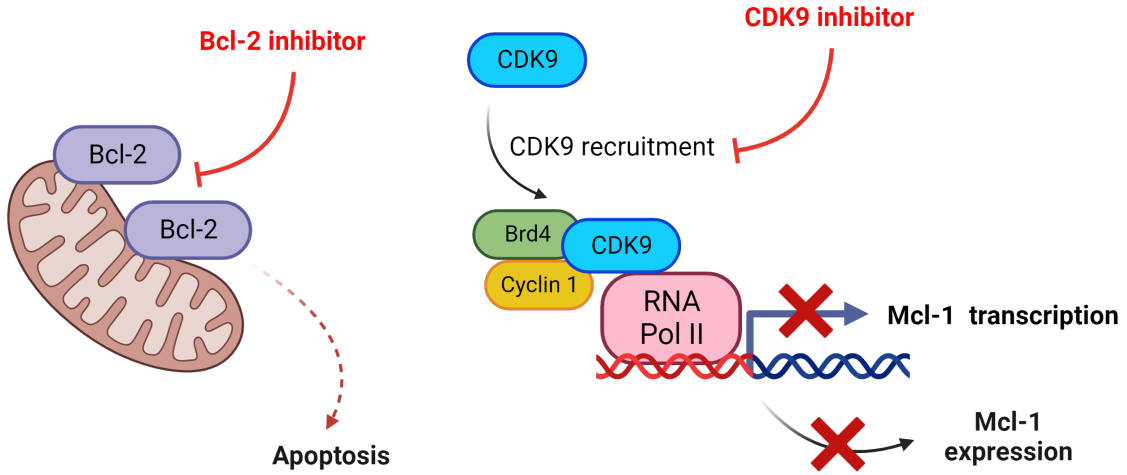


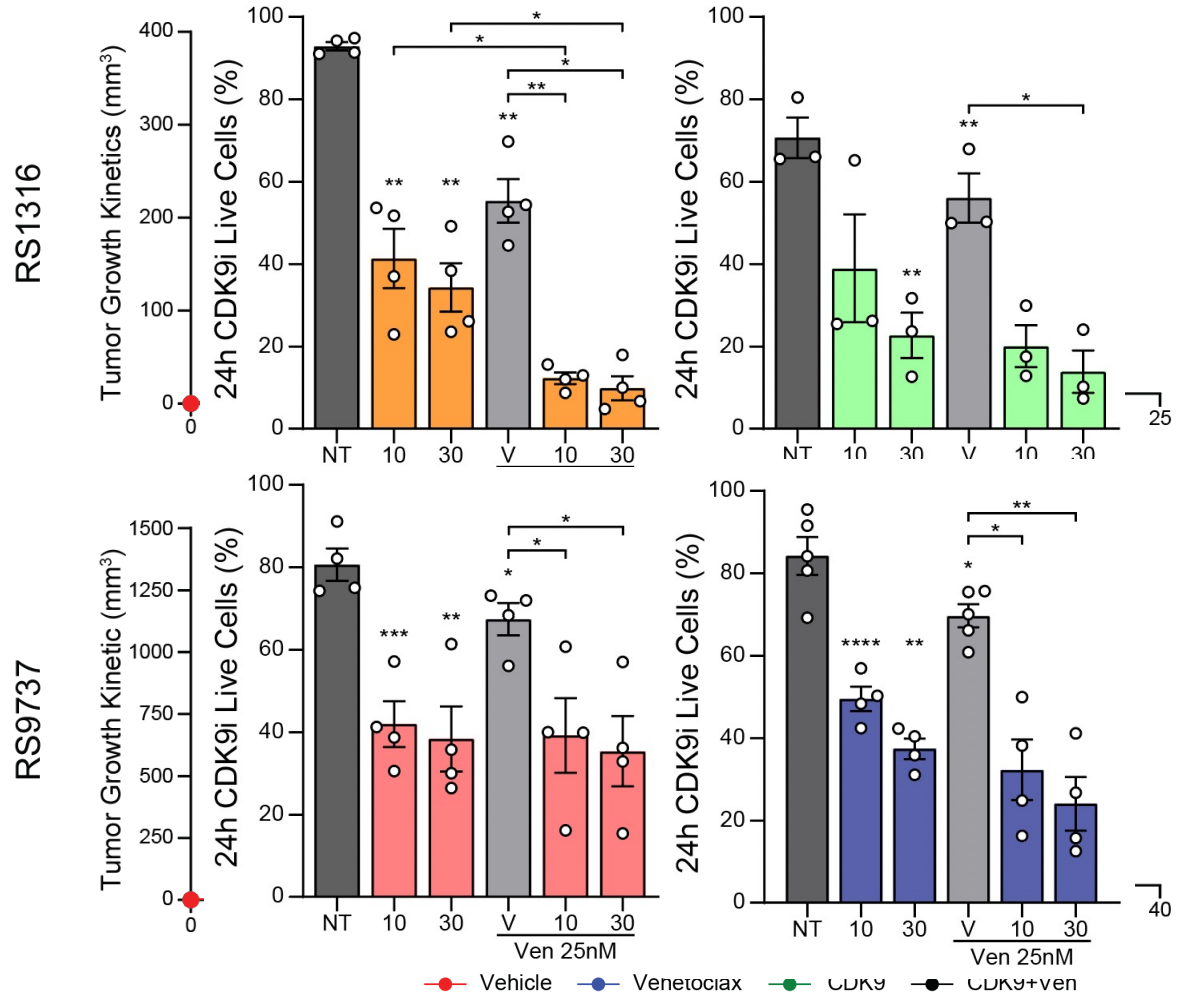




Brandimarte et al, in preparation

Alternative strategies for inducing apoptosis

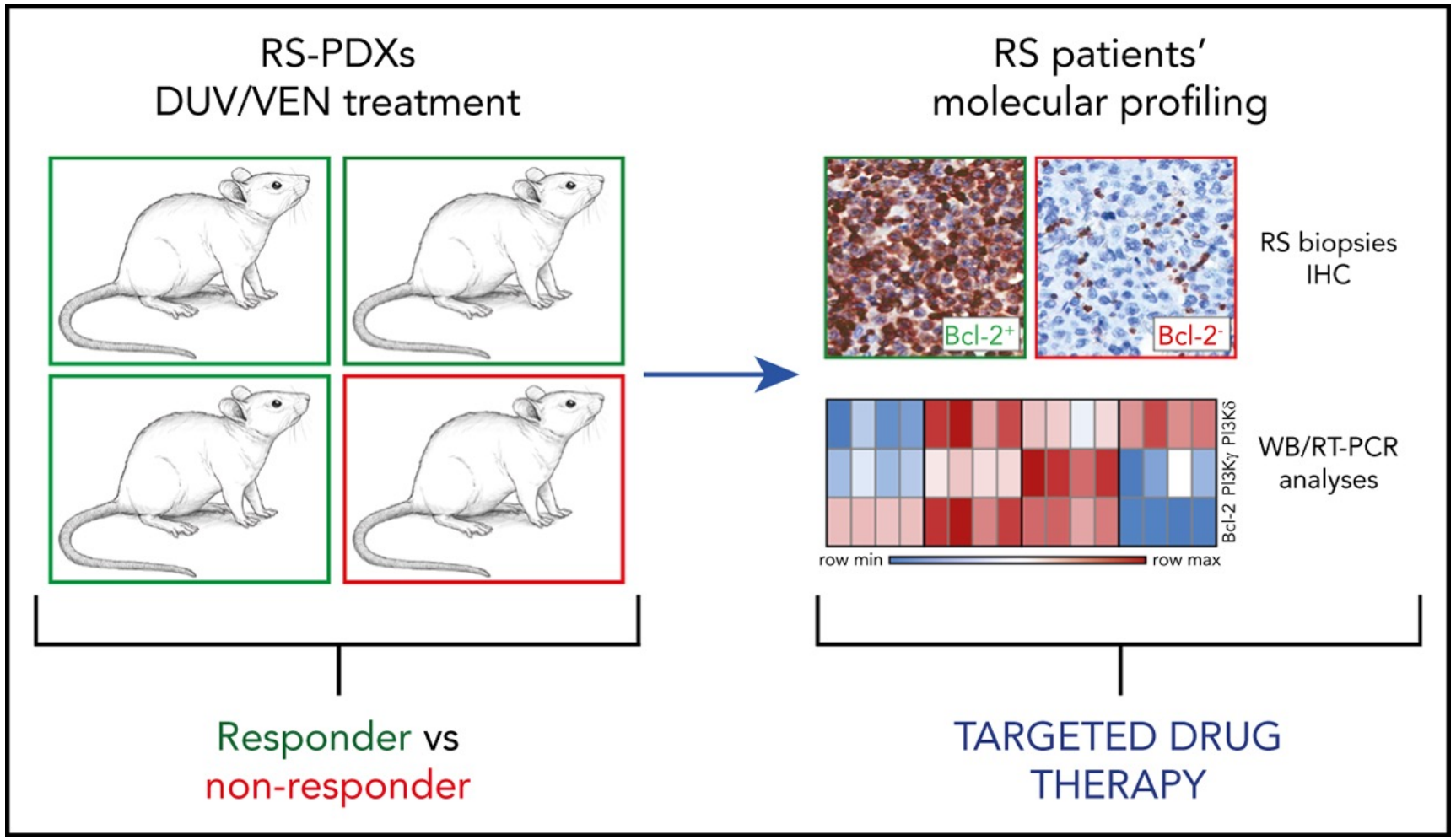




Brandimarte et al, in preparation

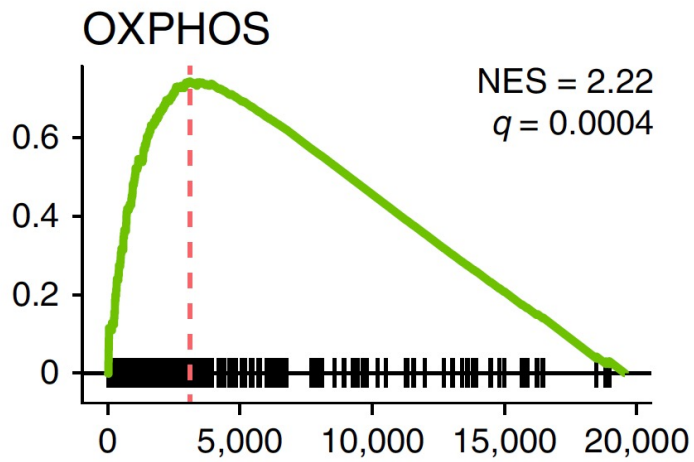
✓ **Combination of CDK9i with bcl2 inhibitors is effective, if both targets are expressed**

Pre-treatment patient profiling is essential

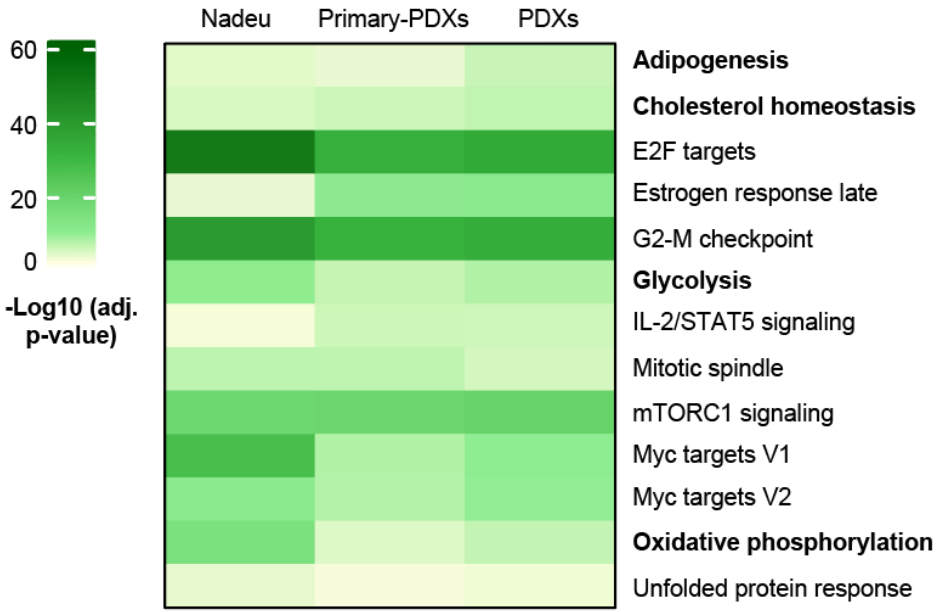


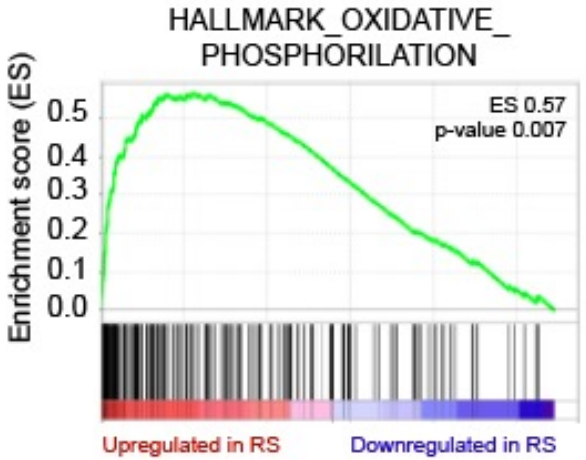
Alternative targets may come from “omic” studies

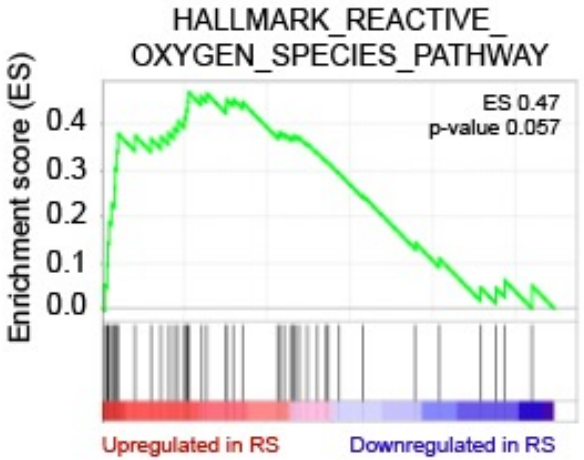
- ✓ RS cells show activation of different metabolic pathways compared to CLL cells

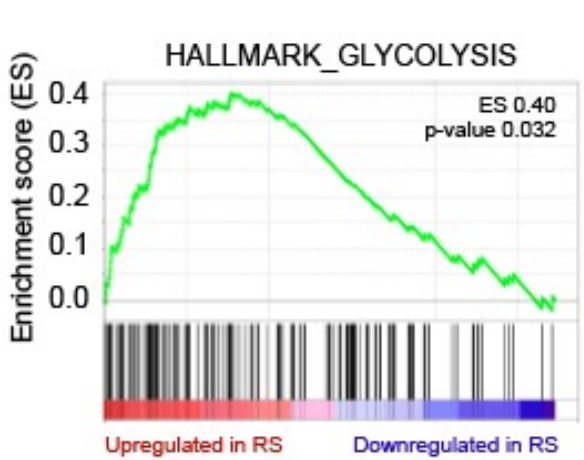


Nadeu F, Nat Med, 2022





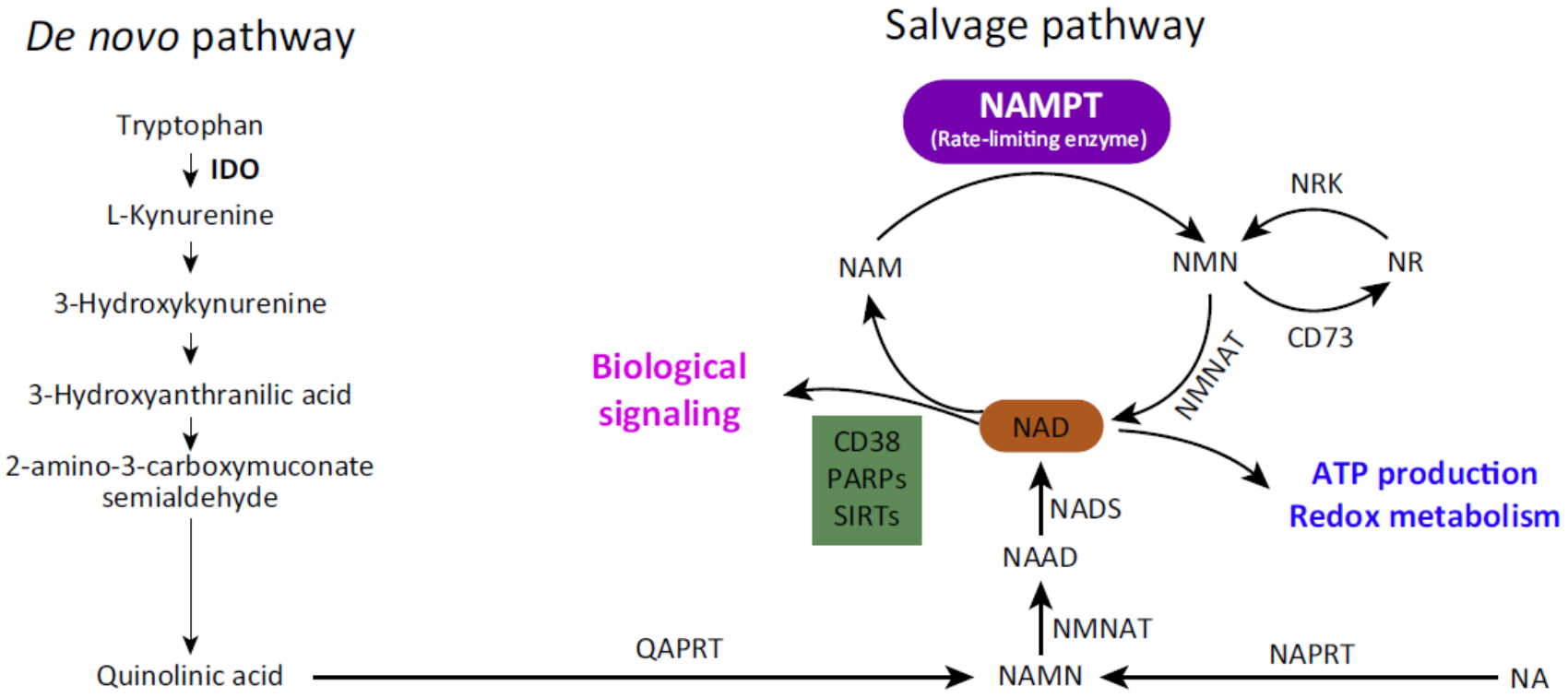




Vaisitti T , in preparation

Among metabolic targets we focused on NAMPT

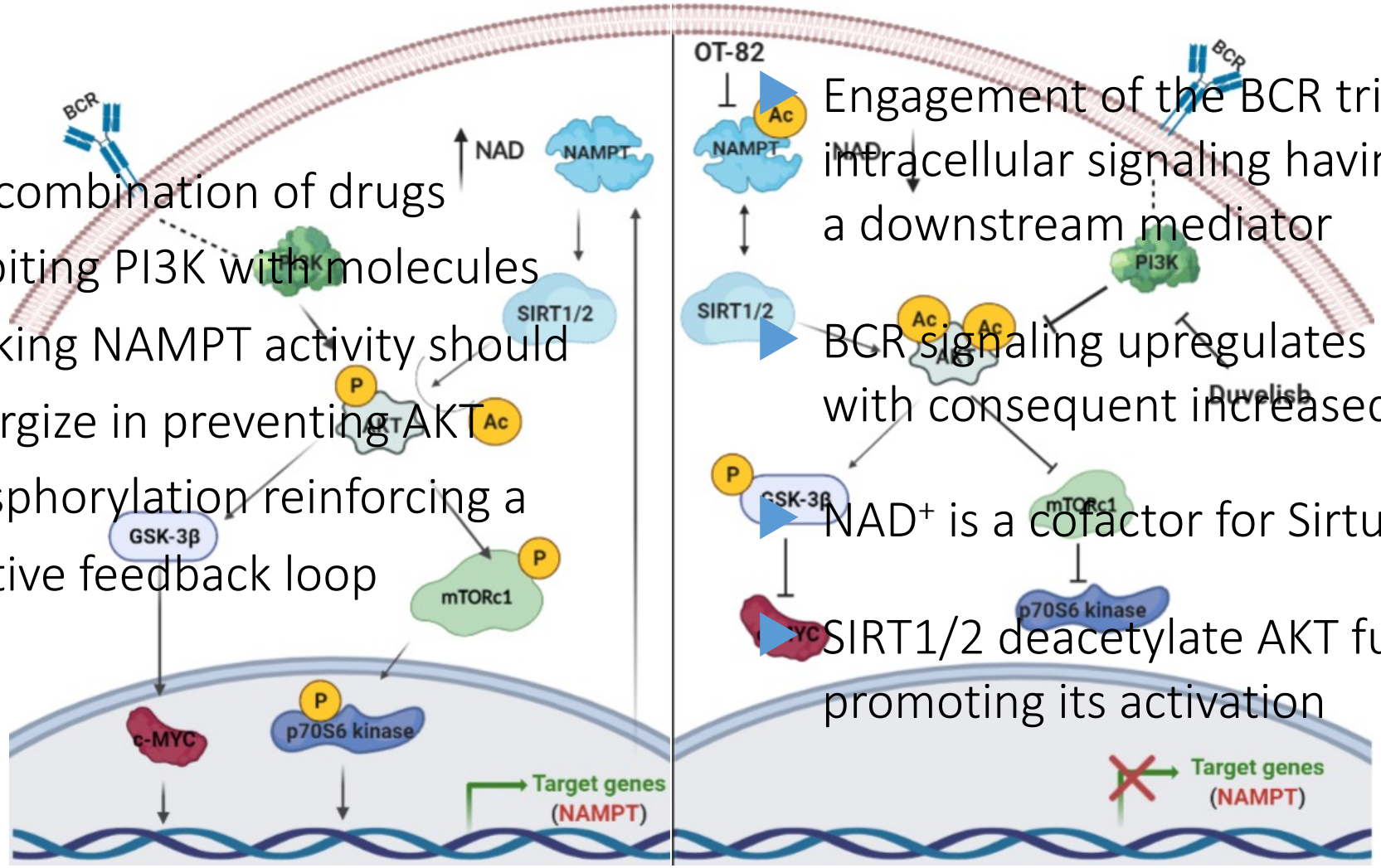
- ✓ NAMPT is the NAD biosynthetic enzyme with the highest expression in CLL
- ✓ NAMPT expression is regulated by BCR signaling
- ✓ NAMPT regulates NAD levels and therefore activity of NAD-dependent enzymes



- ✓ Novel NAMPT inhibitors are available for study

Evidence of positive feedback loop involving BCR NAMPT and SIRTUINS

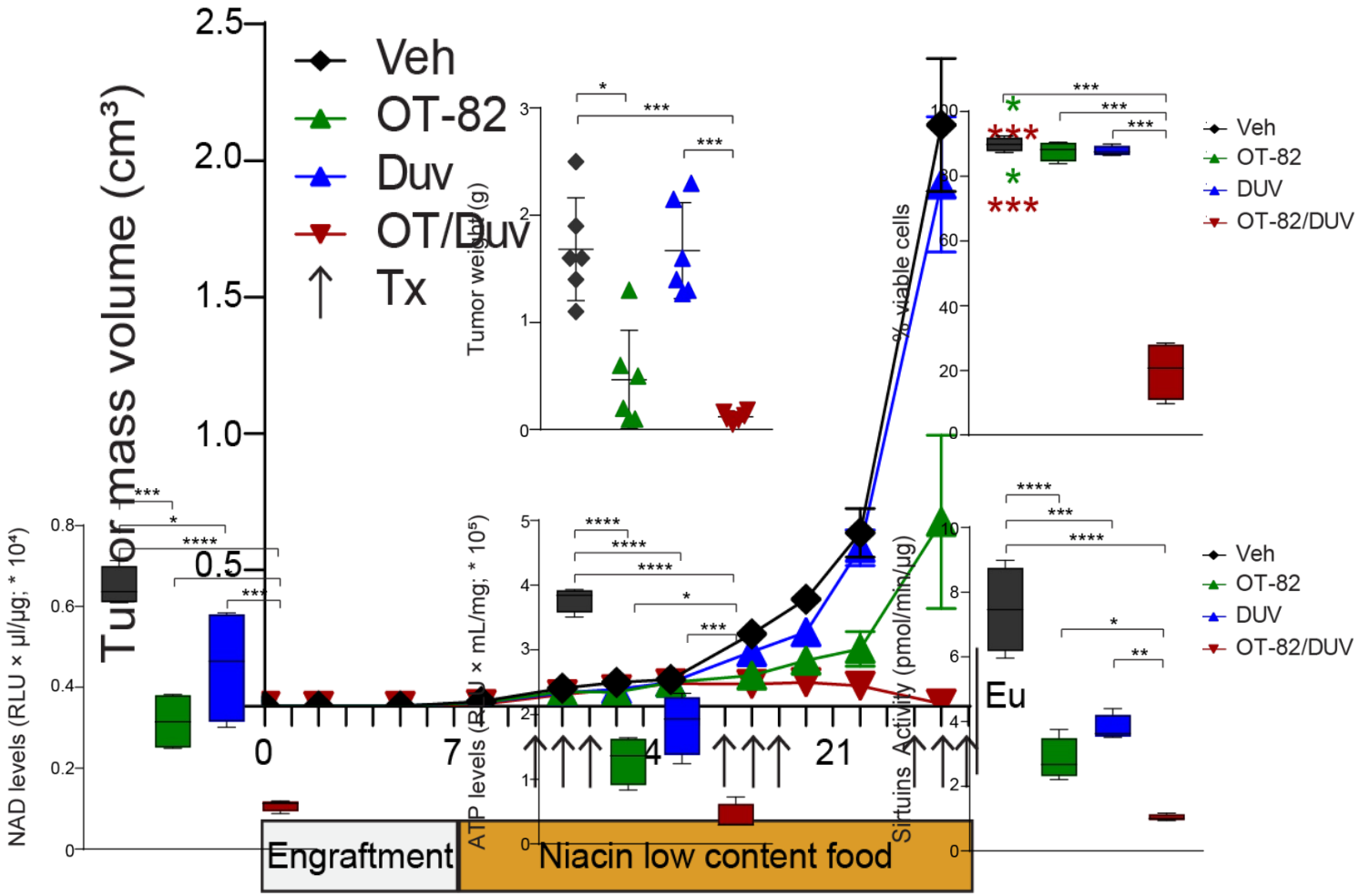
The combination of drugs inhibiting PI3K with molecules blocking NAMPT activity should synergize in preventing AKT phosphorylation reinforcing a positive feedback loop



- Engagement of the BCR triggers an intracellular signaling having AKT as a downstream mediator
- BCR signaling upregulates NAMPT with consequent increased NAD^+
- NAD^+ is a cofactor for Sirtuins
- SIRT1/2 deacetylate AKT further promoting its activation

Messana, GV, submitted

Effects of combination of BCR inhibitors and NAMPT inhibitors



Messana, GV, submitted

✓ Treatment with PI3Ki and NAMPTi significantly decreases tumor growth

Conclusions

- ✓ RS is an unmet clinical need in CLL management, due to the lack of successfull therapies and the difficulties to collect primary samples
- ✓ OMIC studies and mouse models are helping in understanding disease development, hierarchy of genetic lesions
- ✓ RS-PDXs may represent ‘’avatar’’ models for pre-clinical investigation before going back to patients’ bedside
- ✓ Successful therapeutic approaches will likely come from the combination of multiple drugs

Acknowledgments

Collaborators:

Gianluca Gaidano, Riccardo Moia, University of Eastern Piedmont

Isacco Ferrarini, Carlo Laudanna, University of Verona

Dimitar Efremov, ICGEB

Richard R. Furman, John Allan, Weill Cornell Medicine

AIRC

Ministero dell'Istruzione dell'Università e della Ricerca

Ministero della Salute