La terapia con anti BCL2 "un target trasversale " nei linfomi

Maurizio Martelli
Ematologia Università Sapienza Roma

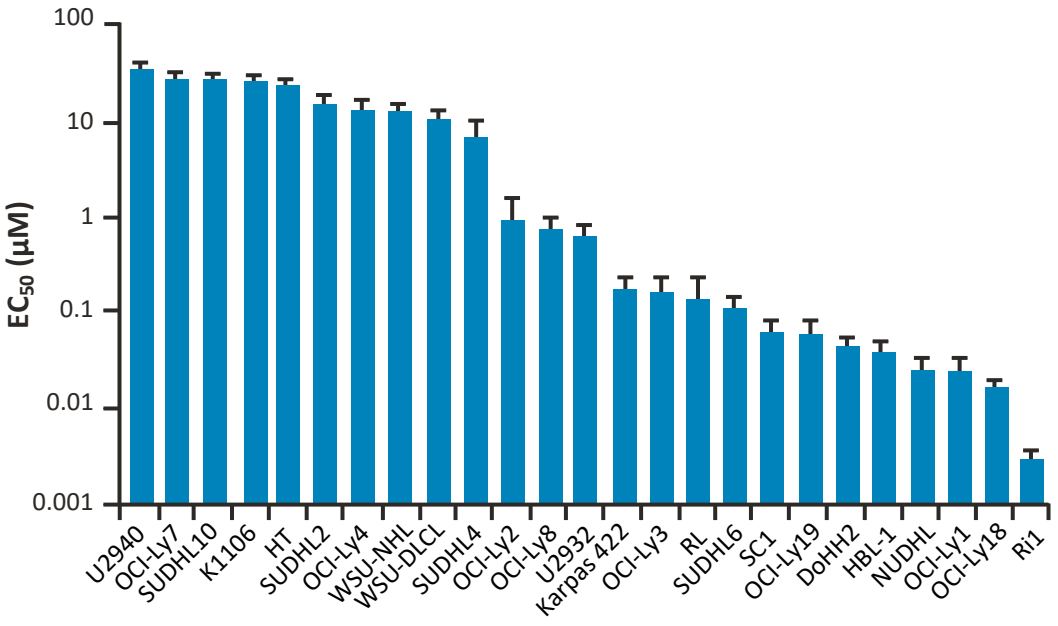
Disclosures Maurizio Martelli

Company name	Research support	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche		X		X	X	
Gilead				X	X	
Novartis				X	X	
Sandoz				X	X	
Eusapharma				X		
Servier				X	X	
Celgene				X	X	
Janssen				X	X	
Incyte	X			X	X	

Venetoclax Demonstrates Single-Agent Activity and Synergy with Other Agents: Preclinical DLBCL and FL Data

Venetoclax has demonstrated single-agent cell-killing activity against DLBCL and FL cell lines[1]

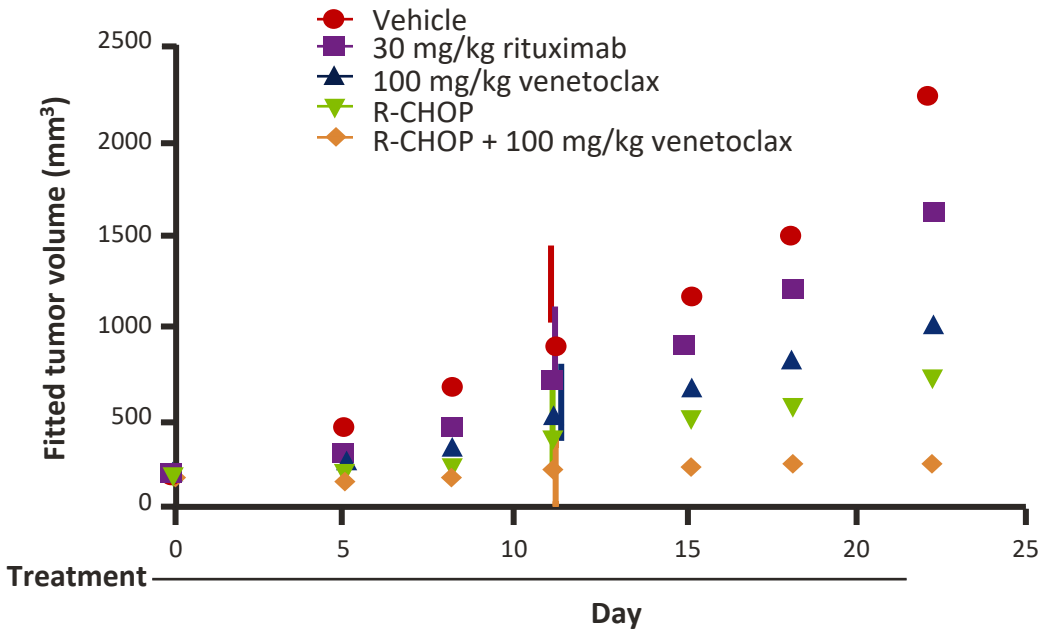
Viability of 25 NHL (DLBCL or FL) cell lines after incubation with increasing concentrations of venetoclax for 48 hours*



Souers AJ, *et al. Nat Med* 2013; 19:202–208 (incl. suppl.);
.).

Venetoclax demonstrated increased efficacy *in vivo* when combined with R-CHOP in a DLBCL xenograft model[2]

Reduction in tumor volume in animals treated with the combination of venetoclax + R-CHOP or each regimen alone



Zelenetz AD, *et al. Blood* 2019; 133:1964–1976 (incl. suppl.).

VOLUME 35 · NUMBER 8 · MARCH 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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Characteristic, n (%)		All N=106	MCL n=28	FL n=29	DLBCL n=41 [a]	Other [b] n=8
Age, years	Median (range)	66 (25–86)	72 (35–85)	64 (46–75)	67 (25–86)	63 (56–73)
Prior therapies	Median (range)	3 (1–10)	3 (1–7)	3 (1–10)	3 (1–8)	4 (2–6)
	Rituximab-refractory	33 (31)	8 (29)	8 (28)	16 (39)	1 (33)
Bulky nodes	>5 cm	49 (48)	16 (59)	8 (29)	22 (54)	3 (38)
	>10 cm	14 (14)	3 (11)	2 (7)	8 (20)	1 (13)
LDH	> Upper Limit of Normal	45 (44)	7 (27)	10 (35)	27 (68)	1 (13)

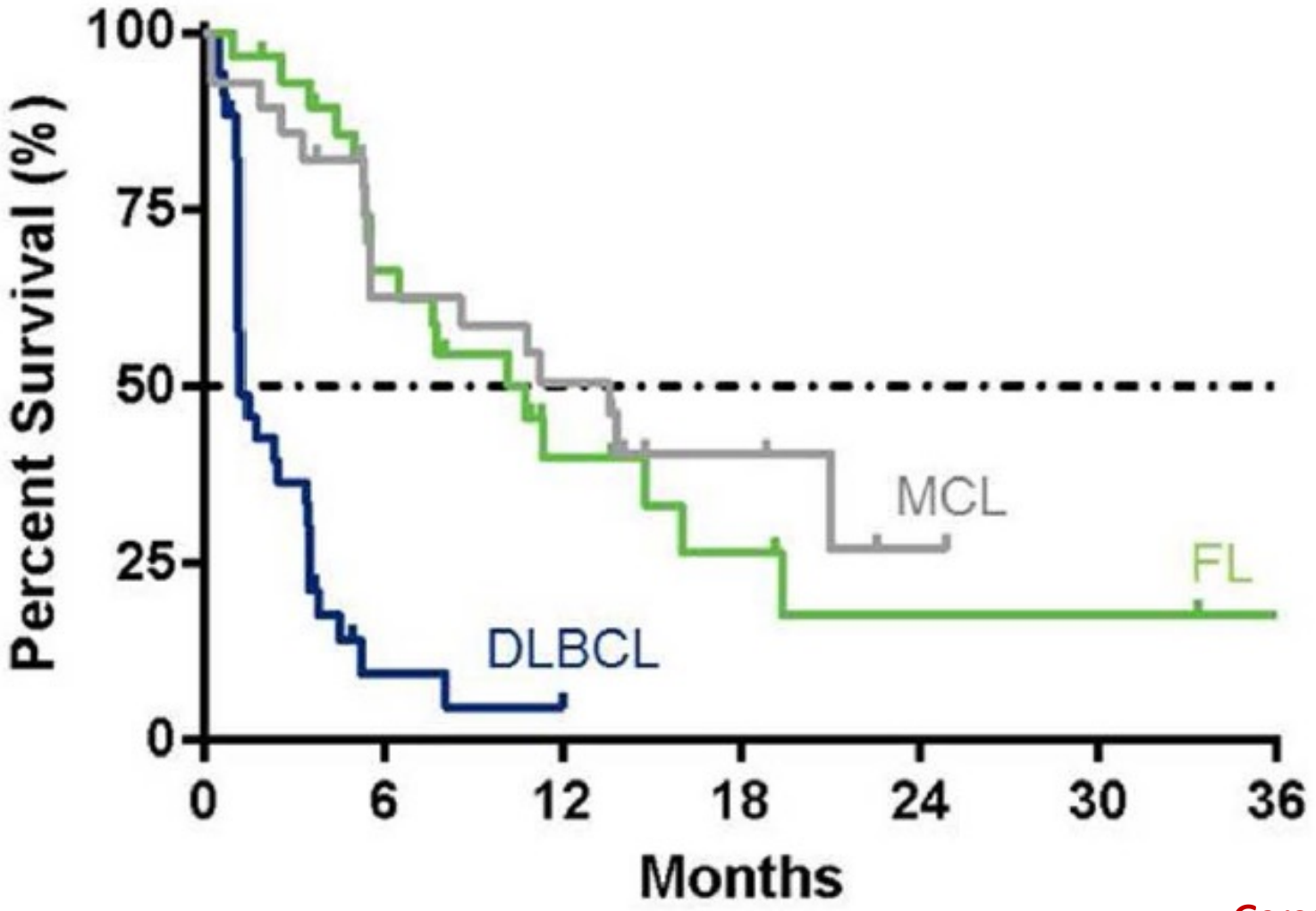
Gerecitano et al,. JCO 2017

Best responses by histology (intention to treat)

Best Response	All Pts 106 (%)	MCL (28)	FL (29)	DLBCL (41)	WM (4)	MZL (3)
ORR	47 (44)	21 (75)	11 (38)	6 (18)	4 (100)	2 (67)
CR	14 (13)	6 (21)	4 (14)	4 (12)	0	0
PR	33 (31)	15 (54)	7 (28)	2 (6)	4 (100)	2 (67)
SD	32 (30)	5 (18)	17 (59)	8 (24)	0	0
PD	24 (23)	2 (7)	1 (3)	19 (56)	0	1 (33)

Gerecitano et al,. JCO 2017

Progression free survival by histology



Gerecitano et al,. JCO 2017

Phase 1 study: treatment adverse events

All Grade AEs (in ≥ 15% patients), n (%)	N=106
Any AE	103 (97)
Nausea	51 (48)
Diarrhea	47 (44)
Fatigue	43 (41)
Decreased appetite	22 (21)
Vomiting	22 (21)
Anemia	19 (18)
Constipation	19 (18)
Headache	19 (18)
Neutropenia	19 (18)
Cough	18 (17)
Back pain	17 (16)
Upper respiratory tract infection	16 (15)

Grade 3/4 AEs (in ≥ 5% patients), n (%)	N=106
Any Grade 3/4 AE	57 (54)
Anemia	17 (16)
Neutropenia	13 (12)
Thrombocytopenia	10 (9)
Fatigue	6 (6)

Serious Adverse Events (in ≥2 patients), n (%)	N=106
Any SAE	35 (33)
Diarrhea	3 (3)
Hyponatremia	3 (3)
Influenza	3 (3)

* Two TLS (1 MCL 200 mg), no clinical sequelae

Gerecitano et al,. JCO 2017

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Objective response in MCL

Best Objective Response, n (%)	All N=106	MCL n=28
Overall Response	**47 (44)**	**21 (75)**
CR	14 (13)	6 (21)
PR	33 (31)	15 (54)
SD	32 (30)	5 (18)
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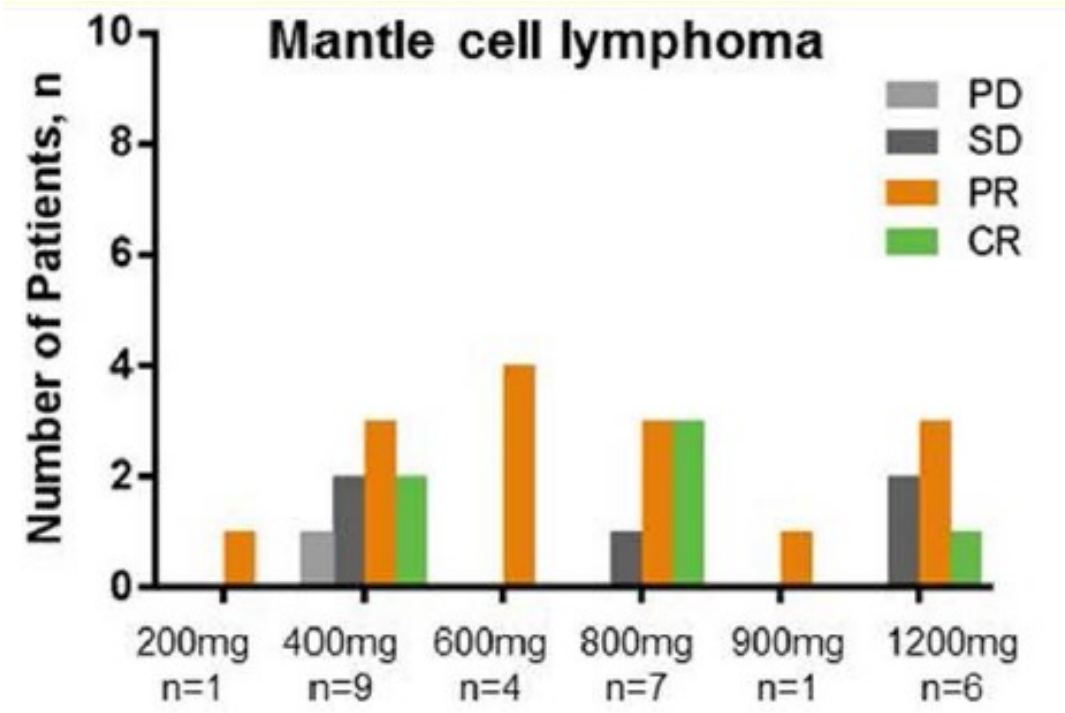
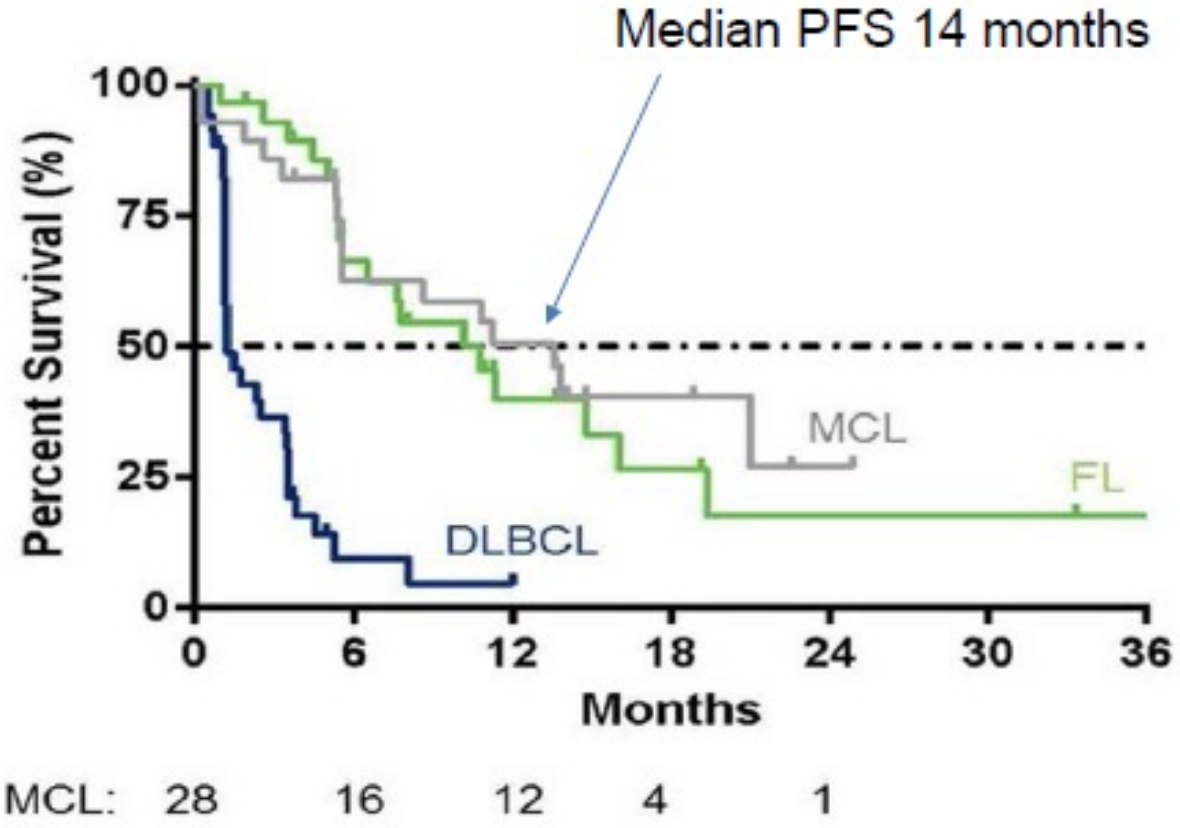


Gerecitano et al,. JCO 2017

MCL: response to Venetoclax monotherapy and PFS

Best Objective Response, n (%)	All N=106	MCL n=28
Overall Response	**47 (44)**	**21 (75)**
CR	14 (13)	6 (21)
PR	33 (31)	15 (54)
SD	32 (30)	5 (18)
PD	23 (22)	1 (4)

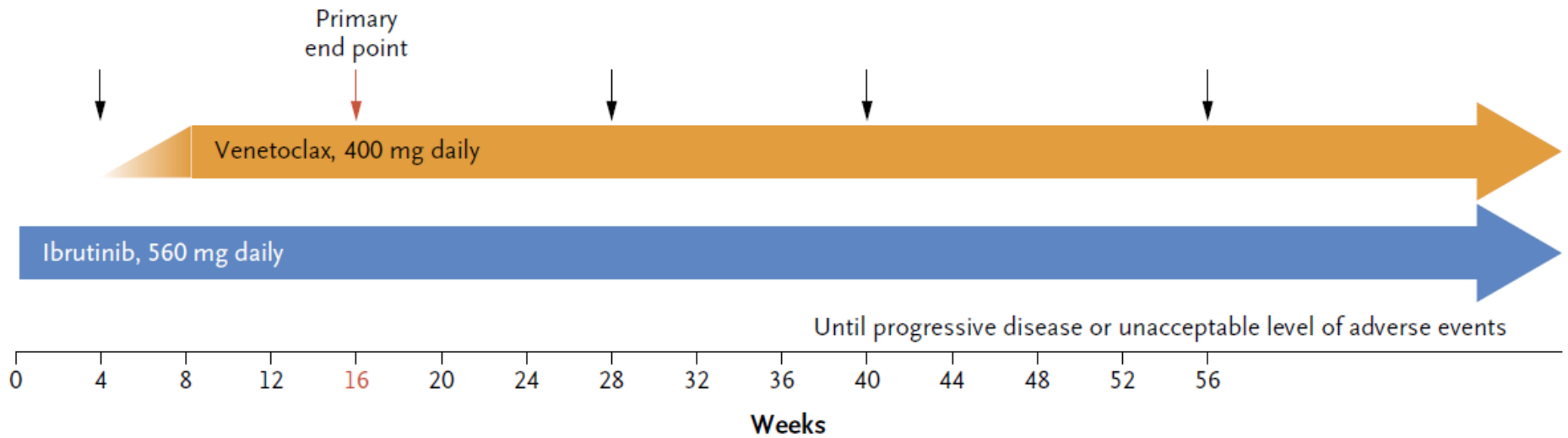


Gerecitano et al,. JCO 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma



Tam CS et al, NEJM 2018

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

24 pts

Characteristic	Value
Median age (range) — yr	68 (47–81)
Sex — no. (%)	
Female	3 (12)
Male	21 (88)
Previous treatment for mantle-cell lymphoma — no. (%)	
Yes	23 (96)
No†	1 (4)
No. of previous therapies among patients who had received therapy — median (range)‡	2 (1–6)
Previous therapy — no./total no. (%)‡	
Autologous transplantation	7/23 (30)
Rituximab	23/23 (100)
Anthracycline	21/23 (91)
High-dose cytarabine	11/23 (48)
Bendamustine	4/23 (17)
Blastic or pleomorphic mantle-cell lymphoma — no./total no. (%)	1/21 (5)
Ki-67 ≥30% — no./total no. (%)	9/21 (43)
TP53 status — no. (%)	
Mutated with deletion	4 (17)
Mutated without deletion	7 (29)
Deletion without mutation	1 (4)

Tam CS et al, NEJM 2018

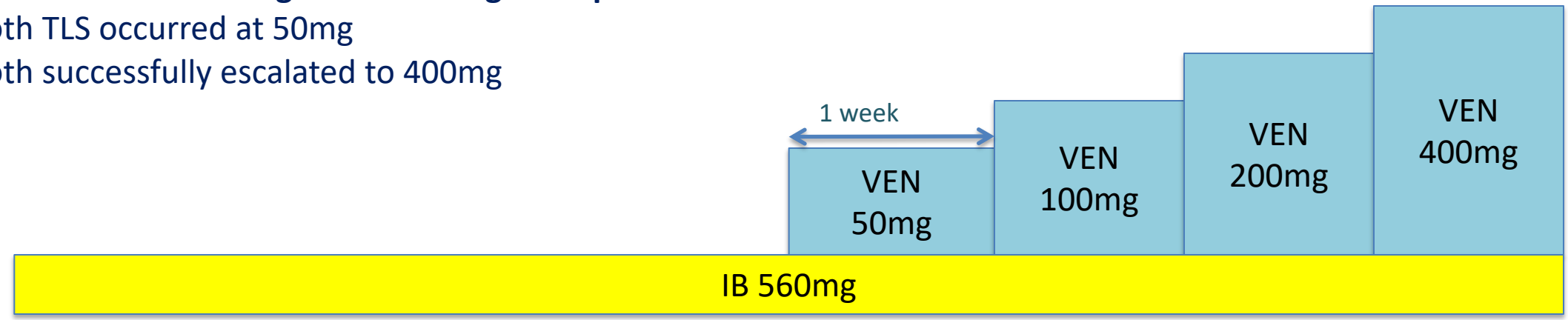
Tumour Lysis Syndrome

N = 16 treated using initial schedule

2 cases of TLS* among 4 baseline high-risk patients

Both TLS occurred at 50mg

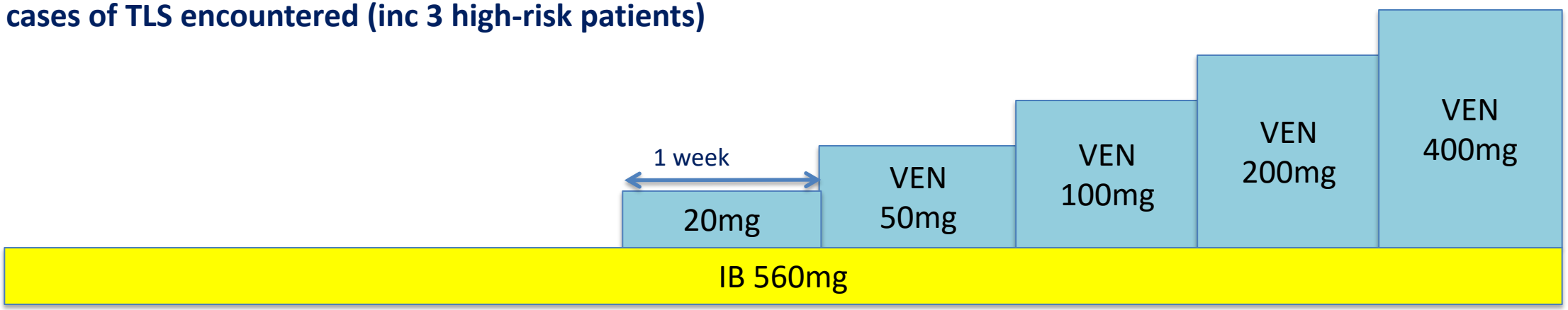
Both successfully escalated to 400mg



one case of grade 3 clinical TLS (acute renal impairment); one case of self-limiting fever, hyperphosphataemia and 400% elevation in LDH, regarded as grade 3 biochemical TLS in absence of alternative explanation.

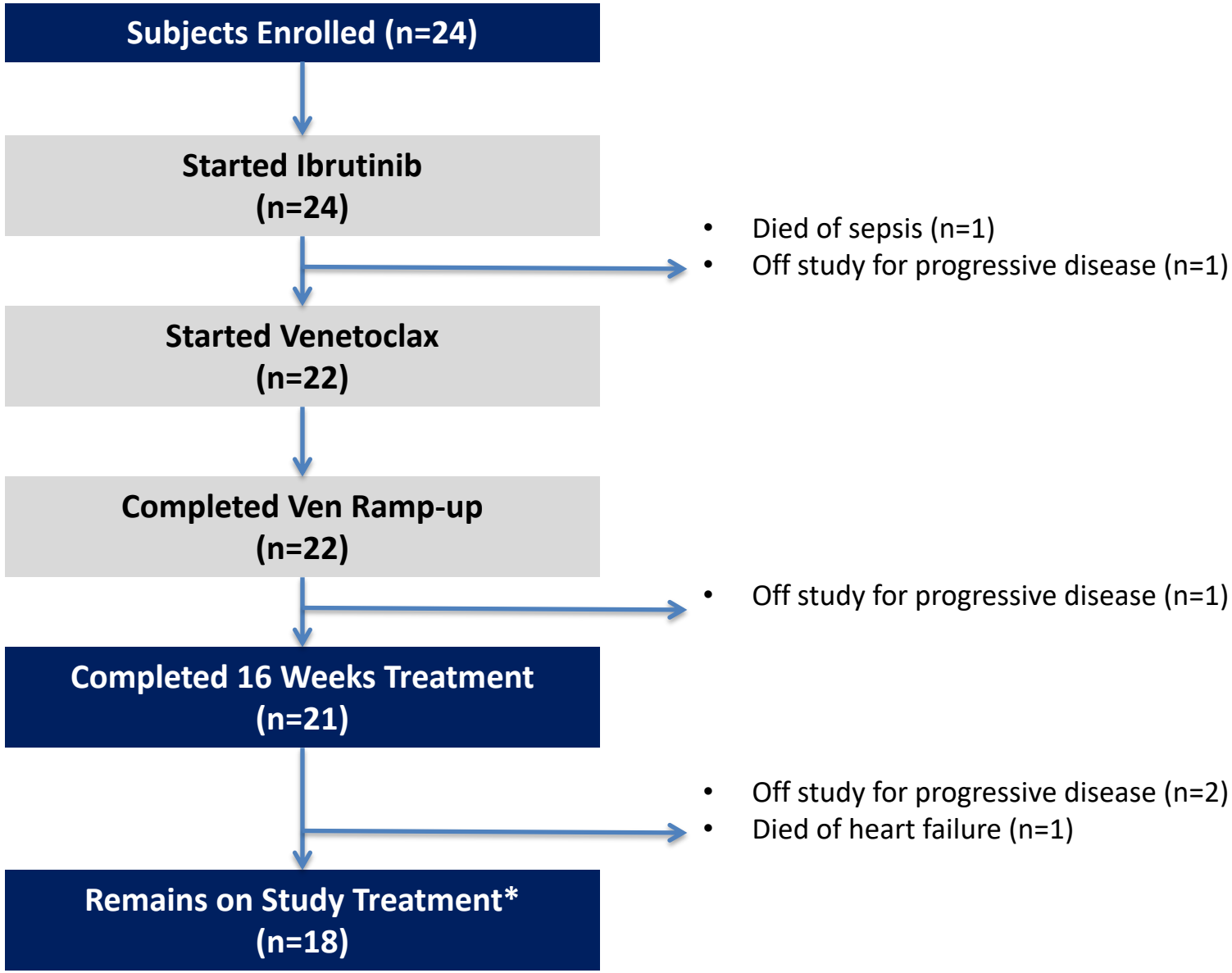
N = 8 treated using revised schedule (20mg start)

No cases of TLS encountered (inc 3 high-risk patients)



Data-Cutoff 10-Jan-2017

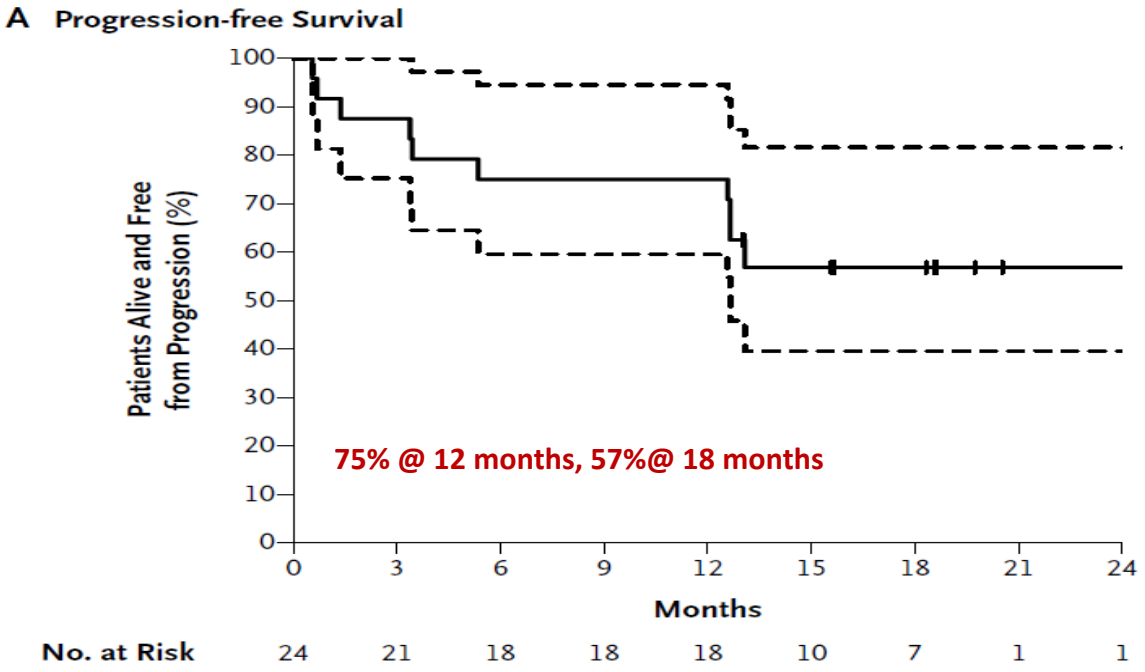
Median Follow-up 8.3 months (1.4 to 17.7+ months)



Tam et al, NEJM 2018

Venetoclax & ibrutinib in relapsed MCL

PFS



Tam et al, NEJM 2018

Response@ wk 16	No PET (N= 24)	PET (N = 24)
CR (%)	10 (42)	15 (62)
PR (%)	4 (17)	2 (8)
PD (%)	3 (12)	4 (17)

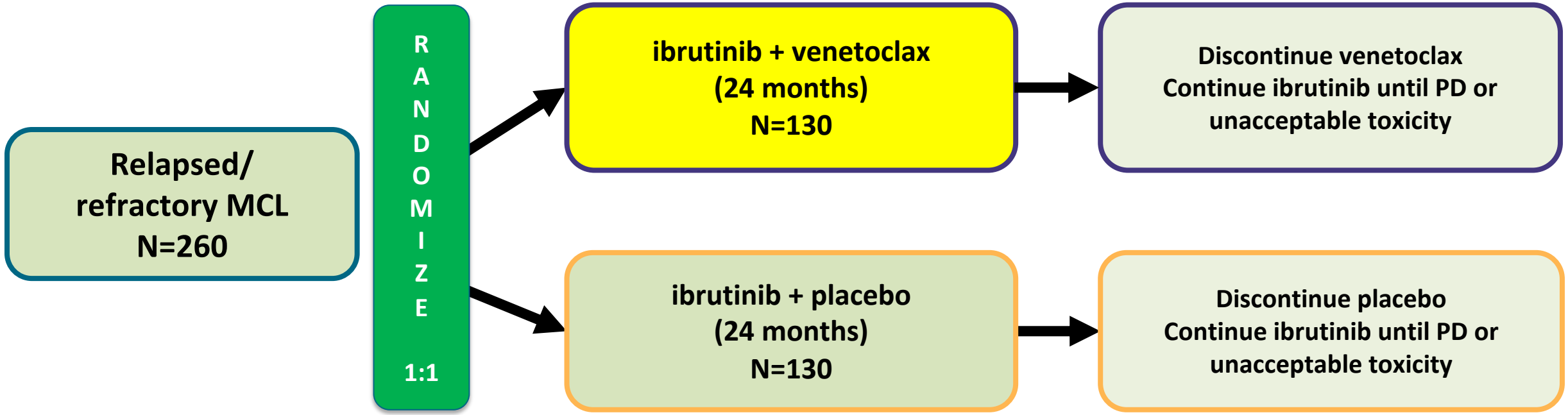
Toxicity mostly Grade 1-2

diarrhea, fatigue

Grade 3-4

- 33% neutropenia
- 12% diarrhea
- 4% bleeding
- 8% atrial fibrillation
- 8% tumor lysis

Phase 3 Study Design of PCYC-1143: SYMPATICO



Primary Endpoint PFS*

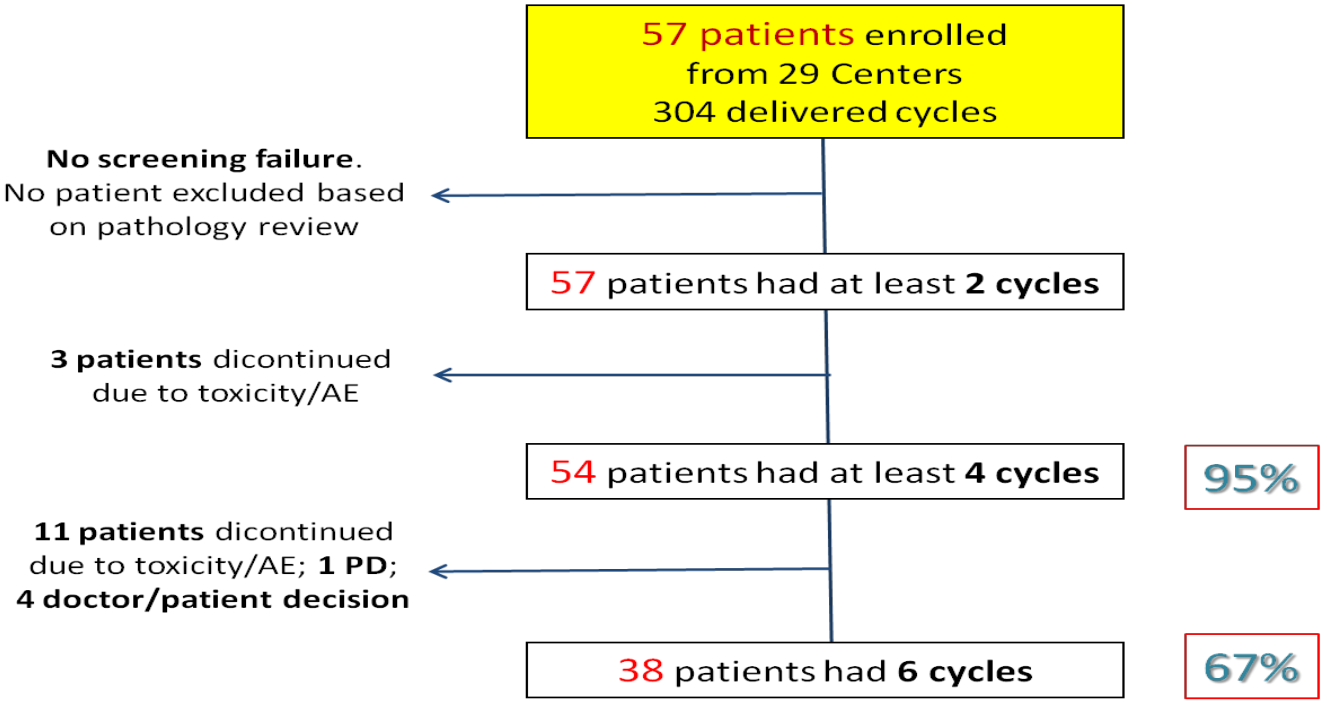
Study start: May 2017 **Estimated end of study March 2022**

FIL R-BAC 500 trial

Patients' characteristics at inclusion

	Overall (57)	%
Age, years		
median (range)	71 (61-79)	
Gender		
male	43	75
Performance Status		
0-1	54	94
AAS		
III-IV	52	91
MIPI risk category		
low	9	16
intermediate	23	40
high	25	44
BM involvement	36	63
Histology		
classical	43	75
pleomorphic	8	14
blastoid	6	11
Ki-67 (%)		
≥30%	16	31
median (range)	20 (5-85)	

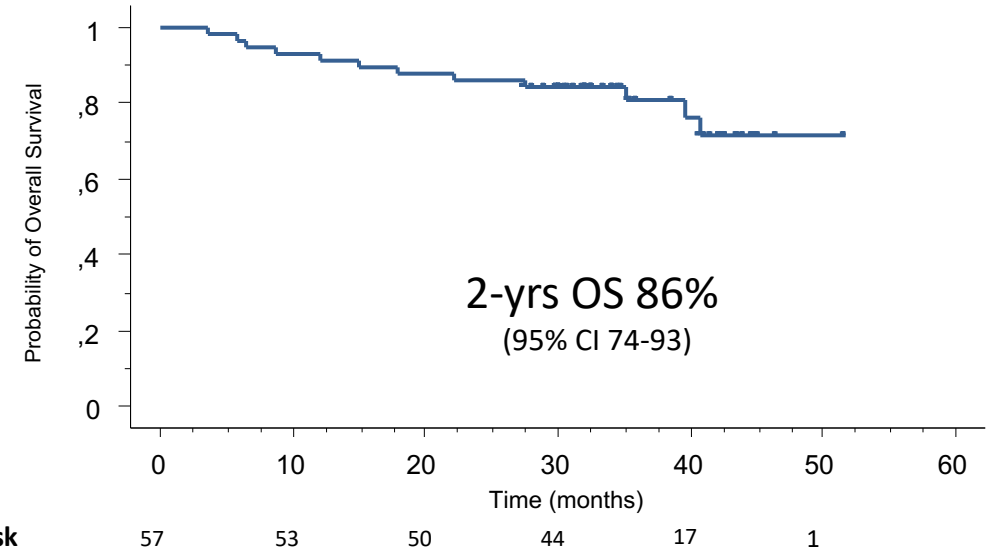
Trial profile



Visco C. et al JCO 2017

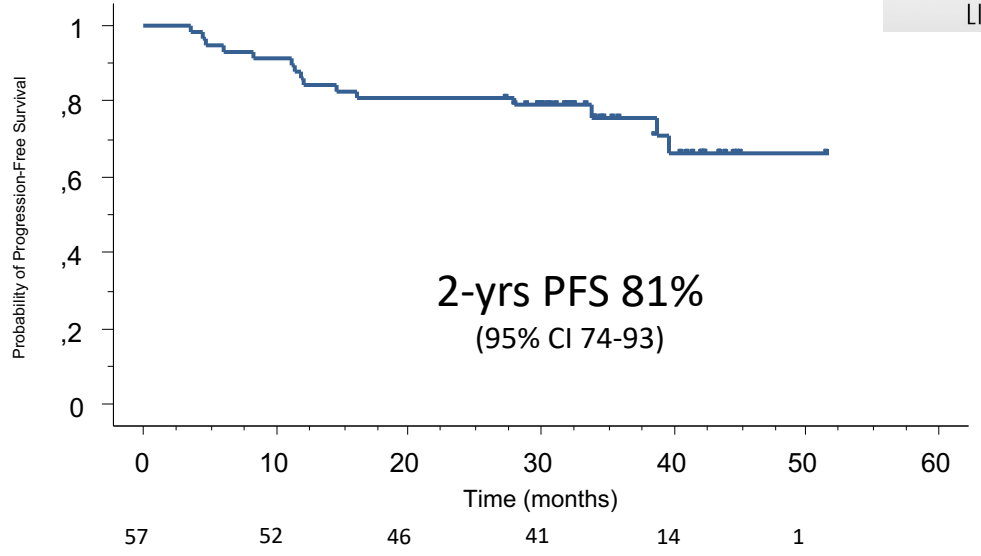
Survival curves *Median follow-up 35 months (28-52)*

OS



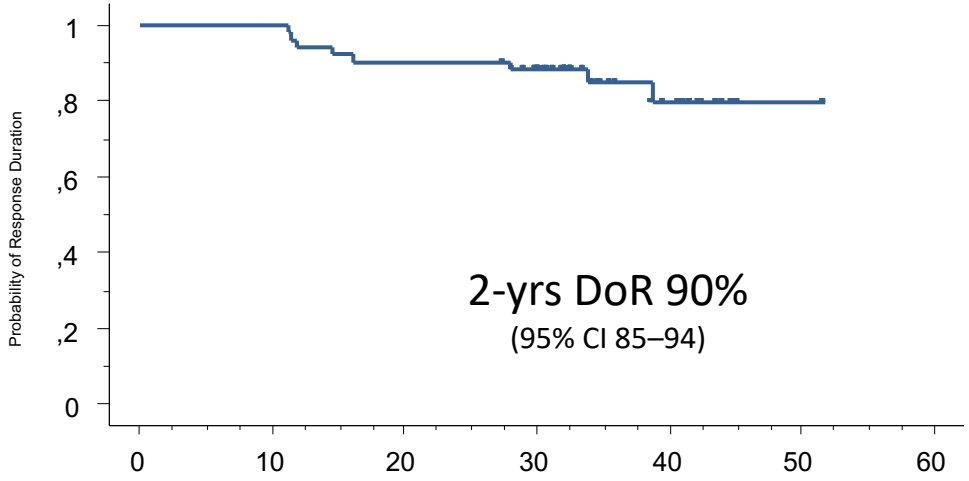
Number at risk	57	53	50	44	17	1

PFS



Number at risk	57	52	46	41	14	1

DoR

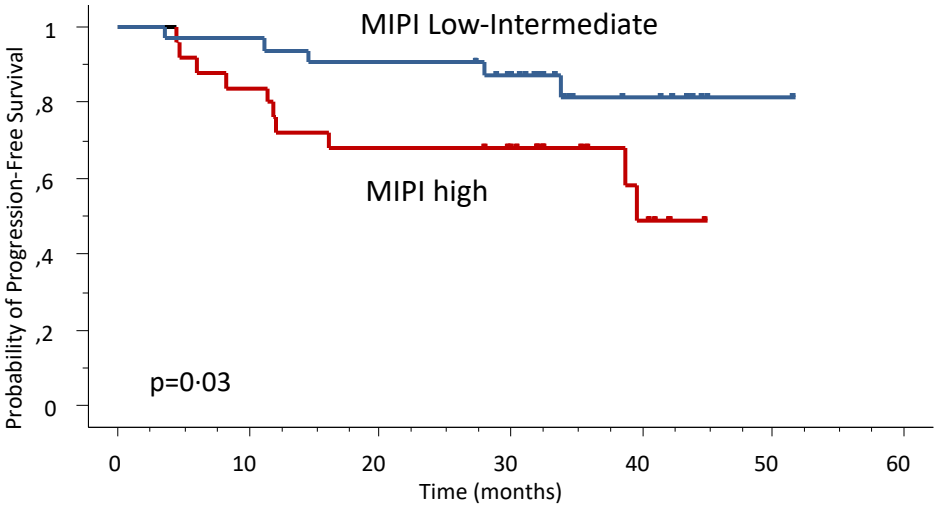


Number at risk	52	52	47	43	14	1

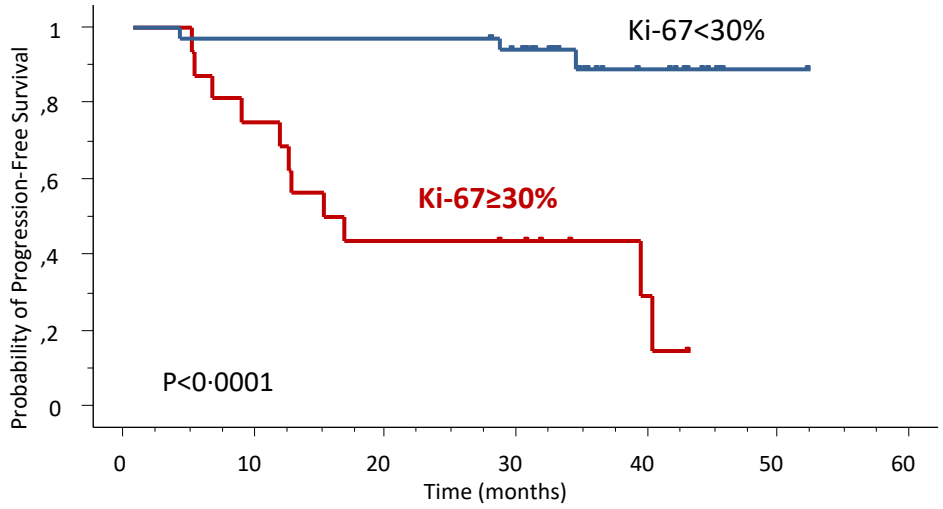
Visco C. et al JCO 2017

Survival curves *Univariate analysis for PFS*

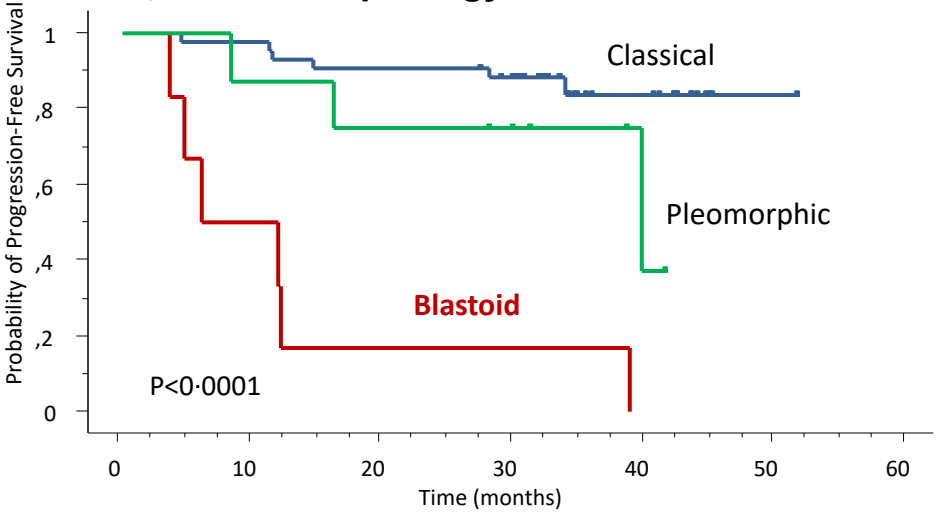
Grouping Variable: **MIPI**

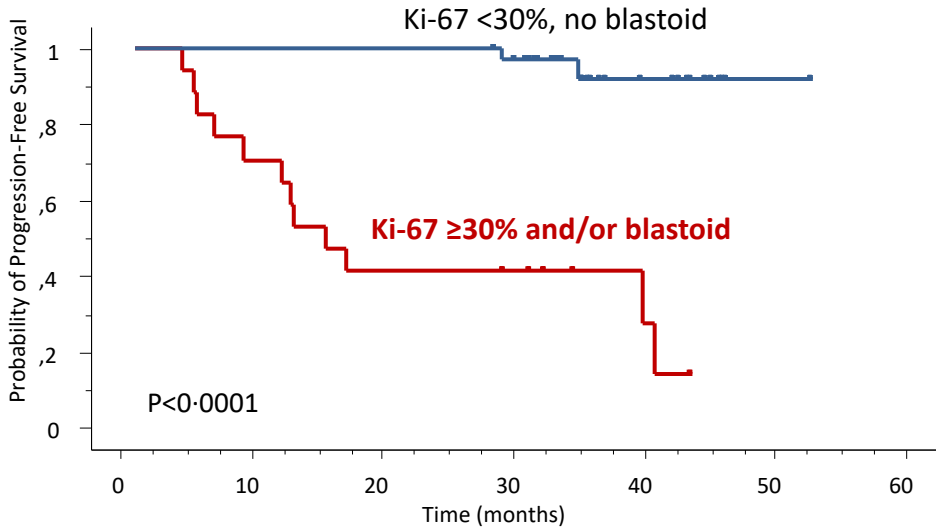


Grouping Variable: **Ki-67**

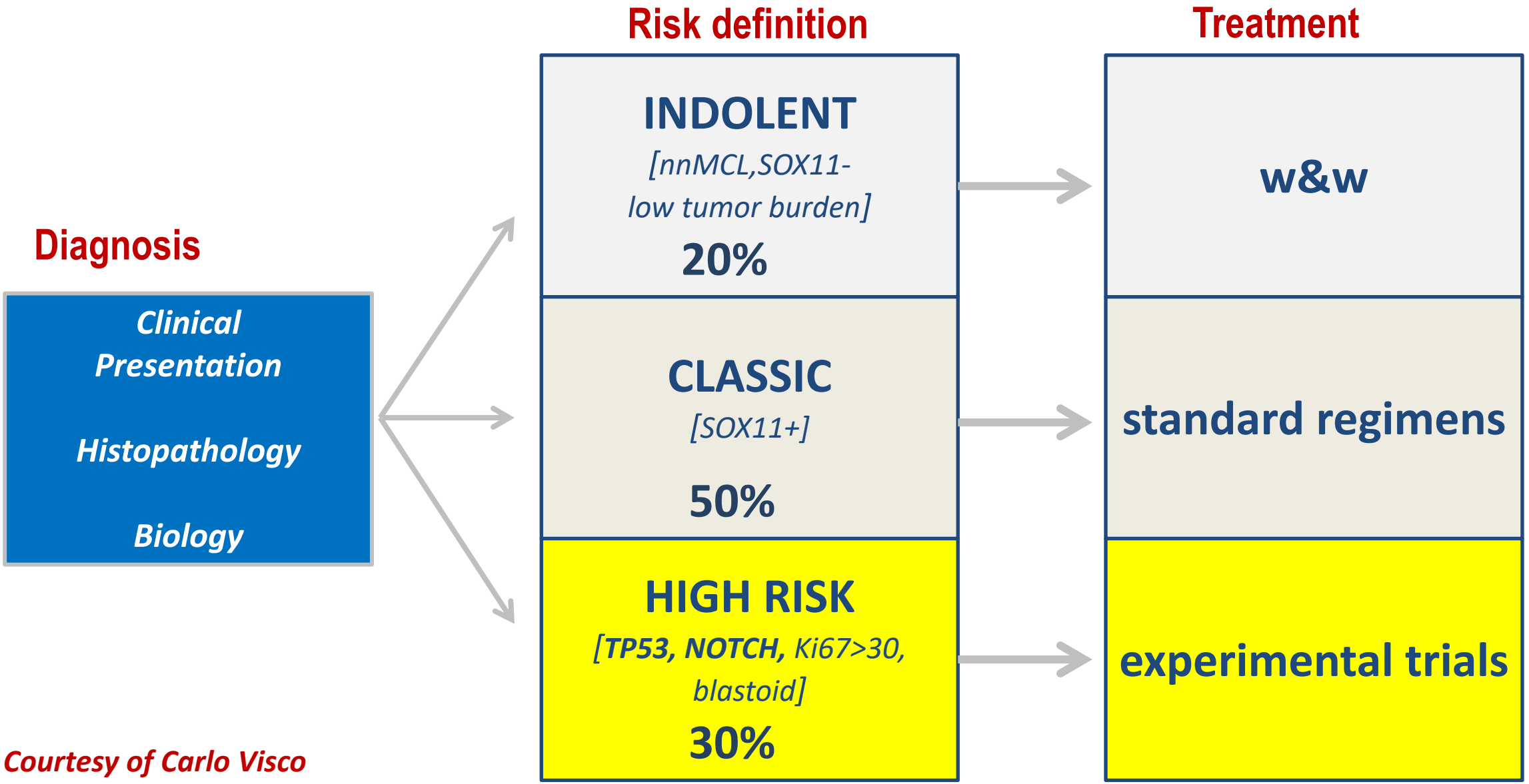


Grouping Variable: **Morphology**





New therapeutic approach in MCL



Courtesy of Carlo Visco

Figure 1: FLOW CHART – TREATMENT SCHEME

FIL V-RBAC

FONDAZIONE ITALIANA LINFOMI

Previously untreated MCL ≥ 65 or 60-65 not eligible to ASCT; fit according to CGA

60%

Classical/Pleomorphic and Ki67<30% [*LR*]

R-BAC500 x 2
Rituximab 375 mg/m2 d1,
Bendamustine 70 mg/m2 d1,2
Cytarabine 500 mg/m2 d1,2,3*; *q28*

PD → Off study

CR or PR or SD* → **R-BAC500 x 4**
Rituximab 375 mg/m2 d1,
Bendamustine 70 mg/m2 d1,2
Cytarabine 500 mg/m2 d1,2,3*; *q28*

Blastoid or Ki67≥30% or P53 mutation [*HR*]

40%

R-BAC500 x 2
Rituximab 375 mg/m2 d1,
Bendamustine 70 mg/m2 d1,2
Cytarabine 500 mg/m2 d1,2,3*; *q28*

CR or PR → **R-BAC500 x 2**
Rituximab 375 mg/m2 d1,
Bendamustine 70 mg/m2 d1,2
Cytarabine 500 mg/m2 d1,2,3*; *q28*

Less than PR → **ABT-199 + R**

Consolidation
(4 cycles, q28)

→ **ABT-199 monotherapy**

Maintenance
(2 years)

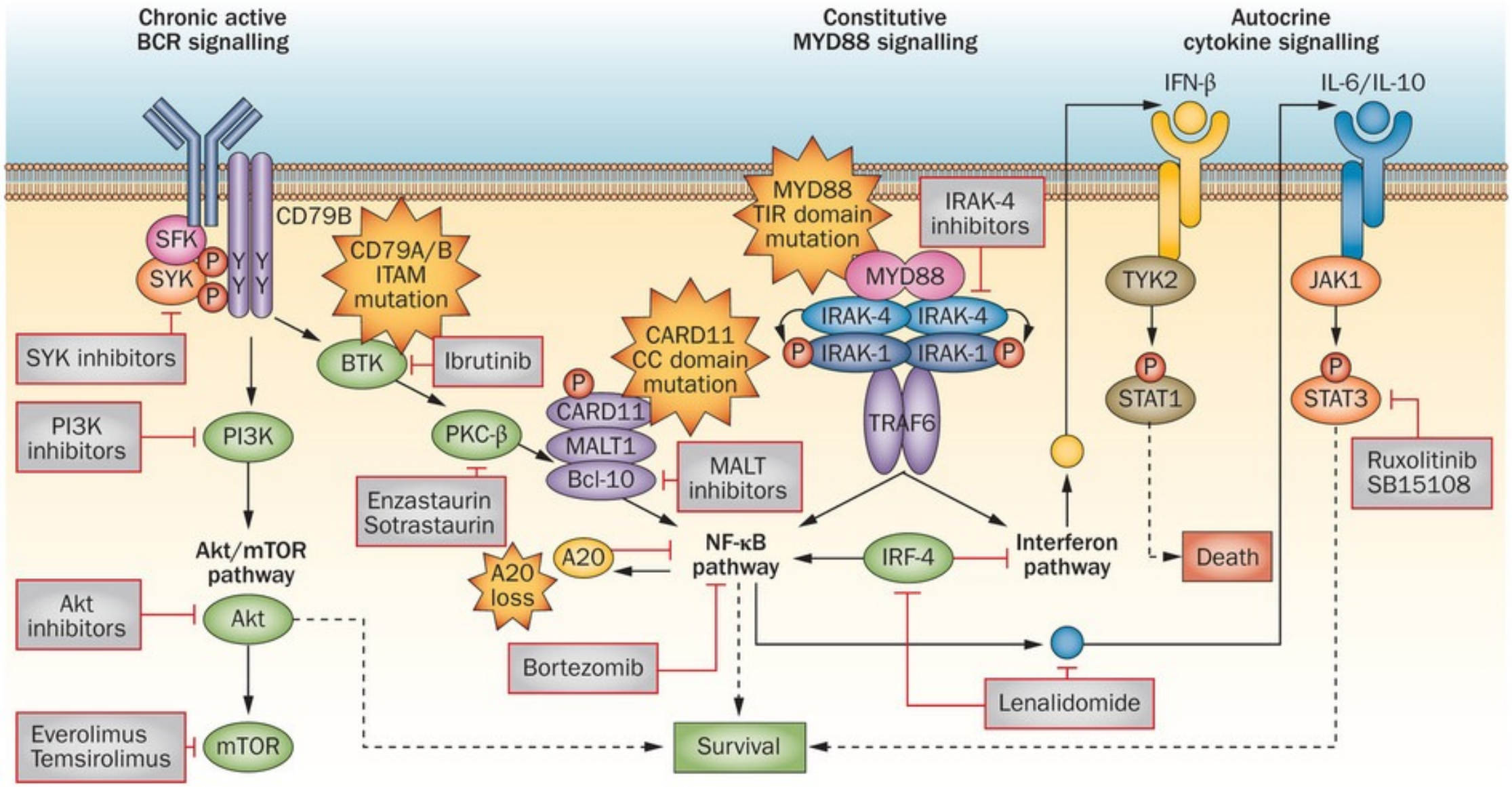
Expected pathology report

PET, CT, MRD
(*screening*)

PET, MRD
(*before consolidation*)

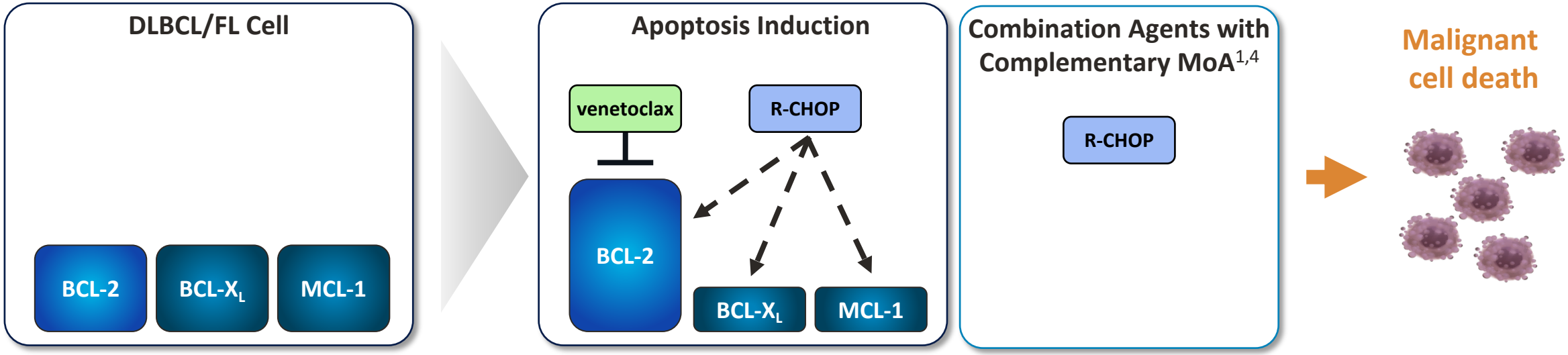
PET, MRD
(*before maintenance*)

Pathways with therapeutic potential in ABC DLBCL



Venetoclax Induces apoptosis in DLBCL and FL cells in combination with other agents

BCL-2 dependency is common in DLBCL and FL;
however, NHL cells can be co-dependent on other BCL-2 family members for survival



R-CHOP indirectly increases sensitivity to BCL-2 inhibition in DLBCL cells

de Jong MR, et al. Int J Mol Sci 2019; 20:6036.

Smith VM, et al. Haematologica 2019

Towards molecular driven therapy: R-CHOP + X novel drugs

New Agent	Mechanism
Lenalidomide	Immunomodulator
Bortezomib	Proteasome inhibitor
Everolimus	mTOR inhibitor
Panobinostat	HDACs inihibitor
Ibrutinib	BTK inhibitor
Tamatinib	Inhibitors of Syk in B-cell signaling pathway
Enzastaurin	PKCβ-selective inhibitors
Venetoclax	Pro-apoptotic anti Bcl-2 family
SELINEXOR	Selective inhibitor of nuclear export (SINE)

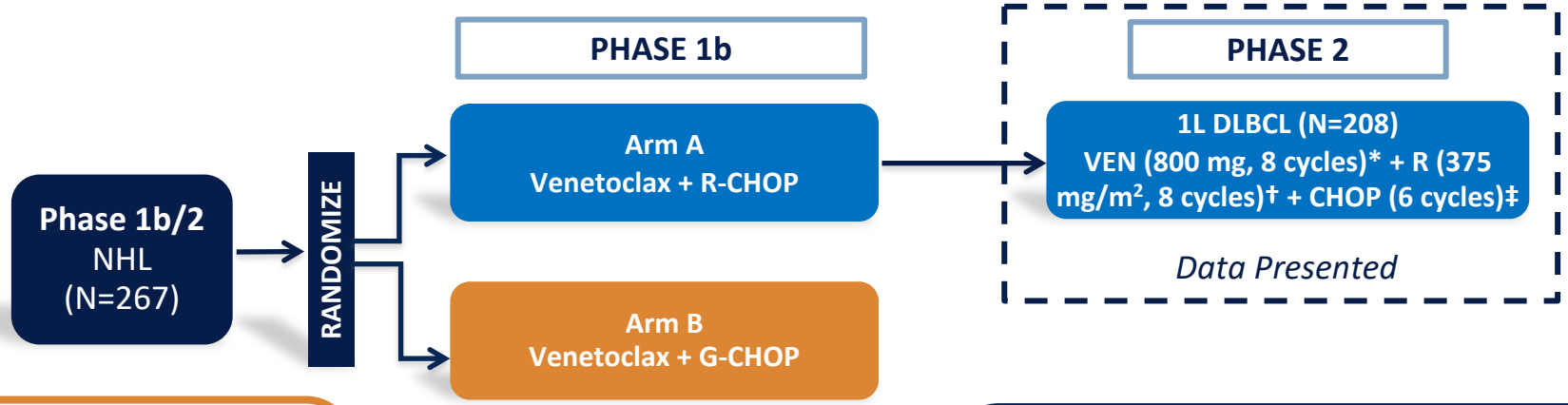
What X?

- **Bortezomib: Bor-RCHOP (Phase 3)**
- **Ibrutinib: IBR-CHOP (Phase 3)**
- **Lenalidomide: R2-CHOP (Phase 3)**
- **Venetoclax: Ven+ R-CHOP (Phase 2)**

CLINICAL TRIALS AND OBSERVATIONS

A phase 2 study of venetoclax plus R-CHOP as first-line treatment for patients with diffuse large B-cell lymphoma

Franck Morschhauser,[1] Pierre Feugier,[2] Ian W. Flinn,[3] Robin Gasiorowski,[4] Richard Greil,[5] Árpád Illés,[6] Nathalie A. Johnson,[7] Jean-François Larouche,[8] Pieternella J. Lugtenburg,[9] Caterina Patti,[10] Gilles A. Salles,[11] Marek Trněný,[12] Sven de Vos,[13] Farheen Mir,[14] Divya Samineni,[15] Su Y. Kim,[16] Yanwen Jiang,[15] Elizabeth Punnoose,[15] Arijit Sinha,[17] Emma Clark,[17] Nathalie Spielewoy,[18] Kathryn Humphrey,[17] Alexandra Bazeos,[17] and Andrew D. Zelenetz[19]



PHASE 2 INCLUSION CRITERIA

- Previously untreated CD20+ DLBCL
- ≥18 years of age
- IPI 2-5
- ECOG PS ≤2
- ≥1 measurable lesion >1.5 cm

PHASE 2 OBJECTIVES

Primary: ***PET-CR (6-8 wks after last R dose, IRC assessed)***

Secondary: ***PFS (INV-assessed), OS, safety***

Biomarker/Exploratory: ***Efficacy in BCL-2 IHC+/- and DH patients, and COO subtypes and clonal sequencing/ctDNA assessment***

Historical control: R-CHOP GOYA IPI 2-5

Baseline patients characteristics

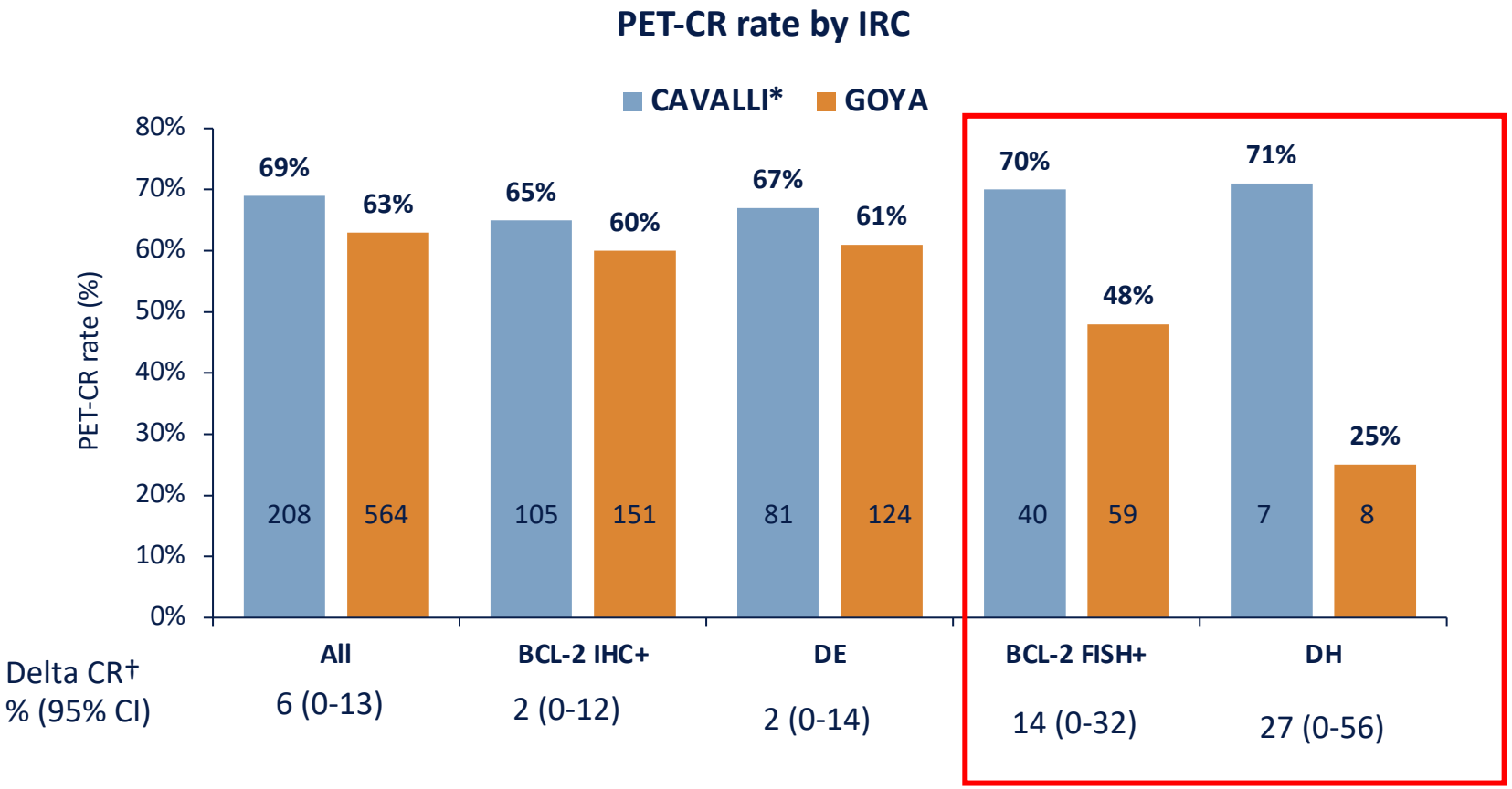
Parameter	CAVALLI phase 2 (N = 206)	GOYA IPI 2 to 5 (N = 564)
Age, median (range), y	65 (18-85)	62 (18-83)
Female	93 (45)	267 (47)
ECOG PS*		
0-1	172 (84)	476 (84)
2	34 (17)	87 (15)
Stage III-IV	177 (86)	478 (85)
IPI		
2-3	155 (75)	455 (81)
4-5	51 (25)	109 (19)
COO	n = 171	n = 373
ABC	48 (28)	104 (28)
GCB	101 (59)	213 (57)
Unclassified	22 (13)	56 (15)
Bcl-2 IHC	n = 179	n = 308
High†	104 (58)	151 (49)
Low	75 (42)	157 (51)
Myc IHC	n = 179	n = 304
Positive	133 (74)	248 (82)
Negative	46 (26)	56 (18)
Double expressor	n = 179	n = 299
Yes	80 (45)	124 (41)
No	99 (55)	175 (59)

Parameter	CAVALLI phase 2 (N = 206)	GOYA IPI 2 to 5 (N = 564)
Bcl-2† and Myc IHC	n = 179	n = 299
Bcl-2 IHC⁺/Myc IHC⁺ (DHL, DEL)	80 (45)	124 (41)
Bcl-2 IHC⁺/Myc IHC⁻	24 (13)	24 (8)
Bcl-2 IHC⁻/Myc IHC⁺	53 (30)	119 (40)
***BCL-2* FISH**	n = 151	n = 265
Positive	40 (26)	59 (22)
Negative	89 (59)	145 (55)
Undetermined	22 (15)	61 (23)
***MYC* FISH**	n = 142	n = 232
Positive	12 (8)	20 (9)
Negative	110 (78)	178 (77)
Undetermined	20 (14)	34 (15)
***BCL-2* & *MYC* FISH**	n = 139	n = 230
BCL-2 FISH⁺/*MYC* FISH⁺ (DHL)	7 (5)	8 (3)

Morschhauser et al. Blood vol.137 Feb 2021

*Si specifica che si tratta di *investigational drug*, e si fa riferimento ad indicazioni terapeutiche attualmente non approvate da EMA

Primary end point: PET-CR Rate by IRC



PET-CR rates were similar in GOYA for BCL-2 IHC+ and DE patients, but higher in CAVALLI for patients with BCL-2 FISH+ and DH status.

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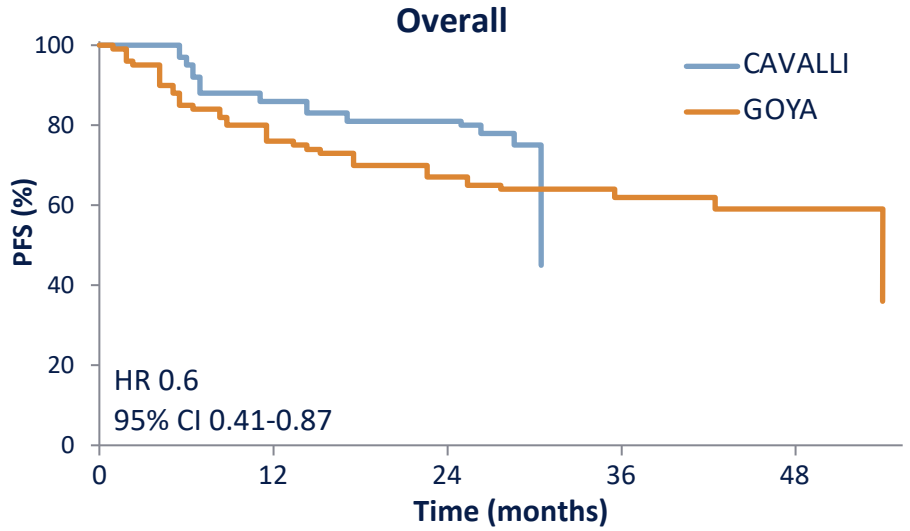
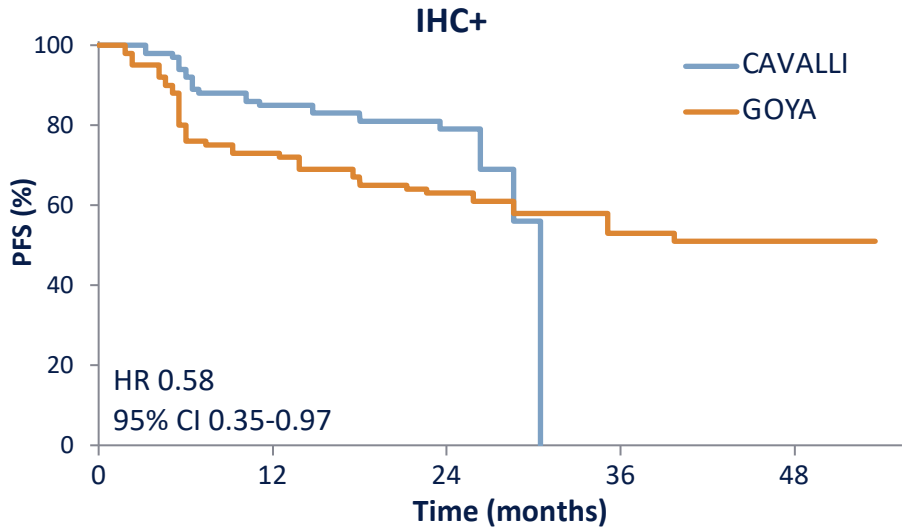
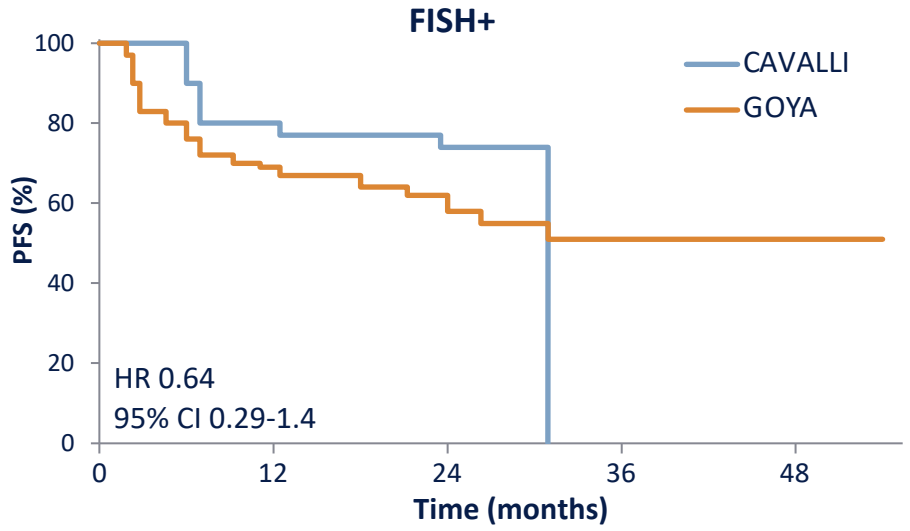
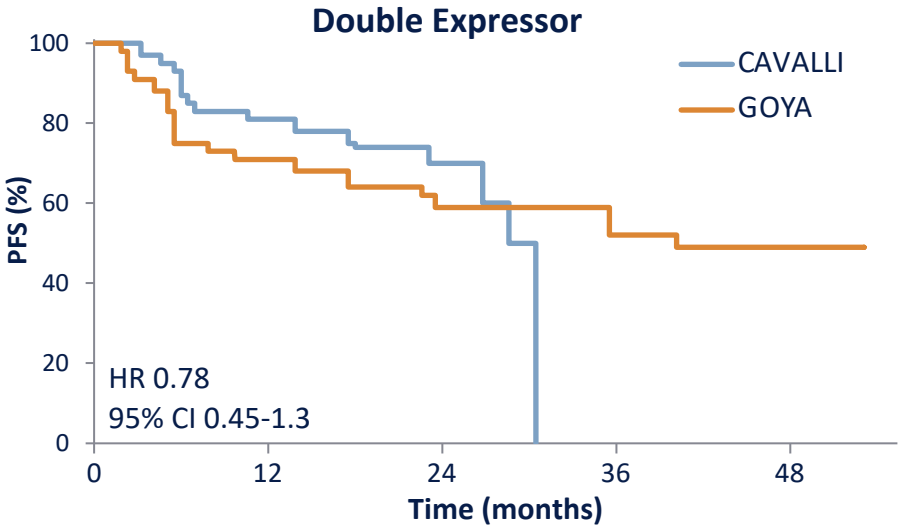
PFS in All Patients and Biomarker Subgroups









Median follow-up: CAVALLI: 22.3 mo (data cutoff: Jul 13, 2018); GOYA: 29.6 mo (data cutoff: Apr 29, 2016)

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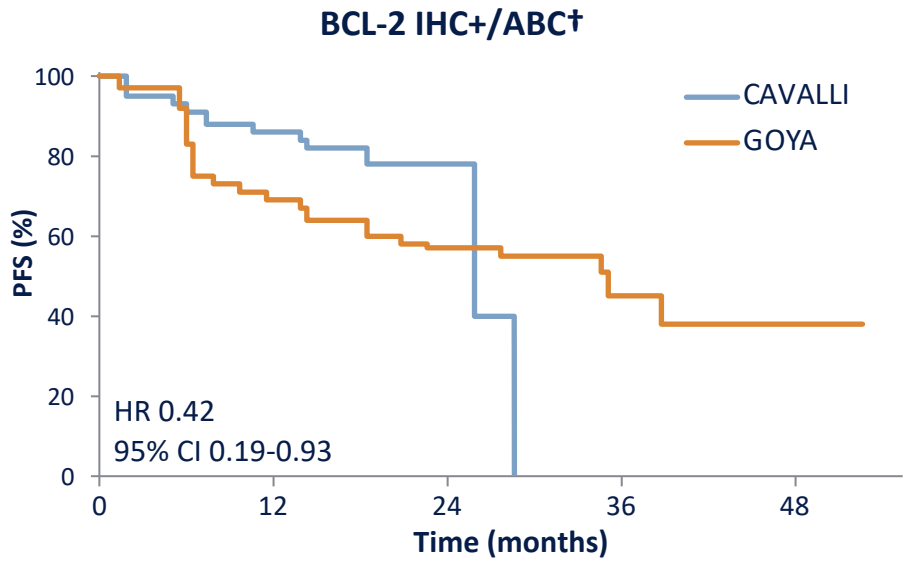
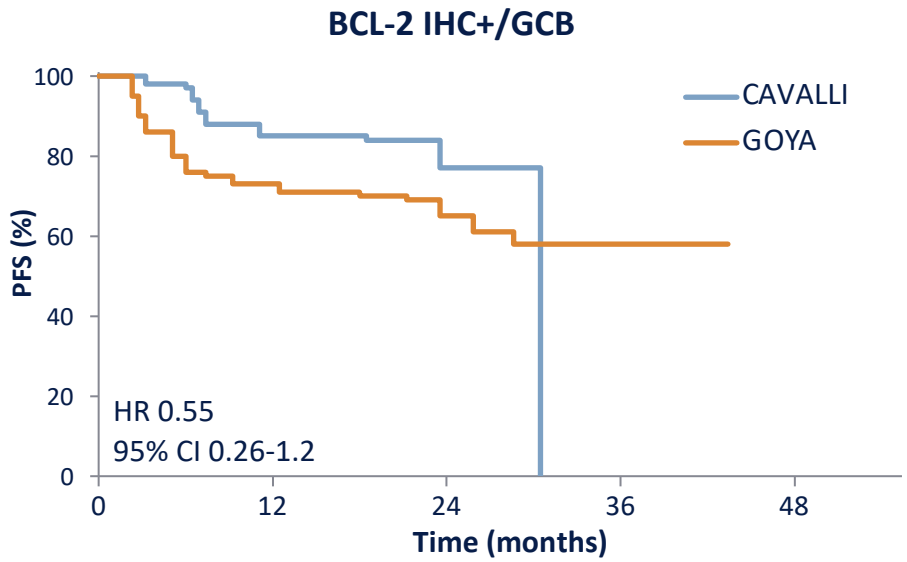
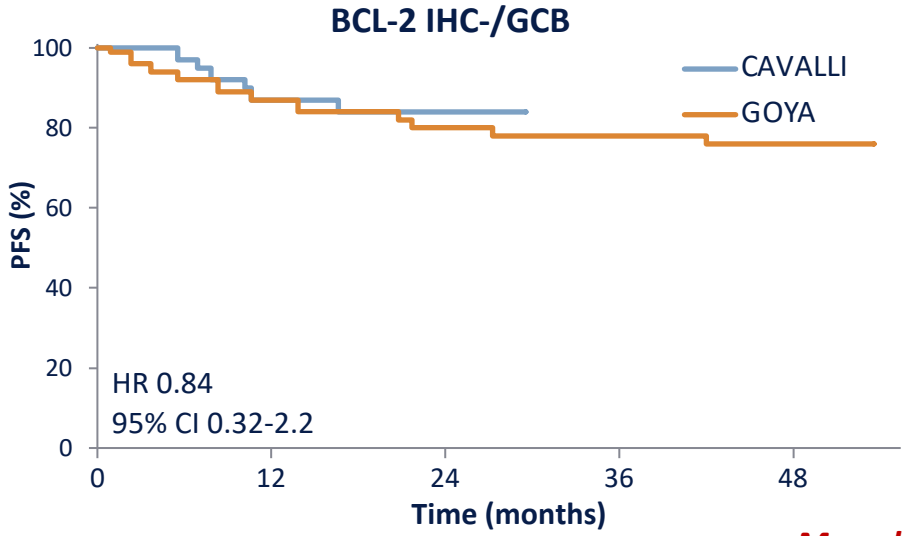
PFS in BCL-2+ Patients in COO Subgroups







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Safety Summary

AEs	CAVALLI (N=208)		GOYA IPI 2-5 (N=564)	
	%	N	%	N
Any AE	99	206	94	528
AE with fatal outcome (Grade 5)	2	4*	5	30
Serious AE	56	116	41	230
Grade 3-4 AE	86	179	66	373
AE leading to withdrawal from any treatment	24	50	10	56
AE leading to withdrawal from VEN treatment	20	41	NA	NA

Grade 3-4 AEs	CAVALLI (N=208)		GOYA IPI 2-5 (N=564)	
	%	N	%	N
Neutropenia	68	141	39	219
Febrile neutropenia	31	64	16	92
Thrombocytopenia	22	45	2	9
Anemia	24	49	9	50
Infections*	22	46	16	90
Pneumonia	4	9	5	28
Sepsis	2	5	1	6
Fatigue	6	12	3	18
Diarrhea	4	9	2	9
Nausea/vomiting	6	12	1	4

*4 fatal AEs reported in CAVALLI (neutropenia, sudden cardiac death, sepsis, and MDS). 3 during follow-up (>6 months after the last dose of VEN) and 1 (C1) due to sepsis with multiple medical issues

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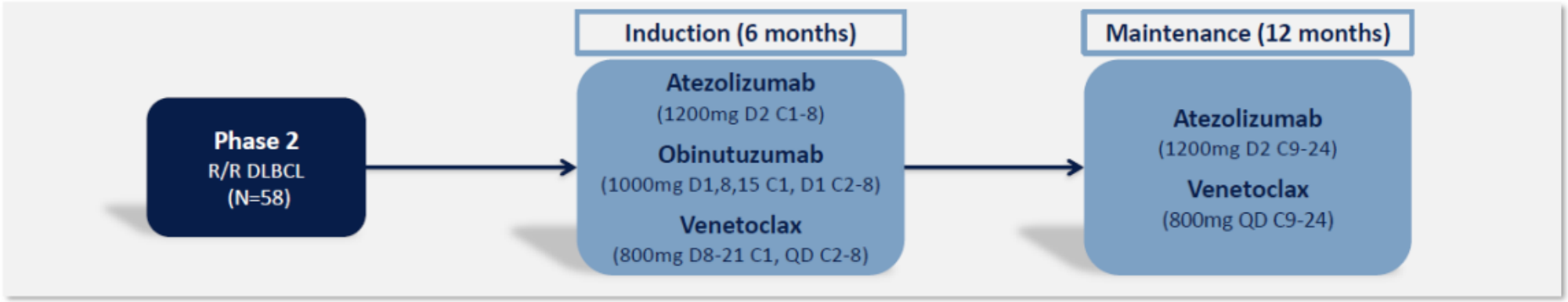
Cavalli study: conclusions

- Higher rates of neutropenia (68% vs 39%), febrile neutropenia (31% vs 16%), thrombocytopenia (22% vs 2%), anemia (24% vs 9%) and infections (22% vs 16%) with the addition of **VEN to R-CHOP**, but no increase in the risk of death
- **VEN+R-CHOP** despite higher AE rates, dose intensity of chemotherapy was maintained at similar levels to historical comparator
- **VEN+R-CHOP** resulted in a PFS benefit in 1L DLBCL BCL-2+ populations, including in ABC and GCB COO subtypes, when compared with historical data from GOYA

GATA: Phase 2 study in R/R DLBCL



INCLUSION CRITERIA

- Adults ≥18 years old with R/R DLBCL after ≥ 1 rituximab and anthracycline containing regimen
- ECOG performance stats 0-2
- ≥1 node or tumor lesion >1.5 cm

EXCLUSION CRITERIA

- CNS or meningeal involvement
- CD20- status at last biopsy
- Prior PML, documented HIV infection, or active hepatitis B
- Active immune-related disease criteria or known active infection

OBJECTIVES

Primary: ***OMRR at EOI***

Secondary: ***PFS, OS, DOR, OMRR, best response***

GATA: Patients' characteristics & Safety

Characteristic, %	N=58
Median follow-up, months (range)	9 (6.9-11.8)
Median age, years (range)	70 (39-85)
Male	53.4%
Ann Arbor Stage IV	84.5%
aaIPI (≥2)	63.2%
≥2 prior lines of therapy	83.6%
Refractory to last therapeutic line	63.6%
Bulky (≥10 cm)	15.5%
ECOG 2	19.0%
DH/TH	6.9%
Autologous transplant	4.6%

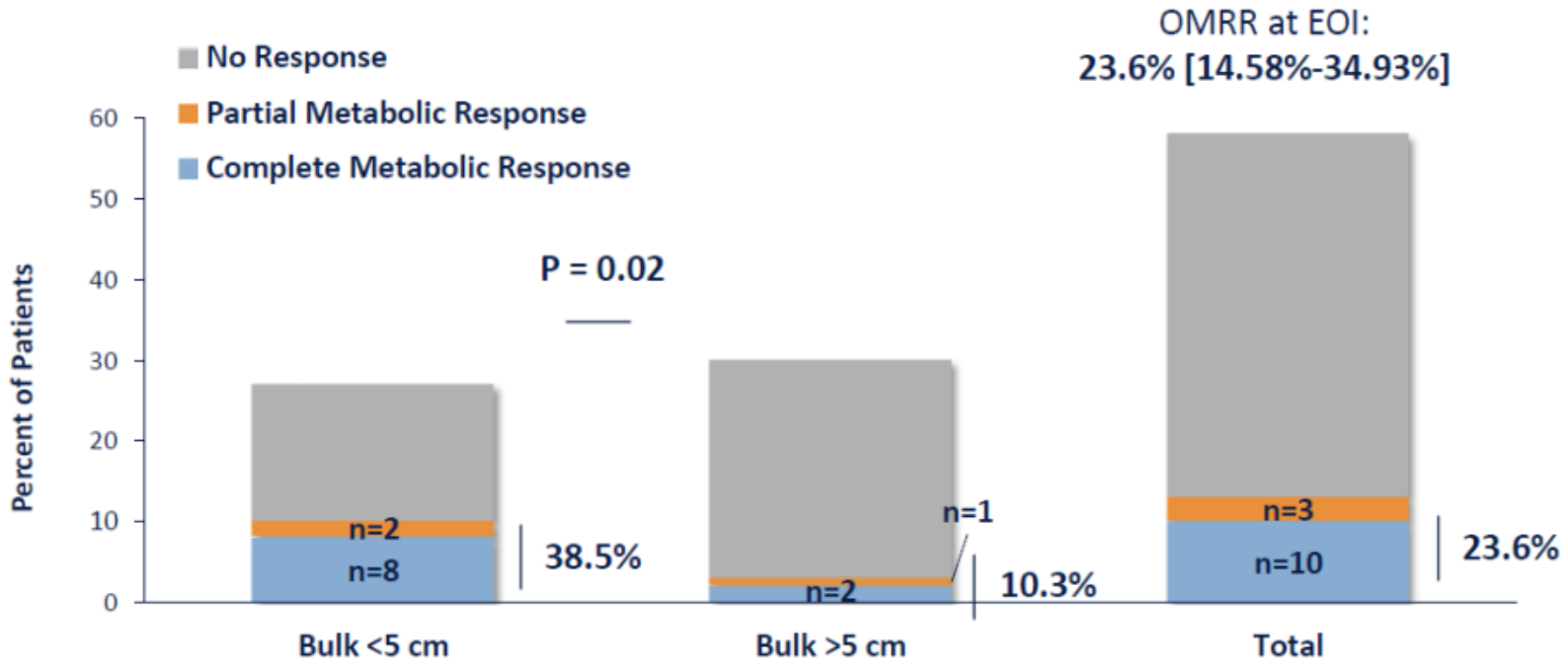
Safety	N=58
Grade 3/4 AEs	48 (84.2%)
Neutropenia	33.3%
Lymphopenia	35.1%
Thrombocytopenia	17.5%
Anemia	10.5%

- **AESI:** A grade 3 autoimmune colitis and a grade 1 hypothyroidism occurred during induction
- 6 (10.5%) had an AE that led to discontinuation of any drug
- No grade 5 AEs were observed

Si specifica che si fa riferimento ad indicazioni terapeutiche ancora in studio e non approvate da EMA

GATA Primary Endpoint: Response

- Median of 4 cycles (1-8) has been administered, with a median follow-up of 9 months (6.9-11.8)
- All 3 drugs were stopped in 78% of patients; mostly for progressive disease
- No difference was observed according to COO:
  - GC → OMRR of 20.8%
  - Non-GC → OMRR of 25.0%



Si specifica che si fa riferimento ad indicazioni terapeutiche ancora in studio e non approvate da EMA

VICER – Phase 1 Study in R/R DLBCL: Study Design and Endpoints

INCLUSION CRITERIA

- R/R DLBCL after rituximab and anthracycline-containing CIT regimen
- ≤2 prior systemic therapies for lymphoma
- ECOG ≤2
- Adequate organ and marrow function

EXCLUSION CRITERIA

- Active TLS
- CNS lymphoma

OBJECTIVES

Primary: **OOMR**

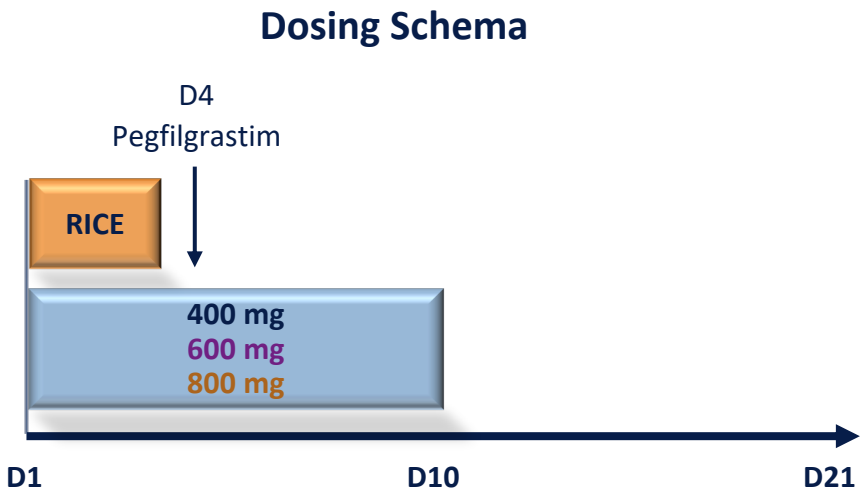
Secondary: ***ORR, proportion of patients proceeding to ASCT, PFS, OS, number of PB stem cells collected, median number of CD34+ cells***

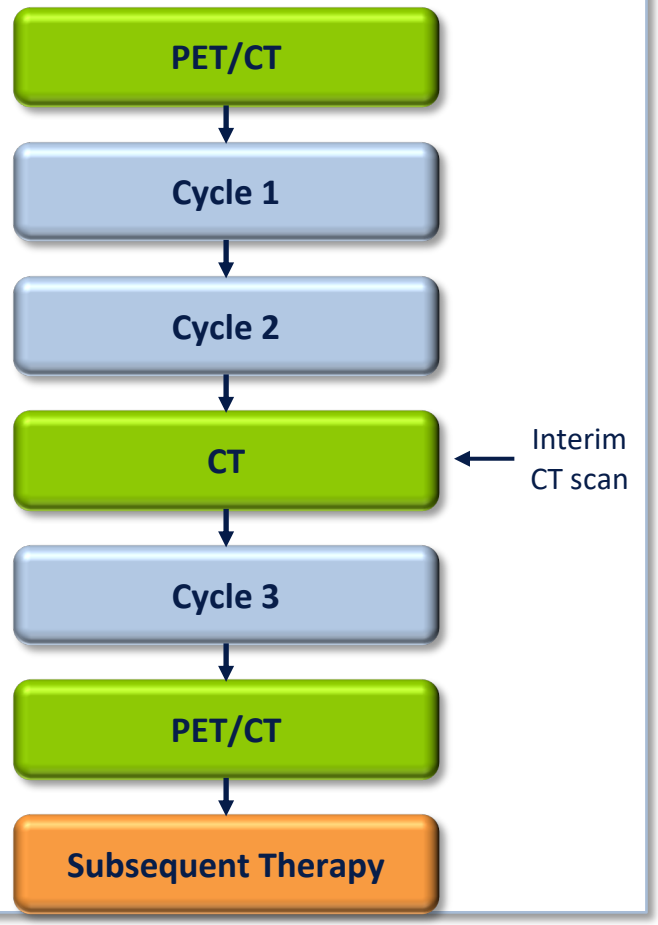
R.

ClinicalTrials.gov. NCT03064867. https://www.clinicaltrials.gov/ct2/show/NCT03064867. Accessed June 2019.

. Caimi PF, et al. Poster #277. 15th ICML; June 18-22,2019; Lugano, Switzerland.

VICER – Dosing Schema





- There are 3 treatment cycles, each lasting 21 days
- RICE is administered in standard doses on D1-3
- Venetoclax is administered D1-10
  - There are 3 dose levels: 400mg, 600mg, and 800mg oral daily
- Allopurinol for TLS prevention D1-10 of cycle 1
- Antimicrobial prophylaxis not mandated but ciprofloxacin was given in 11/18 patients

Caimi P, et al. Oral #397. 60th ASH Annual Meeting; December 1-4, 2018; San Diego, CA.

VICER – Baseline Characteristics

Patient Characteristic	Total, n = 18* (%)
Age, years (median, range)	55.5 (27-78)
Gender	
Female	4 (22)
Male	14 (78)
Disease refractory to prior chemotherapy	11 (61)
Time (months) from diagnosis to relapse (median, range)[2]	12 (3-193)
Bulky disease at enrollment	6 (33)
Involvement of >1 extranodal site	2 (11)
Secondary IPI	
Low (0-1)	12 (67)
High (≥2)	6 (33)
Cell of origin	
GCB	10 (56)
non-GCB	8 (44)
Molecular abnormalities	
Double expressor	8 (44)
Double hit	4 (22)

Caimi P, et al. Oral #397. 60th ASH Annual Meeting; December 1-4, 2018; San Diego, CA.

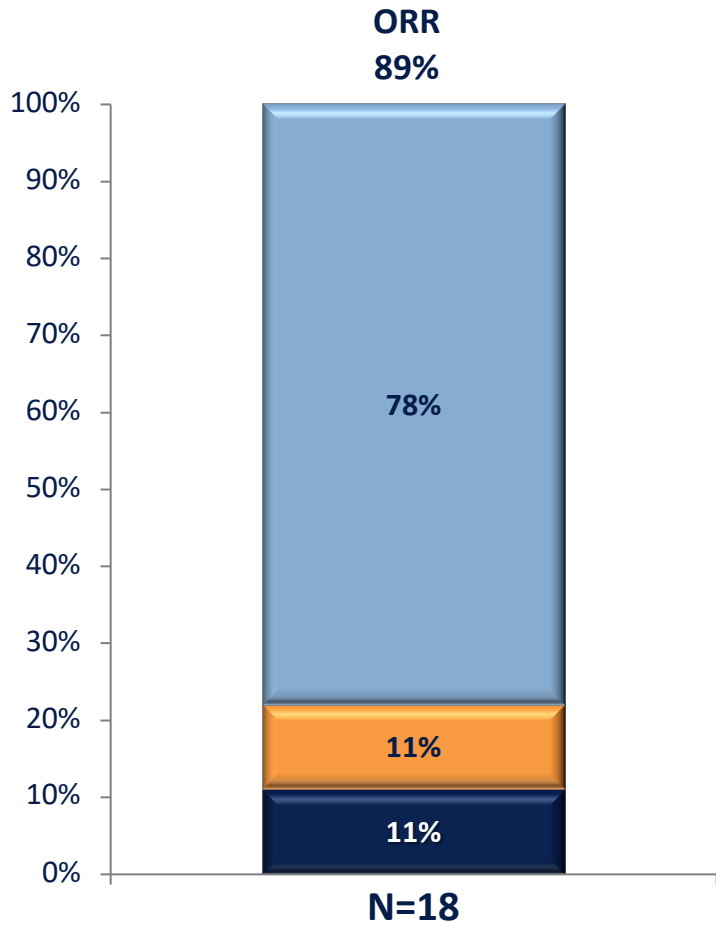
VICER – Safety

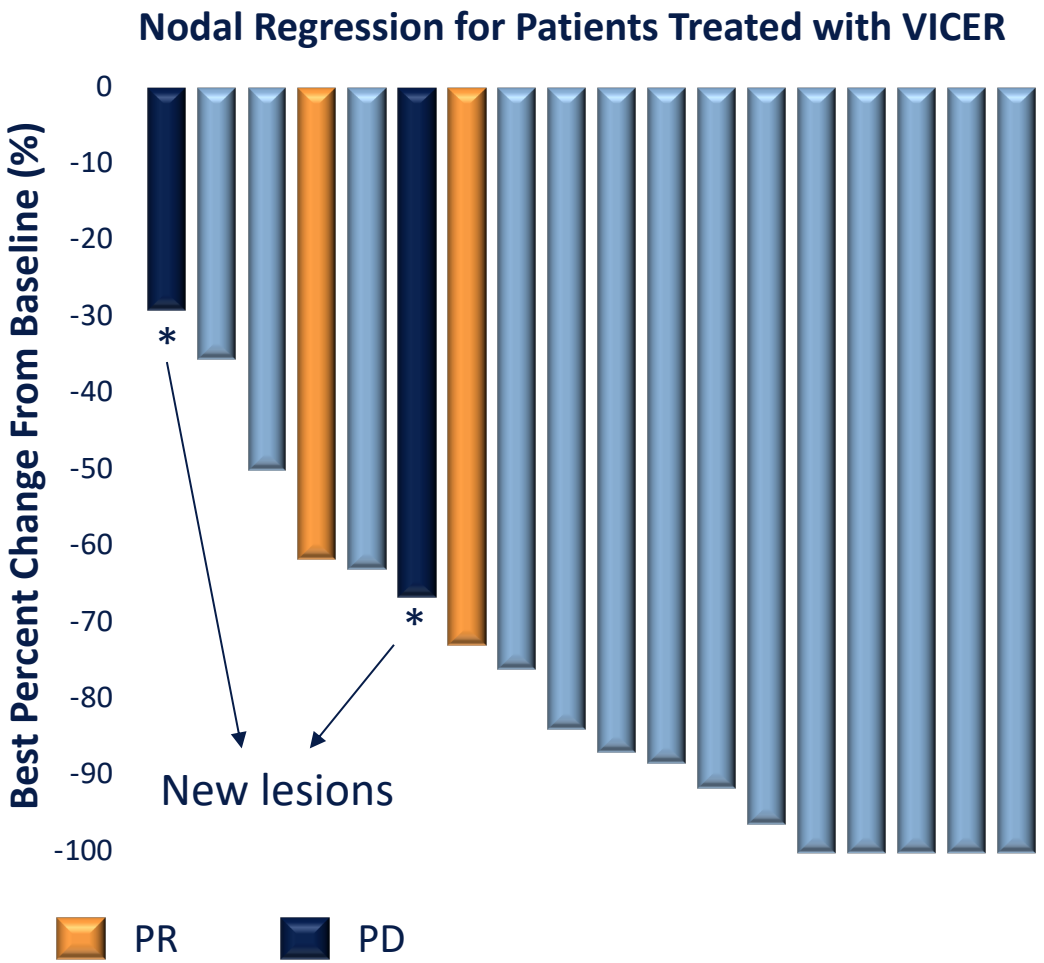
Any grade TEAEs (≥20% of patients)	Total, n = 18 (%)
Thrombocytopenia	17 (94.4)
Neutropenia	15 (83.3)
Anemia	15 (83.3)
Lymphocyte count decreased	13 (72.2)
Fatigue	8 (44.4)
Nausea	8 (44.4)
Diarrhea	7 (38.9)
Sensory neuropathy	6 (33.3)
Anorexia	6 (33.3)
Febrile neutropenia	5 (27.8)
Infection with neutropenia	5 (27.8)
Increased transaminase	5 (27.8)
Constipation	4 (22.2)
Abdominal pain	4 (22.2)

Grade ≥3 TEAEs (≥10% of patients)	Total, n = 18 (%)
Neutropenia*	14 (77.8)
Lymphopenia	12 (66.7)
Thrombocytopenia	11 (61.1)
Anemia	6 (33.3)
Febrile neutropenia*	5 (27.8)
Infection with neutropenia*	5 (27.8)
Elevated transaminase level*	2 (11.1)
TLS*	1 (5.5)
Encephalopathy*†	1 (5.5)

- 3 subjects had ≥1 cycle delayed ≥7 days secondary to hematologic toxicity
  - Total of 5 cycles delayed
- No RICE dose reductions were required,
  1 venetoclax dose reduction 800 → 600mg at C3, DL3
- No treatment-related deaths
- 2 subjects died as a result of PD

VICER – Response





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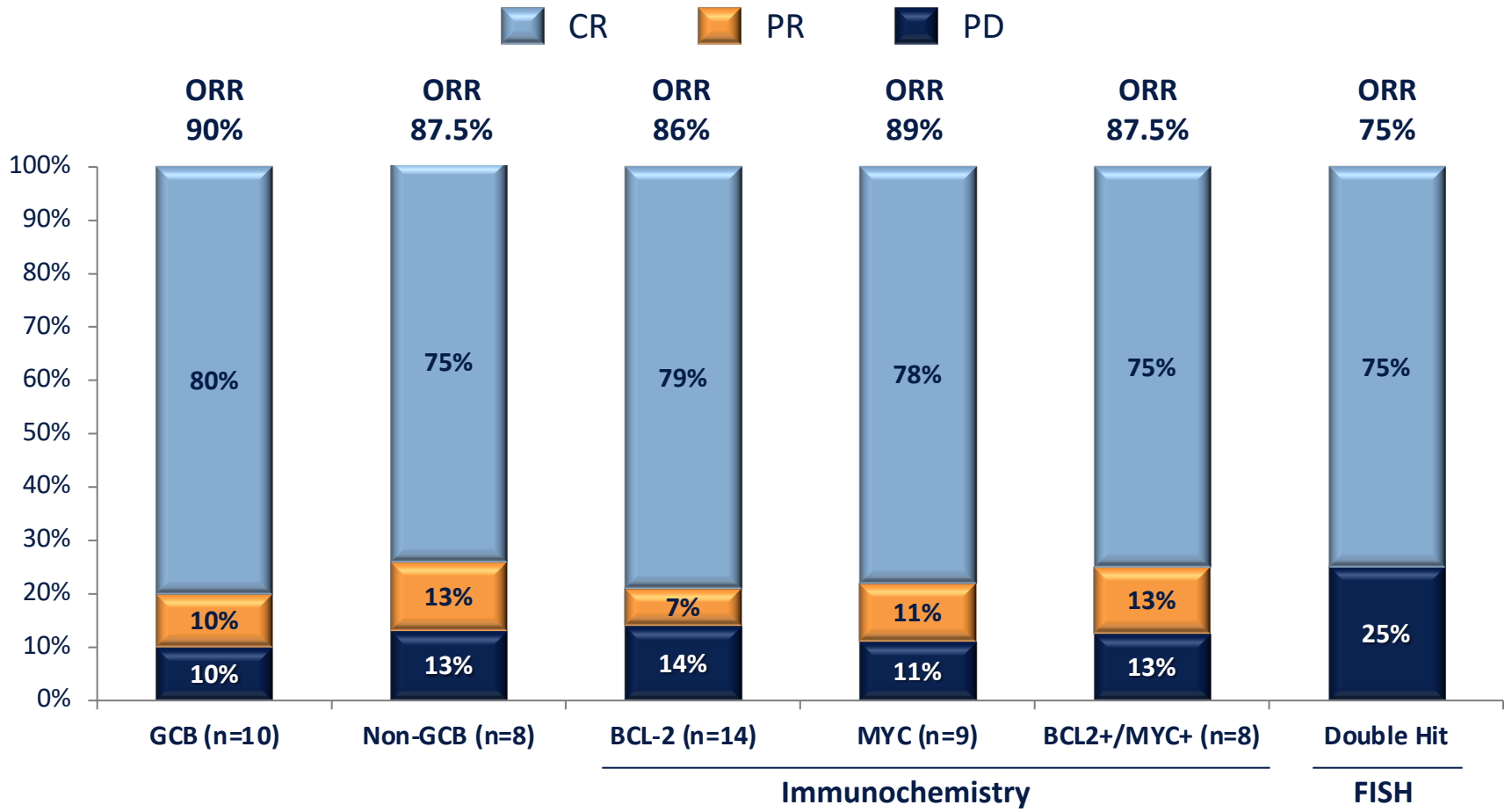
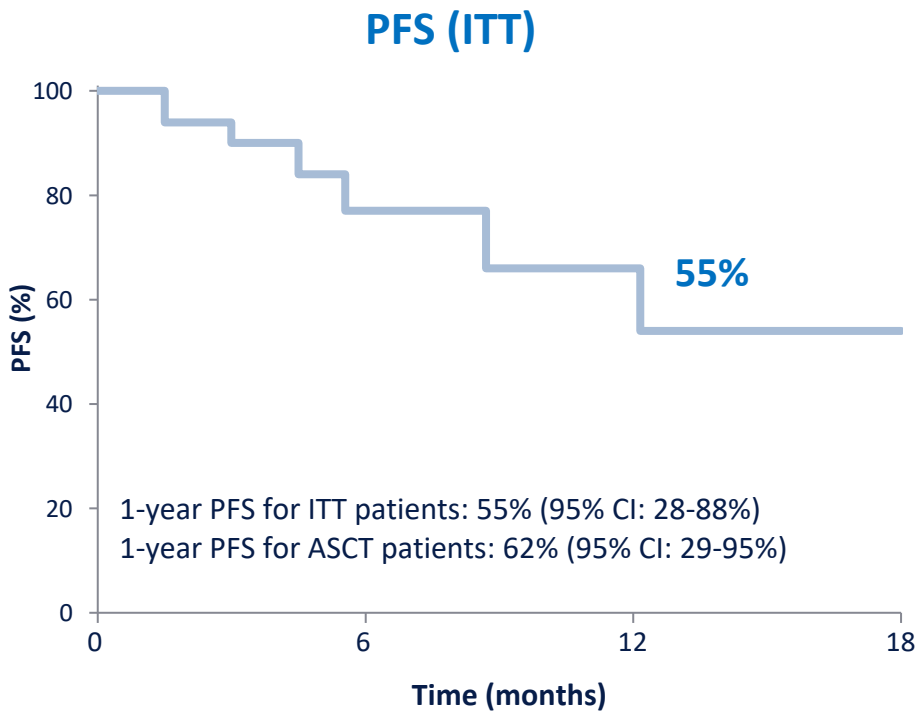
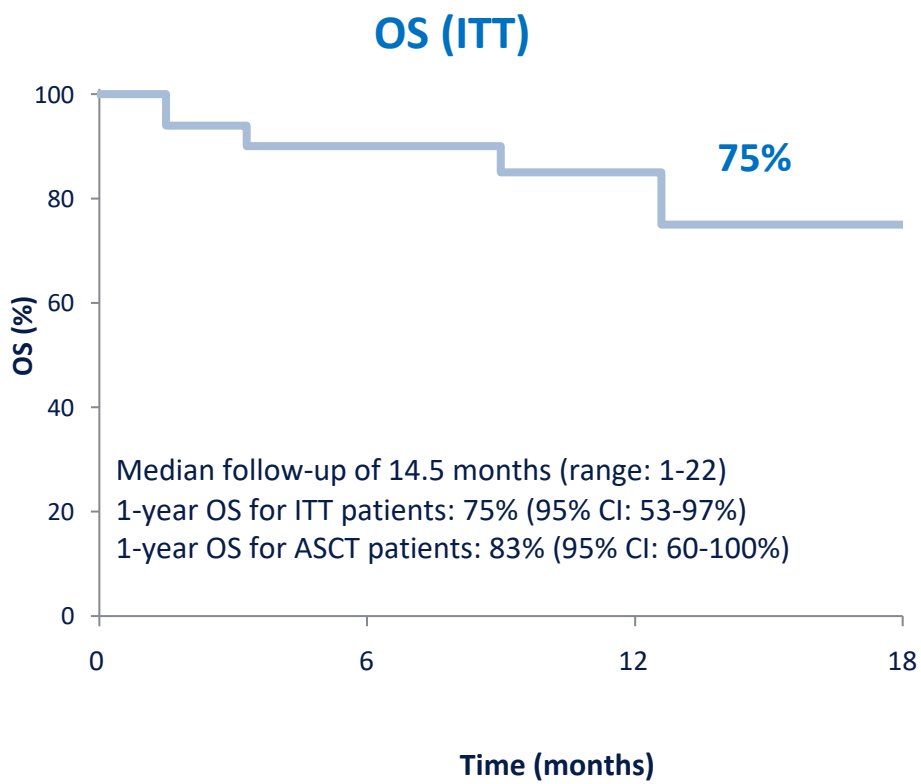
VICER – Response by subgroups



Caimi P, et al. Oral #397. 60th ASH Annual Meeting; December 1-4, 2018; San Diego, CA.

VICER – PFS & Overall Survival





- All responding patients (n=16) proceeded to stem cell mobilization and collection; Two patients failed to achieved CD34+ cell dose targets
- Median CD34+ cell dose collected: 3.71 x 10^6 cell/kg
- 14 patients (78%) underwent ASCT – Median time from day 1 to ASCT = 97 days (76-195)
- All patients had hematopoietic engraftment post ASCT

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All FIL Centers

Grazie per l'attenzione .....


20 ANNI DI EMATOLOGIA A TREVISO
TREVISO | 18-20 NOVEMBRE 2021