Venclexta – New data in CLL, NHL, AML, MM

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Introduction: Venclexta

Venclexta in CLL

Venclexta in AML

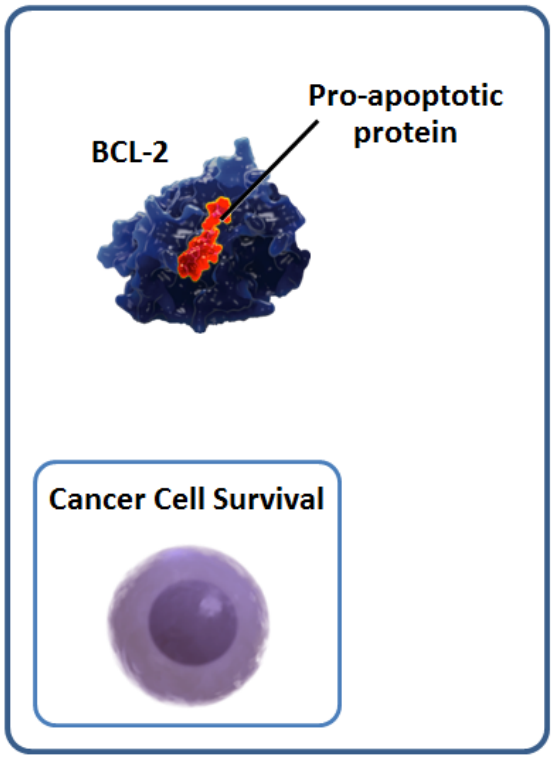
Venclexta in NHL

Venclexta in MM

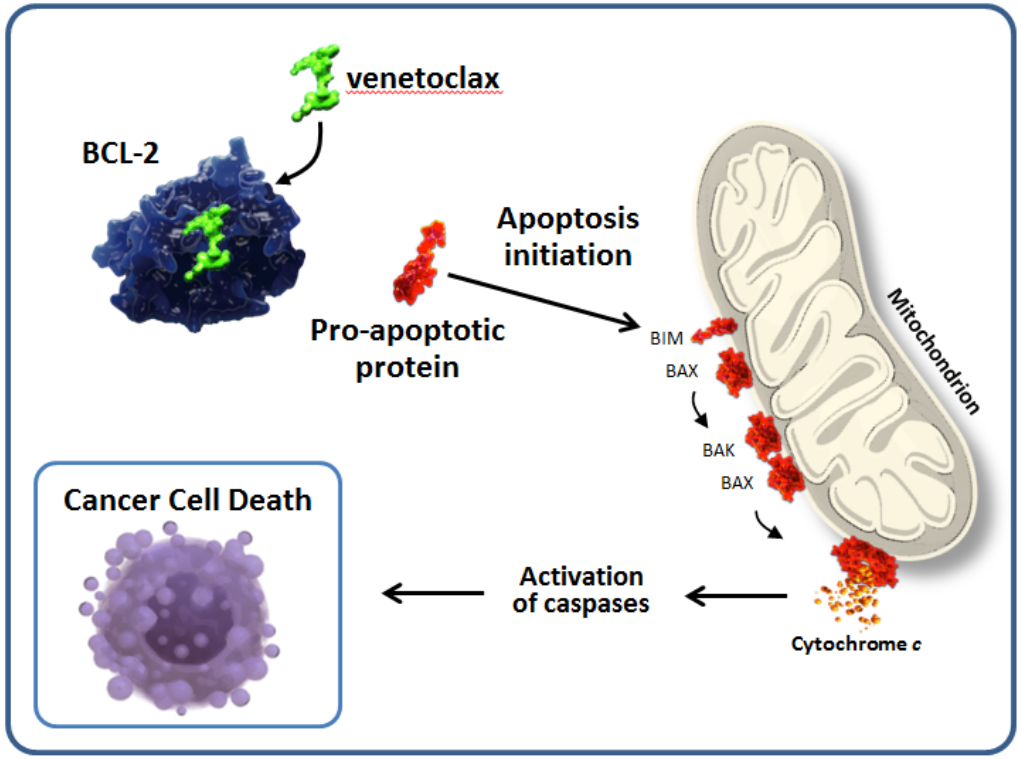
Venclexta development program

MoA: Venetoclax* (BCL-2 inhibitor)

Restoration of apoptosis through BCL-2 inhibition



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.



Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).

MOA=mechanism of action; * venetoclax in collaboration with AbbVie

Introduction: Venclexta

Venclexta in CLL (CLL14)

Venclexta in AML

Venclexta in NHL

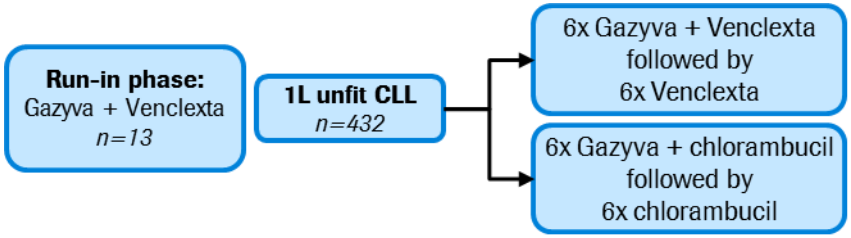
Venclexta in MM

Venclexta development program

Venclexta* + Gazyva in 1L unfit CLL

First efficacy data from Ph3 run-in

CLL14 study design



	Gazyva + Venclexta
Response rates (n=12)	
ORR	12 (100)
CR	7 (58)
PR	5 (42)
MRD in peripheral blood (n=11)	
Negative ($<10^{-4}$)	10 (91)
Intermediate ($\geq 10^{-4}$ and $<10^{-2}$)	1 (9)

Run-in of Phase III (CLL14):

- Gazyva + Venclexta tolerable in elderly patients with CLL and clinically meaningful comorbidities
- The treatment induced substantial responses with a high number of minimal residual disease (MRD) negative responses 3 months after end of therapy (at month 15)
- Ph3 was fully recruited as of August 2016

Fischer K. *et al*., ASH 2016; *Venclexta (venetoclax) in collaboration with AbbVie; CLL=chronic lymphoid leukemia; MRD=minimal residual disease

Introduction: Venclexta

Venclexta in CLL

Venclexta in AML

Venclexta in NHL

Venclexta in MM

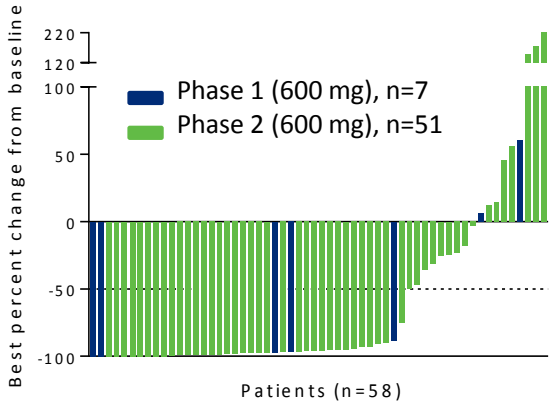
Venclexta development program

Venclexta* + LDAC in 1L unfit AML

61% ORR achieved

Response, n (%)	Venclexta + LDAC All patients (n=61)
ORR	**37 (61)**
CR/CRi	**33 (54)**
CR	13 (21)
CRi	20 (33)
PR	4 (7)
PD	23 (38)

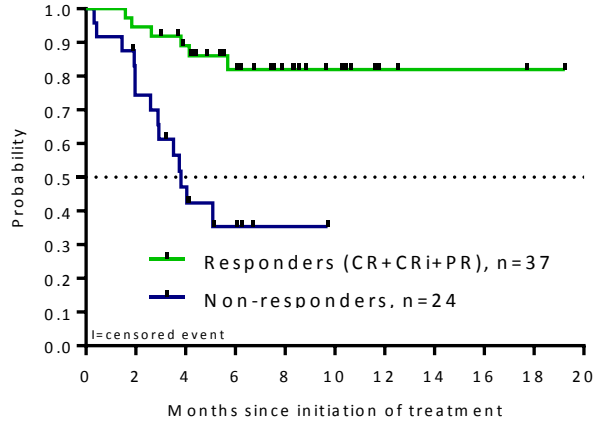
Bone marrow blast count



Phase II results:

- ORR of 61% in all patients
- 71% of patients achieved a ≥50% decrease in BM and peripheral blast counts
- Combination demonstrates significant and durable activity in patients aged ≥65y with treatment-naïve AML ineligible to receive intensive chemotherapy

Overall survival



Wei AH. *et al*., ASH 2016; *Venclexta in collaboration with AbbVie; AML=acute myeloid leukemia; LDAC=low dose cytarabine; ORR=overall response rate; CR=complete response; CRi=complete remission with incomplete marrow recovery; PR=partial response; PD=progressive disease; BM=bone marrow

Introduction: Venclexta

Venclexta in CLL

Venclexta in AML

Venclexta in NHL (CAVALLI, CONTRALTO)

Venclexta in MM

Venclexta development program

Venclexta* in NHL

Early CD20+chemo combination data

Response by PET-CT, n (%)	NHL	
	Arm A Ven+R-CHOP (n=24)	Arm B Ven+G-CHOP (n=25)
ORR	**21 (88)**	**21 (66)**
CR	19 (79)	18 (56)
PR	2 (8)	3 (9)
PD	**2 (8)**	**0**
Missing	**1 (4)**	**4 (13)**

Zelenetz AD. *et al*., ASH 2016

Response rates by PET-CT by investigator at 6-month (primary), n (%)	Arm A VEN + R (N=53)	Arm B VEN + BR (N=51)	Arm C BR (N=51)
ORR	**16 (30)**	**38 (75)**	**39 (77)**
CR	7 (13)	32 (63)	31 (61)
PR	9 (17)	6 (12)	8 (16)
SD	**2 (4)**	**0**	**0**
PD	**24 (45)**	**2 (4)**	**6 (12)**
Data not available	**11 (21)**	**11 (22)**	**6 (12)**

Zinzani PL. *et al*., ASH 2016

Phase I/II interim results (CAVALLI):

- ORR is promising in NHL population
- High CR rate (7/8; 87.5%) observed in the DLBCL population with co-expression of BCL-2 and Myc, who have a poor prognosis.
- Ph2 completed enrollment of 210 patients

Phase II interim results (CONTRALTO):

- Longer follow-up is required to establish the role of Ven + BR in R/R FL
- Higher BCL-2 expression may be associated with higher CR rates with Ven + BR

*Venclexta in collaboration with AbbVie; NHL=non-hodgkin`s lymphoma; R/R FL=relapsed/refractory follicular lymphoma; ; R=Rituxan; B=bendamustine; ORR=overall response rate; PET-CT=positron emission tomography-computed tomography; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; PFS=progression free survival

Introduction: Venclexta

Venclexta in CLL

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Venclexta development program

Venclexta* in R/R MM
Combination efficacy data

	Venclexta + dexamethasone + bortezomib		
	All patients (n=66)	non-refractory to bortezomib (n=39)	refractory to bortezomib (n=26)
ORR, n (%)	**44 (67)**	**35 (90)**	**8 (31)**
sCR	3 (5)	3 (8)	0
CR	10 (15)	8 (20)	1 (4)
VGPR	15 (23)	14 (36)	1 (4)
PR	16 (24)	10 (26)	6 (23)

Moreau P. *et al.*, ASH 2016

Phase I combination results:

- Combination was well tolerated
- Patients non-refractory to bortezomib had an ORR of 90% and reponses were more durable (median TTP, 11.3 vs 1.8 months)
- Results support on-going Ph3 trial in R/R MM

*Venclexta in collaboration with AbbVie; R/R MM=relapsed/refractory multiple myeloma; ORR=objective response rate; sCR=surgical complete response; CR=complete response; VGPR=very good partial response; PR=partial response; TTP=time to progression

Introduction: Venclexta

Venclexta in CLL

Venclexta in AML

Venclexta in NHL

Venclexta in MM

Venclexta development program

Development program in NHL

Venclexta trials in NHL…

	Compound	Combination	Study name	Indication	Ph1	Ph2	Ph3	
NHL	***Gazyva***	*+bendamustine*	*GADOLIN*	FL (iNHL) (Rituxan refractory)				✓
	Gazyva	*+CHOP*	*GOYA*	1L DLBCL (aNHL)				✗
	Gazyva	*+chemo*	*GALLIUM*	1L FL (iNHL)				✓
	Venclexta*	***+Rituxan/+Rituxan****+bendamustine*	*CONTRALTO*	R/R FL (iNHL)				ASH
	Venclexta	***+Rituxan****+CHOP*	*CAVALLI*	1L DLBCL (aNHL)				ASH
	Venclexta	***+Rituxan****+bendamustine*		R/R NHL				
	Venclexta			R/R CLL and R/R NHL				
	Venclexta	***+Gazyva/Rituxan+polatuzumab***		R/R DLBCL (aNHL) and R/R FL (iNHL)				
	polatuzumab	***+Rituxan/Gazyva***	*ROMULUS*	R/R DLBCL (aNHL) and R/R FL (iNHL)				
	polatuzumab	***+Gazyva/Rituxan+bendamustin***		R/R DLBCL (aNHL) and R/R FL (iNHL)				
	polatuzumab	***+Gazyva****+CHP****/Rituxan****+CHP*		1L DLBCL (aNHL)				
	polatuzumab	***+Gazyva/Rituxan****+lenalidomide*		R/R DLBCL (aNHL) and R/R FL (iNHL)				
	Tecentriq	***+Gazyva*** *or +tazemetostat1***		R/R DLBCL (aNHL) and R/R FL (iNHL)				
	Tecentriq	***+Gazyva****+lenalidomide*		R/R FL (iNHL)				
	Tecentriq	***+Gazyva/Rituxan****+benda or CHOP*		1L FL (iNHL) and 1L DLBCL (aNHL)				
	Tecentriq	***+Gazyva/Rituxan+polatuzumab***		R/R DLBCL (aNHL) and R/R FL (iNHL)				
	idasanutlin	***+Gazyva/Rituxan***		R/R DLBCL (aNHL) and R/R FL (iNHL)				
	undisclosed ADC			R/R NHL				

iNHL=indolent non-hodgkin`s lymphoma; aNHL=agressive NHL; DLBCL=diffuse large B cell lymphoma; FL=follicular lymphoma; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; * Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; polatuzumab vedotin in collaboration with Seattle Genetics; **External collaboration; ADC=antibody drug conjugate

Development program in CLL, MM, AML, MDS

…*CLL, MM and AML*

	Compound	Combination	Study name	Indication	Ph1 Ph2 Ph3	
CLL	***Gazyva***	*+chemo*	*CLL11*	CLL		✓
	Gazyva	*+FC/bendamustin/Clb*	*GREEN*	CLL and R/R CLL		
	Venclexta	***+Rituxan***		R/R CLL and SLL		
	Venclexta	***+Gazyva***	*CLL14*	CLL		ASH
	Venclexta	***+Rituxan***	*MURANO*	R/R CLL		
	Venclexta			R/R CLL 17p		✓
	Venclexta			R/R CLL after ibru/idel		ASH
	Venclexta	***+Rituxan****+bendamustine*		R/R CLL and untreated CLL		ASH
	Venclexta	***+Gazyva***		R/R CLL and untreated CLL		
MM	***Venclexta***			R/R MM		ASH
	Venclexta	*+bortezomib+dexamethasone*		R/R MM		ASH
	Tecentriq	*monotherapy or +daratumumab** or +lenalidomide or +lenalidomide+daratumumab*		R/R MM		
AML	***Venclexta***			AML		
	Venclexta	*+decitabine/+azacitidine*		AML		
	Venclexta	*+low dose cytarabine (LDAC)*		1L AML		ASH
	Venclexta	***+Cotellic +idasanutlin***		R/R AML unfit for chemo		
	LSD1 inhibitor			AML		
	idasanutlin	*+cytarabine*		R/R AML		
MDS	***Tecentriq***	*+azacitidine*		MDS		
	aCD20/CD3 TCB1			Hematologic tumors		

CLL=chronic lymphoid leukemia; R/R CLL=relapsed/refractory CLL; MM=multiple myeloma; AML=acute myeloid leukemia; MDS=myelodysplastic syndrome; FC=fludarabine, cyclophosphamide; *Venclexta in collaboration with AbbVie; Gazyva in collaboration with Biogen; Cotellic in collaboration with Exelixis; **External collaboration

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