Gazyva – New standard of care in FL (iNHL)

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Introduction: Gazyva

Gazyva in NHL

Gazyva development program

MabThera/Rituxan SC

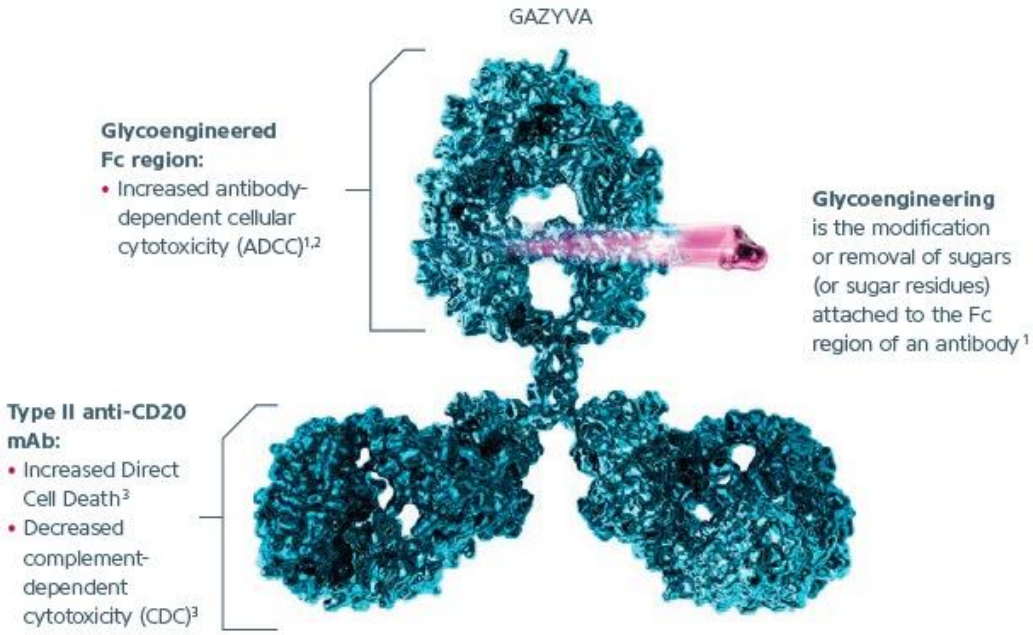
MoA: Gazyva (glycoengineered anti-CD20 MAb)
Optimized for enhanced ADCC and ADCP

Product profile

- Gazyva is a type II anti-CD20 antibody with a glycoengineered Fc portion to enhance binding to the FcγRIII receptor on immune cells and a variable region that binds CD20 in a distinct orientation

- Compared to Rituxan, Gazyva enhances:

    1. Direct cell death
    2. Antibody-dependent cell-mediated cytotoxicity (ADCC)
    3. Antibody-dependent cellular phagocytosis (ADCP)



MOA=mechanism of action; ADCC=antibody-dependent cellular cytotoxicity; ADCP=antibody-dependent cellular phagocytosis; Gazyva (obinutuzumab); Rituxan (rituximab);

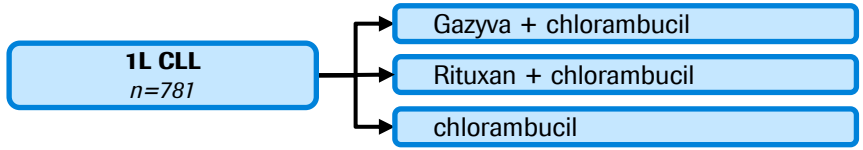
1. Mössner E. et al., Blood 2010; 2. Ferrara C. et al., Biotechnol Bioeng 2006; 3. Dalle S. et al., Mol Cancer Ther 2011

Gazyva initial trial program completed

New standard of care in iNHL and CLL

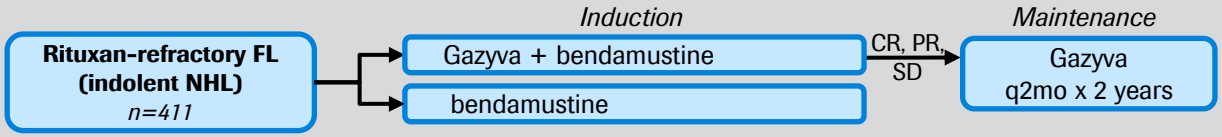
Primary end-point:

CLL11: Ph III 1L Chronic Lymphocytic Leukemia (CLL)



PFS
Approved in Q4 2013 ✓

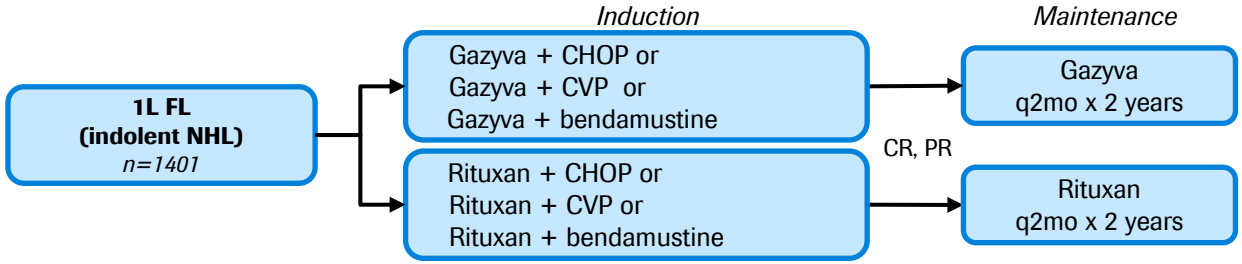
GADOLIN: Ph III Rituxan-refractory Follicular Lymphoma (FL)



American Society of Hematology
San Diego, 3-6 Dec

PFS
Approved in Q1 2016 ✓

GALLIUM: Ph III 1L Follicular Lymphoma (FL)



American Society of Hematology
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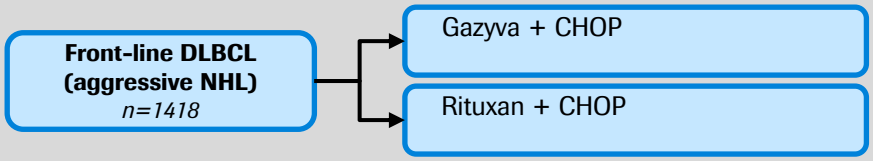
PFS
Stopped at interim analysis ✓

GOYA: Ph III 1L Diffuse Large B-cell Lymphoma (DLBCL)



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PFS
Endpoint not met ✗

Gazyva in collaboration with Biogen; CHOP=Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; CVP=Cyclophosphamide, Vincristine and Prednisolone

Introduction: Gazyva

Gazyva in NHL (GALLIUM; GADOLIN; GOYA)

Gazyva development program

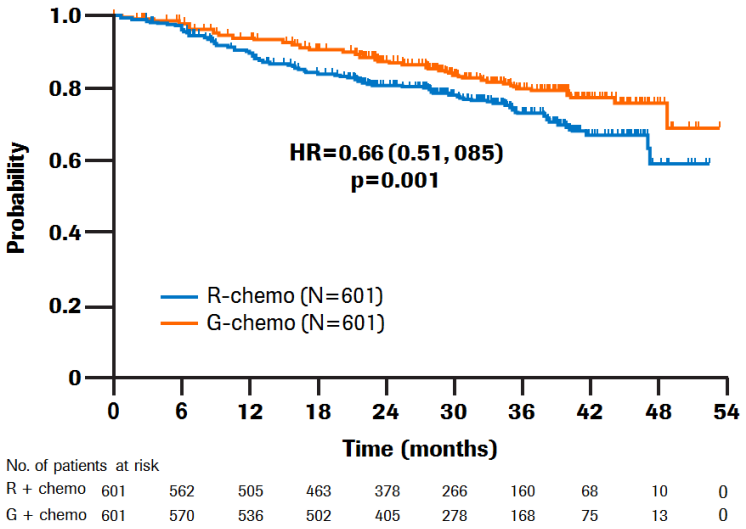
MabThera/Rituxan SC

Gazyva in 1L FL (iNHL)

34% PFS improvement over Rituxan

	Rituxan + chemo (n=601)	Gazyva + chemo (n=601)
PFS by INV		
Pts with event, n (%)	144 (24.0)	101 (16.8)
HR	**0.66; p=0.001**	
Event-free at 3 yrs (%)	73.3	80.0
PFS by IRC		
Pts with event, n (%)	125 (20.8)	93 (15.5)
HR	**0.71; p=0.014**	
Event-free at 3 yrs (%)	77.9	81.9
OS		
HR	0.75; p=0.21	
Time to new treatment		
HR	0.68; p=0.009	

PFS by INV



GALLIUM phase III results:

- Primary endpoint met at interim analysis (median observation time of 35 months)
- Investigator assessed PFS HR expected to translates to a 1.5x longer mPFS (9 years instead of 6 years)
- Gazyva based immunochemotherapy and maintenance new standard of care in 1L FL

Marcus R. *et al*., ASH 2016; FL=follicular lymphoma; R=Rituxan; G=Gazyva; PFS=progression free survival; INV=investigator; IRC=independent review committee; HR=hazard ratio; OS=overall survival; Data cut-off: January 31, 2016

Gazyva in Rituxan-relapsed FL (iNHL)

42% OS benefit in FL patients

Roche

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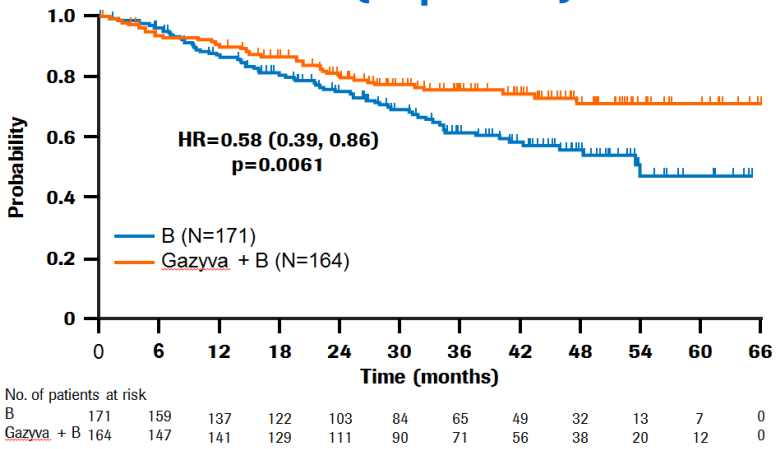
	Gazyva+B iNHL (n=204)	B iNHL (n=209)	Gazyva+B FL (n=164)	B FL (n=171)
PFS				
mPFS	25.8	14.1	25.3	14.0
HR	**0.57**; p<0.0001		**0.52**; p<0.0001	
OS				
mOS	NR	NR	NR	53.9
HR	**0.67**; p=0.0269		**0.58**; p=0.0061	
TTNT (time to new treatment)				
mTTNT	40.8	19.4	33.6	18.0
HR	**0.59**		**0.57**	

OS (FL patients)



GADOLIN phase III update:

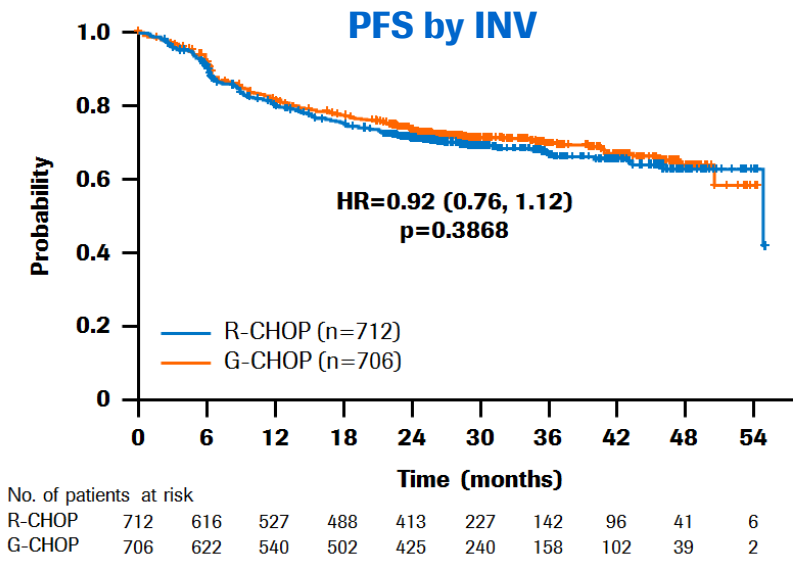
- OS benefit in FL patients and all iNHL patients
- PFS benefit confirmed by nearly two years of additional follow-up
- Results establish Gazyva + bendamustine induction followed by Gazyva maintenance as standard of care for Rituxan-relapsed FL patients

Cheson B. *et al*., ASH 2016; FL=follicular lymphoma; iNHL=indolent non-hodgkin`s lymphoma; B=bendamustine; PFS=progression free survival; OS=overall survival; HR=hazard ratio; Data cut-off: April 1, 2016

Gazyva in 1L DLBCL (aNHL)

Outcome informs future research activities

	Rituxan + CHOP (n=712)	Gazyva + CHOP (n=706)
PFS by INV		
Pts with event, n (%)	215 (30.2)	201 (28.5)
HR	0.92; p=0.3868	
Event-free at 3 yrs (%)	66.9	69.6
PFS by IRC		
HR	0.89; p=0.2736	
Event-free at 3 yrs (%)	70.6	72.5
OS		
Pts with event, n (%)	126 (17.8)	126 (17.7)
HR	1.00; p=0.9982	
Event-free at 3 yrs (%)	81.4	81.2



GOYA phase III results:

- G-CHOP did not improve INV-assessed PFS compared with R-CHOP
- Outcomes for secondary time-to-event endpoints were consistent with that for the primary endpoint
- R-CHOP remains standard of care in this setting

Vitolo U. *et al*., ASH 2016; DLBCL=diffuse large B cell lymphoma; aNHL=agressive non-hodgkin`s lymphoma; G=Gazyva; R=Rituxan; CHOP=Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; PFS=progression free survival; INV=investigator; HR=hazard ratio; OS=overall survival; Data cut-off: April 30, 2016

Introduction: Gazyva

Gazyva in NHL

Gazyva development program

MabThera/Rituxan SC

Development program in NHL

Gazyva trials in DLBCL…

	Compound	Combination	Study name	Indication	Ph1 Ph2 Ph3	
NHL	***Gazyva***	*+bendamustine*	*GADOLIN*	FL (iNHL) (Rituxan refractory)		✓ ASH
	Gazyva	*+CHOP*	*GOYA*	1L DLBCL (aNHL)		✗ ASH
	Gazyva	*+chemo*	*GALLIUM*	1L FL (iNHL)		✓ ASH
	Venclexta*	***+Rituxan/+Rituxan****+bendamustine*	*CONTRALTO*	R/R FL (iNHL)		
	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)		ASH
	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

…and CLL

	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	
	Venclexta	***+Rituxan****+bendamustine*		R/R CLL and untreated CLL	
	Venclexta	***+Gazyva***		R/R CLL and untreated CLL	
MM	***Venclexta***			R/R MM	
	Venclexta	*+bortezomib+dexamethasone*		R/R MM	
	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	
	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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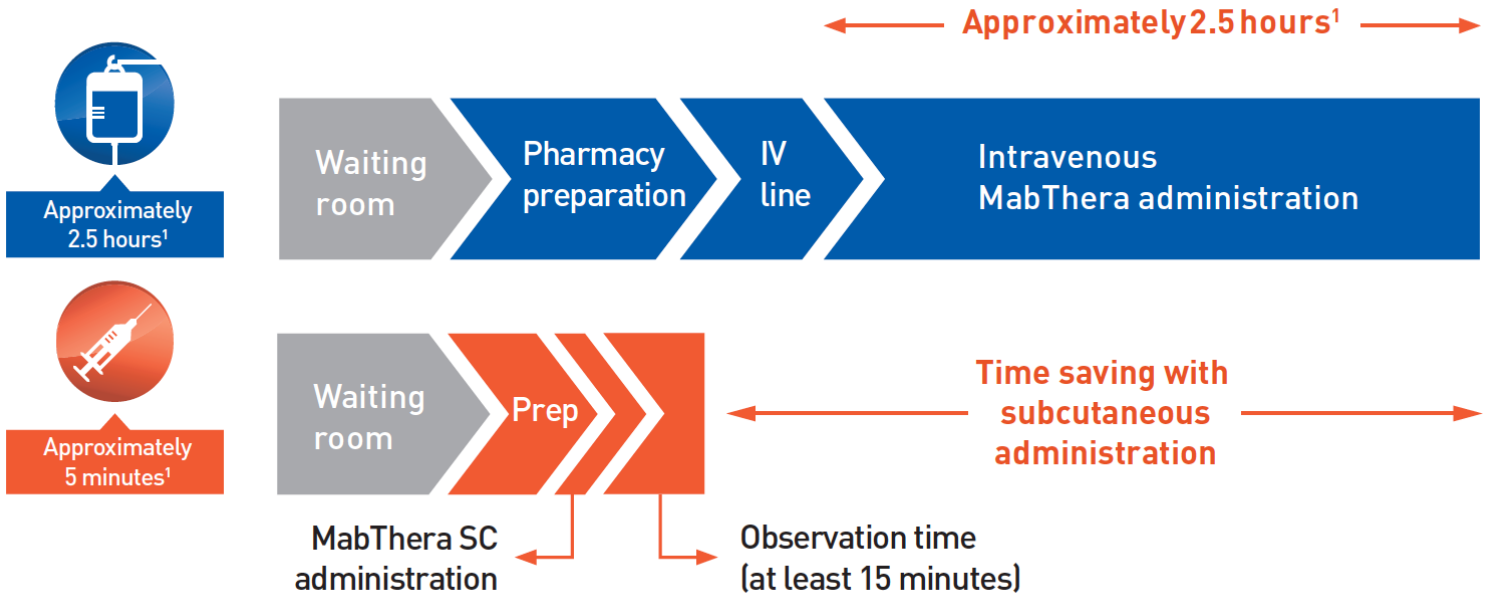
MabThera/Rituxan SC

MabThera/Rituxan SC

Launches ongoing, strong uptake in most markets

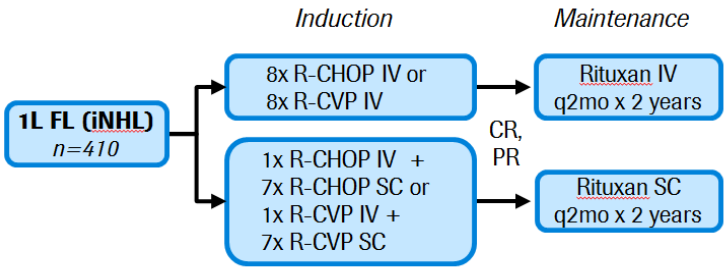


- Approved in the EU in NHL and CLL
- Encouraging initial uptake in the EU markets, comparable to Herceptin SC
- Rituxan SC filed in the US in August 2016

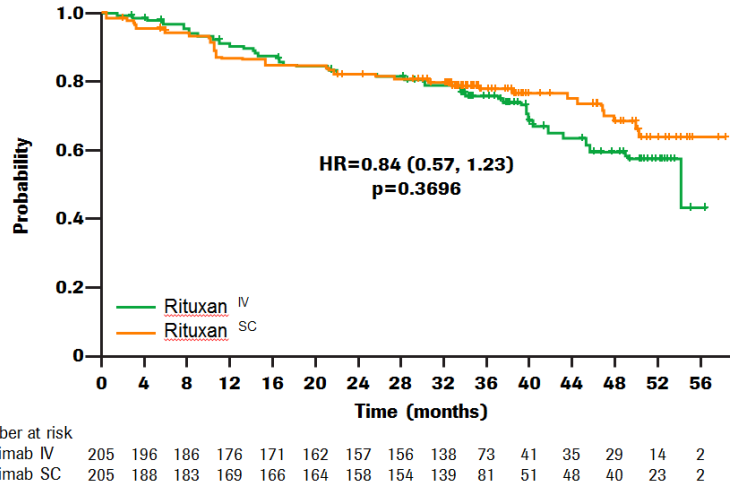
SC=subcutaneous; MabThera/Rituxan SC partnered with Halozyme

Rituxan SC in 1L FL (iNHL)

Reducing healtcare burden without compromising on safety and efficacy



Progression free survival



SABRINA phase III update:

- Comparable response rates and time-to-event data for SC versus IV administration
- No new clinically relevant safety signals were identified
- SC administration has positive implications for patients and healthcare professionals

Davies A.. *et al*., ASH 2016; FL=follicular lymphoma; SC=subcutaneous; IV=intravenous; R=Rituxan; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; CVP=Cyclophosphamide, Vincristine and Prednisolone; PFS=progression free survival; OS=overall survival; ORR=overall response rate; CR=complete responses; CRu=complete response unconfirmed; EOI, end-of-induction; OS, overall survival; HR=hazard ratio

Doing now what patients need next