Tables S1-S14

Table S1

Novel potential Drug Targets in DLBCL-NOS, including relapsed/refractory DLBCL

Target	Molecular Subtype	Molecular signature	Target in refractory DLBCL?	Inhibitor, Antibody, SiRNA	Study
Signaling Receptors:					
PD-1	HR? NA	NA	Yes	Pidilizumab, Nivolumab, MPDL3280A (anti-PD-1 antibodies)	[1-4]
CD19	NA	NA	Yes	Anti-CD19 CAR T cells (T cells expressing anti-CD19 CARs recognize and kill CD19+ target cells)	[5, 6]
CD22	NA	NA	Yes	Epratuzumab (anti-CD22 mAb)	[7]
CD43	ABC, type-3	NA	Yes	NA	[8, 9]
CD52	NA	NA	Yes	Alemtuzumab (anti-CD52mAB)	[10]
Cytoskeleton:					
Tubulin CD19 (indirect drug target)	NA	NA	Yes	SAR3419, an anti-CD19 antibody conjugated to the cytotoxine Maytansine DM4, a potent inhibitor of tubulin polymerization and microtubule assembly	[11-14]
Tubulin CD22 (indirect drug target)	ABC, GCB,	NA	NA	Pinatuzumab-Vedotin CD22 antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE).	[15]
Tubulin CD30 (indirect drug target)	ABC, GCB,	"CD30"	Yes	Brentuximab vedotin (anti-CD30 antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE).	[16-18]
Tubulin CD79B (indirect drug target)	ABC, GCB,	NA	NA	Polatuzumab-Vedotin (anti CD79B antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE).	[15]
Ezrin-Radixin-Moesin (ERM) family	ABC, GCB, type-3 (n.c.i.)	BCR (n.c.i.)	NA	Ezrin inhibitors NSC668394, NSC305787 (Interference with ERM function impairs BCR survival signaling)	[19]

DNA (Genome):					
DNA CD22 (indirect drug target)	NA	NA	Yes	Inotuzumab ozogamicin (INO) Anti-CD22 antibody linked to the DNA damaging toxin N-acetyl-γ-calicheamicin dimethyl hydrazide (CalichDMH) (induces DNA double strand breaks)	[14, 20]
mRNA Translation Machinery: (i.e. Oncogene translation)					
Elongation Factor 2	NA	NA	Yes	Moxetumomab Pasudotox (HA22/ BL22) Anti-CD22 antibody linked to a to an ADP-ribosylating Pseudomonas Exotoxin (Inhibits protein synthesis)	[13, 14, 21]
Translation initiation complex eIF4F (eIF4E, eIF4G and eIF4A)	ABC, GCB, type-3 (n.c.i.)	BCR (n.c.i.)	NA	eIF4A inhibitor Silvestrol mTORC1 inhibitor CC214-1	[22, 23]
NF-κB Pathway:					
26S proteasome	ABC, (GCB?, type-3)	BCR, HR, (n.c.i.)	Yes	Bortezomib, carfilzomib (26S inhibitors)	[24-27]
NF-κB/RELA/p65, NF-κB1/p50, NF-κB2/p52 RELB	ABC (GCB?, type-3)	BCR, HR, (n.c.i.)	Yes	BAY-11-7082 (NF-κB inhibitor)	[28-33]
IκB kinase (IKK) complex	ABC (GCB?, type-3)	BCR, (n.c.i.)	NA	*IKKα* siRNA, MLX, MLN120B (IKKβ inhibitors)	[34, 35]
NIK	ABC (GCB?, type-3) (n.c.i.)	BCR Non-BCR	NA	Mouse model for DLBCL NIK inhibitors AM-0216, AM-0561, PBS-1086 tested in multiple myeloma	[31-33, 36, 37]
IκB-ζ	ABC (GCB?, type-3)	BCR, (n.c.i.)	NA	*IκB-ζ* siRNA	[38]
MALT1	ABC	BCR, (n.c.i.)	NA	MI-2, mepazine, thioridazine, and promazine (MALT inhibitors)	[39-42]
CARD11	ABC	BCR, (n.c.i.)	NA	zVRPR-fmk (CARD11 inhibitor)	[43, 44]
MYD88	ABC	BCR/	NA	*MYD88* siRNA	[45]

		MYD88 mutation, (n.c.i.)			
Ubiquitinylation/ Neddylation					
CSN5 COP9-signalosome (CSN) deneddylating activity	ABC, GCB	(n.c.i.)	NA	Doxocycline	[46]
UBC13/UEV1A	ABC, GCB	BCR, (n.c.i.)	NA	NSC697923	[47]
RNF31	ABC	BCR/ RNF31 mutations, (n.c.i.)	NA	Stapled RNF31 N-Q622L peptide	[48]
NEDD8	ABC, GCB	NA	NA	MLN4924, a NEDD8-activating enzyme inhibitor	[49, 50]
IFNα/β Signaling:					
IRF4	ABC	BCR, (n.c.i.)	Yes	Lenalidomide	[51, 52]
Cereblon	ABC, GCB, type-3 (n.c.i.)	BCR, (n.c.i.)	Yes	Lenalidomide, CC-122 *Cereblon*-siRNA	[51-56]
BCR Signaling:					
CD79A, CD79B	ABC	BCR, CD79A/B mutation	NA	siRNA	[57, 58]
BTK	ABC	BCR, (n.c.i.)	Yes	Ibrutinib	[27, 57]
SYK	ABC	BCR, (n.c.i.)	NA	Fostamatinib (R788)(SYK inhibitor) Entospletinib (GS-9973)	[57, 59-61]
PKCβ	ABC	BCR, CD79A/B mutation,	NA	Enzastaurin, Sotrastaurin/AEB071 (PKCβ inhibitor)	[57, 58, 62]
SRC family	ABC	BCR, (n.c.i.)	NA	Dasatinib, pp2	[57, 63, 64]
PLCγ2	ABC, GCB, type-3 (n.c.i.)	BCR, (n.c.i.)	NA	U73122 (PLC-inhibitor)	[64]
PI3K/AKT/mTORC Pathway:					
PI3K/PI3Kδ	ABC, GCB, type-3	BCR, HR, (n.c.i.)	Yes	NVP-BKM120 Idelalisib BAY 80-6946	[65-67]
AKT	ABC, GCB, type-3 (n.c.i.)	BCR, HR, MD, (n.c.i.)	Yes	MK-2206, nelfinavir	[68-70]
mTORC1	ABC, GCB, type-3	BCR, (n.c.i.)	Yes	Rapamycin Everolimus	[71-74]

				Temsirolimus CC-223, AZD2014, BEZ235, QL-X-138, PRT062070, OSI-027	
mTORC2	ABC, GCB, type-3 (n.c.i.)	BCR, HR, MD, (n.c.i.)		CC-223, AZD2014, BEZ235, QL-X-138, PRT062070, OSI-027	[73, 75]
Inhibitor of Apoptosis:					
BCL2	GCB, (ABC, type-3)	MD, (n.c.i.)	Yes	ABT-737, A263, ABT-199 GX15-070 (obatoclax) (BH3-mimetics)	[26, 76-84]
MCL1	ABC, (GCB, type-3)	NA	Yes	GX15-070 (obatoclax)	[76, 77, 80, 85-88]
MCL1 (CDK1, CDK2, CDK5, CDK9)	ABC, (GCB, type-3)	MD, (n.c.i.)	NA	Dinaciclib	[89]
BCL-XL	NA	NA	NA	ABT-737, A263, ABT-199, GX15-070 (obatoclax)	[26, 79]
BFL-1	NA	NA	NA	GX15-070 (obatoclax)	[76, 77, 85-87]
XIAP	NA	NA	Yes	Small-molecule XIAP antagonist 1396-12	[90]
Survivin	ABC, GCB, type-3 (n.c.i.)	NA	Yes	YM155	[91-94]
MDM2	ABC, (n.c.i.)	MD, (n.c.i.)	NA	Nutlin-3a	[95]
B Cell specific Transcription Factors:					
BCL6	ABC, (GCB, type-3)	BCR, HR, MD, (n.c.i.)	NA	RI-BPI	[96-100]
YY1	ABC, GCB, type-3	MD? (n.c.i.)	NA	*YY1* siRNA	[101-103]
FOXP1	ABC, (n.c.i.)	NA	Yes (n.c.i.)	*FOXP1* siRNA	[104-106]
β-catenin	NA	NA	NA	*FOXP1* siRNA, *β-catenin* siRNA,	[105]
Stress Proteins:					
HSP70 HSP90α HSP90β	ABC, GCB, type-3 (n.c.i.)	OxPhos (Hsp90α) BCR (Hsp90β)	Yes (n.c.i.)	IPI-504 PU-H71	[97, 107-109]
JAK/STAT Pathways:					
IL10/IL10R	ABC, GCB, type-3	NA	NA	Anti IL10R blocking antibody	[110, 111]

	(n.c.i.)				
JAK1 JAK2	ABC, GCB, type-3	NA	NA	Fedratinib (TG101348)	[111-113]
STAT1	GCB, (ABC, type-3) (n.c.i.)	HR, (n.c.i.)	NA	*STAT1*-siRNA	[112]
STAT3	ABC, (GCB, type-3) (n.c.i.)	NA	NA	Fedratinib (TG101348)	[114-117]
C-MYC Pathway:					
c-MYC	ABC, GCB, type-3 (n.c.i.)	MD (n.c.i.)	Yes	*c-MYC* siRNA	[118-121]
BRD4 BRD2	ABC, (GCB, type-3?) (n.c.i.)	MD, BCR (n.c.i.)	Yes (n.c.i.)	JQ1, PFI-1, CPI203, I-BET151, OTX015, ARV-825 (PROTAC)	[122-131]
PRPS2	NA	MD, (n.c.i.)	NA	*PRPS2* siRNA	[132]
Aurora A kinase	ABC, GCB, type-3, (n.c.i)	MD, (n.c.i.)	Yes	Alisertib (MLN8237)	[133, 134]
Epigenetic Modifiers:					
DNMTs	NA	NA	Yes (n.c.i.)	Decitabine /5-aza-2′-deoxycytidine (DAC/5-AZA), Azacytidine (AZA)	[135]
EZH2	GCB, (n.c.i.)	NA	NA	GSK126, CPI-360	[136-143]
HDACs (HDAC1-4, 6)	GCB, ABC, type-3 (n.c.i.)	NA	Yes (n.c.i.)	Vorinostat Panobinostat LBH589 Ricolinostat	[115, 144-146]
Sirtuins (SIRT1)	ABC, GCB (n.c.i.)	NA	Yes (n.c.i.)	Cambinol, Niacinamide	[144, 145, 147]
ROS-OxPhos-Pathways:					
PPARγ	ABC, GCB, type-3	OxPhos	NA	T0070907 and GW9662	[148]
γ-glutamyl cysteine synthase (GCS)	ABC, GCB, type-3	OxPhos	NA	*GCS*-siRNA	[148]
fatty acid oxidation program	ABC, GCB, type-3	OxPhos	NA	4-bromocrotonic acid (BrCA)	[148]
RAS/RAF/MEK/ERK Signaling:					
ERK1	GCB, type-3	NA	NA	ERK inhibitor no. 76 [3-(2-	[149, 150]

ERK2 CHK2	(n.c.i.)			aminoethyl)-5-((4-ethoxyphenyl) methylene)-2,4-thiazolidinedione CHK2 inhibitor II (2-(4-(4-chlorophenoxy) phenyl)-1H-benzimidazole-5-carboxamide hydrate)	
MEK	NA	NA	NA	AZD6244	[151]
Other Kinases:					
PIM1 PIM2	ABC, GCB, type-3	NA	NA	ETP-39010	[152-154]
JNKs	ABC, (n.c.i.)	(BCR?) NA	NA	SP600125	[155]
CDK1, CDK2, CDK5, CDK7, CDK8, CDK9,	ABC, (GCB, type-3) (n.c.i.)	MD, (n.c.i.)	NA	Dinaciclib Seliciclib (CYC202, R-roscovitine)	[89, 156, 157]
Mitogenic Signaling:					
p70S6K/p85S6K	NA	NA	NA	Rapamycin	[158]
CDK1	NA	NA	NA	UCN-01	[158]
KSP	ABC, GCB (n.c.i.)	NA	NA	SB-743921	[159]
NOTCH Pathway/ DELTEX Family:					
DTX3L	ABC, GCB, type-3	HR, BCR (n.c.i.)	NA	NA	[160]
NOTCH1 NOTCH2	ABC, (GCB?), type-3	HR, (n.c.i.)	NA	NA	[137, 161-163]
ARTD Family:					
ARTD8? ARTD9	ABC, GCB, type-3	HR, BCR (n.c.i.)	NA	NA *ARTD9* siRNA	[112, 160, 164, 165]
PTM Enzymes:					
Rab geranylgeranyl transferase (prenylation of the oncogenic Rab family)	NA	NA	Yes (n.c.i.)	FTI-277 GGTI-298	[166]
Angiogenesis:					
VEGF	NA	Stromal II	NA	Bevacizumab (Avastin)	[167-169]
PDGFRβ	NA	NA	NA	Imatinib	[170]

Metastasisation:					
CXCR4	GCB, ABC (n.c.i.)	NA	NA	AMD3100	[171-173]
FoxM1	GCB, ABC (n.c.i.)	NA	NA	Thiostrepton	[174]
Drug Resistance:					
ABCG2 (Stroma induced drug tolerance)	NA	NA	NA	Fumitremorgin C	[175]
Thioredoxin-1	NA	NA	NA	PX-12	[176]
ALDH1A1	NA	NA	Yes (n.c.i.)	Diethylaminobenzaldehyde (DEAB)	[177]
Signaling Inhibitors:					
PDE4B (PDE2,3,7 ?) (inactivates cAMP and abrogates its inhibitory effects in DLBCL)	NA	NA	NA	BAY 60-7550/ cilostamide, cilostazol, siguazodan, milrinone, roflumilast/ papaverine, BRL-54680	[178-180]
AKT-14-3-3ζ signaling:					
AKT	NA	NA	NA	Akt inhibitor VIII	[181]
14-3-3ζ	NA	NA	NA	*14-3-3ζ* siRNA	[182]
Autophagy:					
General inhibition	NA	NA	NA	Chloroquine/3-methyladenine/Bafilomycin A 1	[65]
Constitutive activation of DNA damage response (DDR) pathway					
CHK1/2	ABC, GCB, type-3 (n.c.i.)	NA	NA	PF-0477736 AZD-7762	[183]

DLBCL diffuse large B cell lymphoma, *ABC* activated B cell-like, *GCB* germinal center B cell-like, *OxPhos* oxidative phosphorylation subtype, *BCR* BCR-activated B-cell (antigen) receptor/proliferation subtype**,** *HR* host response signature subtype, *MD* c-MYC-driven signature subtype, *n.c.i.* not completely investigated, *NA* not available, *type-3* unclassified DLBCL-NOS, *NF-κB* nuclear factor-kappa B, *IKK* inhibitor of kappa B kinase, *IKB* inhibitor of kappa B, *MALT1* mucosa-associated lymphoid tissue lymphoma translocation protein 1, *CARD11* caspase recruitment domain family, member 11, *MYD88* myeloid differentiation primary response 88, *UBC13/UEV1A* ubiquitin-conjugating enzyme, *RNF31* ring finger containing protein 31, *NEDD8* neural precursor cell expressed, developmentally down-regulated 8, *IRF4* interferon-regulatory factor 4, *BTK* Bruton's tyrosine kinase, *SYK* spleen tyrosine kinase, *PKCβ*

protein kinase Cβ, *PLCγ2* phospholipase C gamma 2, *mTORC1* mammalian target of rapamycin (mTOR) complex 1, *PI3K* phosphoinositide 3-kinase, *BCL* B-cell lymphoma protein, *MCL1* myeloid cell leukemia 1, *XIAP* X-linked inhibitor of apoptosis, E3 ubiquitin protein ligase, *MDM2* murine double minute E3 ubiquitin ligase, *YY1* Ying Yang 1, *FOXP1* forkhead box P1, *HSPs* heat shock proteins, *IL* interleukin, *JAK* Janus kinase, *STAT* signal transducer and activator of transcription, *BRD* BET bromodomain protein, *PROTAC* proteolysis targeting chimera, *PRPS2* phosphoribosyl-pyrophosphate synthetase 2, *DNMTs* DNA methyltransferases, *EZH2* enhancer of zeste homologue 2, *HDACs* histone deacetylases, *PPAR* peroxisome proliferators activated receptor, *ERK* extracellular signal-regulated kinase, *PIM1* (proviral integration site for the Moloney murine leukemia virus) kinase 1, *CDK* cyclin-dependent kinase, *KSP* kinesin spindle protein, *DTX3L* deltex (DTX)-3-like E3 ubiquitin ligase, *ARTD* ADP-ribosyltransferase diphteria toxin like, *VEGF* vascular endothelial growth factor, *PDGFRβ* platelet-derived growth factor receptor beta, *CXCR4* chemokine (C-X-C motif) receptor 4, *FoxM1* forkhead box M1, *ABCG2* ATP-binding cassette, sub-family G, member 2, *ALDH1A1* aldehyde dehydrogenase 1A1, *PDE* phosphodiesterases

Table S2

Novel single experimental agents in clinical trials in relapsed/refractory DLBCL-NOS

Inhibitor or Agent	Target or Agent mechanism	No. of patients	Response rate (DLBCL Subtype)	Response duration	Clinical trials	Study
Pidilizumab (after ASCT)	PD-1	66 (24)	ORR: 51% CR: 34% PR: 17% SD: 27% PD: 11%	DOR: 10m 16m-PFS: 70% 16m-OS: 85%	Phase I/II	[1, 2] Trial-No: NCT00532259
Nivolumab (after ASCT)	PD-1	120 (estimated)	NA	NA	Ongoing Phase II	Trial-No: NCT02038933
Daratumumab	CD38	NA	NA	NA	Ongoing Phase II	Trial-No: NCT02413489
Bortezomib	Proteasome (NF-κB)	53 (estimated)	NA	NA	Ongoing Phase II	Trial-No: NCT01965977
IMO-8400 (TLR7/8/9 antagonist)	TLR7/8/9	NA	NA	NA	Ongoing Phase I/II	Trial-No: NCT02252146
Lenalidomide (after ASCT)	CRBN (IRF4) (Immuno- modulatory drug)	52/47	ORR: 29/28% CR/CRu: 10/11% PR: 19/17% SD: 25/26% PD: 38/47%	DOR: 7.9m DOR(CR): 15m PFS(CR): 16.8m PFS(PR): 7.3m OS: NA	Phase II	[184-186] Trial-No: NCT00765245
Lenalidomide	CRBN (IRF4) (Immuno- modulatory drug)	40 (GCB: 23, non-GCB: 17)	ABC/type-3: ORR: 52.9% CR: 23.5 % PR: 24 % SD: 0% PD: 40% GCB: ORR: 8.7% CR: 4.3 % PR: 24 % SD: 30.4 PD: 61%	PFS: 6.2m OS: 13.5m PFS: 1.7m OS: 14m	Phase II	[187]
Lenalidomide	CRBN (Aiolos, Ikaros, IRF4) (Immuno- modulatory drug)	51/25 (IHC: GCB 23, ABC 28) (GEP: GCB 14, ABC 11)	ABC/type-3 (IHC): ORR: 28.6% GCB (IHC): ORR: 26.1% ABC (GEP): ORR: 45% GCB (GEP): ORR: 21 %	ABC/type-3 (IHC): med. PFS: 15.1 wks med. OS: 32.2 wks GCB (IHC): med. PFS: 10.1 wks med. OS: 30 wks ABC (GEP): med. PFS: 82 wks med. OS: 108 wks	Ongoing phase II/III	[188] Trial-No: NCT01197560

				GCB (GEP): med. PFS: 13.2 wks med. OS: 30 wks		
CC-122	CRBN (Aiolos, Ikaros, IRF4) (Immuno-modulatory drug)	NA	NA	NA	Ongoing phase I	Trial-No: NCT01421524
CC-122	CRBN (Aiolos, Ikaros, IRF4) (Immuno-modulatory drug)	5	ORR: 40% CR: 20% PR: 20% (preliminary data)	NA	Ongoing phase I	[189]
CC-122	CRBN (Aiolos, Ikaros, IRF4) (Immuno-modulatory drug)	21	ORR: 24% CR: 5% PR: 14.5 % (preliminary data)	NA	Ongoing phase I	[56]
Ibrutinib (PCI-32765)	BTK	80 (75) (ABC: 38 GCB: 20 Type-3: 17) 125	ABC: ORR: 37% CR: 17 % PR: 24 % GCB: ORR: 5.3%	ABC: PFS: 2m OS: 10.3m GCB: PFS: 1.3m OS: 3.35m	Phase I/II Ongoing phase III/b	[190-192] Trial-No: NCT01325701 Trial-No: NCT01804686
ACP-196	BTK	NA	NA	NA	Ongoing phase I	Trial-No: NCT02112526
Fostamatinib (R788)	SYK	23	ORR: 22 % CR: 4.4 % PR: 17.6% SD: 17.4% PD: 50%	NA	Phase I/II	[59] Trial-No: NCT00446095
Fostamatinib (R788)	SYK	68	NA	NA	Phase II	Trial-No: NCT01499303
Entospletinib (GS-9973)	SYK	NA	NA	NA	Ongoing phase II	Trial-No: NCT01799889
Navitoclax (ABT-263)	BCL2 family	6	NA	NA	Phase I ongoing phase II	[193] Trial-No: NCT00406809
ABT-199 (GDC-0199)	BCL2	20 (estimated)	NA	NA	Ongoing phase I	[194, 195] Trial-No: NCT01328626
Temsirolimus	mTORC1	27	ORR: 28.1 %	DOR: 2.4m	Phase II	[72]

			CR/CRu: 12.5% PR: 15.6% SD: 18.8% PD: 46.9%	PFS: 2.6m OS: 7.3m 3y-OS: 27.1%		Trial-No: NCT00290472
Everolimus (RAD001)	mTORC1	47	ORR: 30% CR/CRu: 0% PR: 14%	NA	Phase II	[71]
CC-223	mTORC1 mTORC2	NA	NA	NA	Ongoing phase I/II	[75] Trial-No: NCT01177397
Enzastaurin (LY317615)	PKCβ	55 (40)	ORR: 5.5% CR/CRu: 5.5%	≥2m-PFS: 22% ≥4m-PFS: 12% ≥20m-PFS: 7.3%	Phase I/II	[196] Trial-No: NCT00042666
Idelalisib (GS-1101, CAL-101)	PI3Kδ	NA	NA	NA	Ongoing phase I Ongoing phase II	[66, 197] Trial-No: NCT01796470
Idelalisib (GS-1101, CAL-101)	PI3Kδ	NA	NA	NA	Ongoing phase I	Trial-No: NCT02457598
Bay 80-6946	PI3Kδ	17 (NA) (Preliminary data)	ORR: 11.2% CR/CRu: 5.6% PR: 5.6% SD: 40.3% PD: 46.9% (Preliminary data)	NA	Ongoing phase II	[67] Trial-No: NCT01660451
Copanlisib	PI3Kδ, PI3Kα	NA	NA	NA	Ongoing phase II	Trial-No: NCT02391116
Panobinostat (LBH-589)	HDACs	NA	NA	NA	Ongoing phase I/II	[198] Trial-No: NCT01238692
Ricolinostat (ACY-1215)	HDAC6	NA	NA	NA	Ongoing phase I/II	[146] Trial-No: NCT02091063
Decitabine (DAC)	DMNT1-3	42	NA	NA	Ongoing phase I	Trial-No: NCT00109824
MK-2206	AKT	NA	NA	NA	Ongoing phase II	Trial-No: NCT01481129
BKM-120	PI3K	NA	NA	NA	Ongoing phase II	Trial-No: NCT01693614
CPI-0610	BRD2-4 (BET)	NA	NA	NA	Ongoing phase I	Trial-No: NCT01949883
ISIS-STAT3Rx (Antisense Oligonucleotide Inhibitor of STAT3)	STAT3	NA	NA	NA	Ongoing phase I/II	Trial-No: NCT01563302
Obinutuzumab (GA101) Third-	CD20	25	ORR: 32% BOR: 20%	DOR: 9.8m PFS: 2.7m	Phase II	[199] Trial-No: NCT00517530

generation anti-CD20 mAb						
ABC294640	Sphingosine kinase 2	NA	NA	NA	Ongoing phase I	Trial-No: NCT02229981

DLBCL diffuse large B cell lymphoma, *ABC* activated B cell-like, *GCB* germinal center B cell-like, *ORR* overall response rate, *BOR* best ORR, *PR* partial response, *CR* complete response, *CRu* unconfirmed CR, *SD* stable disease, *PD* progressive disease, *DOR* median duration of response, *OS* median overall survival, *PFS* median progression-free survival, *NA* not available/not applicable, *wks* weeks, *m* months, *y* year, *ASCT* autologous stem-cell transplantation, *PD-1* programmed cell death 1, *NF-κB* nuclear factor-kappa B, *TLR* Toll like receptor, *IRF4* interferon-regulatory factor 4, *BTK* Bruton's tyrosine kinase, *SYK* spleen tyrosine kinase, *PKCβ* protein kinase Cβ, *PLCγ2* phospholipase C gamma 2, *DNMTs* DNA methyltransferases, *PI3K* phosphoinositide 3-kinase, *BCL* B-cell lymphoma protein, *BRD* BET bromodomain protein, *STAT* signal transducer and activator of transcription, *CRBN* cereblon

Table S3:

Experimental clinical studies combining novel experimental agents with conventional (immuno-) chemotherapy (R-CHOP, DHAP) in first-line treatment of newly diagnosed DLBCL

Treatment	Targets	DLBCL-NOS Subtype	Age	No. of patients	Response rate	Response duration	Clinical trial	Study
Bortezomib + CHOP/DA-EPOCH	Proteasome (NF-κB)	ABC	54 (18-78) years	49 (44)	ABC: ORR: 83 % CR: 41.5% PR: 41.5% GCB: ORR: 13 % CR: 6.5% PR: 6.5%	ABC: DOR: 10.2m PFS: 2.8m OS: 10.8m GCB: DOR: 10.2m PFS: 2.8m OS: 3.4m	Phase II	[24] Trial-No: NCT00057902
Bortezomib + EPOCH	Proteasome (NF-κB)	NA	50	NA	NA	NA	Phase II	Trial-No: NCT00054665
Enzastaurin (LY317615) +/- R-CHOP	PKCβ CD20	NA	100	100 (57/43)	R-CHOP/enza: ORR: % CR/CRu: 36% PR: % R-CHOP: ORR: % CR/CRu: 26% PR: %	R-CHOP/enza: DOR: 36m 1y-PFS: 72% 2y-PFS: 59% R-CHOP: DOR: 23m 1y-PFS: 55% 2y-PFS: 49%	Phase II	[200] Trial-No: NCT00451178
Enzastaurin (LY317615) + R-GEMOX	PKCβ CD20	NA	NA	NA	NA	NA	Phase II	Trial-No: NCT00436280
Lenalidomide + Rituximab	CRBN (IRF4) CD20	GCB, ABC, type3, (n.c.i)	62 (43-79) years	17	ORR: 41.5% CR: 35%	DOR: 26.5m 2y-PFS: 38% 2y-OS: 45%	Phase II	[201]
Lenalidomide + Rituximab		GCB, ABC, type3 (n.c.i)	65 (24-84) years	32	ORR: 28 % CR: 22.2 % PR: 6% SD: 28% PD: 37%	DOR: 10.2m PFS: 2.8m OS: 10.2m	Phase II	[202] Trial-No: NCT00294632
Lenalidomide + R-ICE/BEAM	CRBN (IRF4) CD20	GCB, ABC, type3 (n.c.i)	61.5 (41-75) years	15	ORR: 73% (GCB: 100%) CR: 60% PR: 13%	DOR: 8m	Phase I/II	[203] Trial-No: NCT01241734
Ofatumumab (Arzerra) + DHAP	CD20	NA	NA	NA	NA	NA	Phase III	Trial-No: NCT01014208

Veltuzumab + 90Y-Epratuzumab-Tetraxetan (Radio-immuno-therapy)	CD20 CD22 Radio-immuno-therapy (radio-labeled anti CD22 antibody, 90Y-epratuzumab tetraxetan)	NA	73 (52-84) years	8	ORR: 50% CR: 37.5% PR: 12.5% SD: 12.5%	NA	Phase I	[204] Trial-No: NCT01101581
Azacytidine (AZA) (CC-486) + R-CHOP	DMNTs CD20	NA	65 (43-83) years	12	ORR: 92% CR: 92%	DOR: 13m	Phase I	[135]

DLBCL diffuse large B cell lymphoma, *ABC* activated B cell-like, *GCB* germinal center B cell-like, *ORR* overall response rate, *PR* partial response, *CR* complete response, *CRu* unconfirmed CR, *SD* stable disease, *PD* progressive disease, *DOR* median duration of response, *OS* median overall survival, *PFS* median progression-free survival, *NA* not available/not applicable, *m* months, *y* year, *ASCT* autologous stem-cell transplantation, *R-CHOP* rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, *R-GEMOX* rituximab, gemcitabine and oxaliplatin, *DHAP* dexamethasone, cytarabine, and cisplatinum, *R-ICE* rituximab, ifosfamide, carboplatin, and etoposide, *BEAM* carmustine, etoposide, cytarabine, melphalan, *type-3* unclassified DLBCL-NOS, *MMAE* microtubule disrupting agent monomethyl auristatin E, *NF-κB* nuclear factor-kappa B, *IRF4* interferon-regulatory factor 4, *PKCβ* protein kinase Cβ, *CRBN* cereblon

Table S4

Ongoing experimental clinical studies combining novel experimental agents with conventional (immuno-) chemotherapy (R-CHOP, DHAP) in first-line treatment of newly diagnosed DLBCL

Treatment	Targets	Clinical trial	Study
Lenalidomide + DA-EPOCH-R	CRBN (IRF4) CD20	Ongoing Phase I/II	Trial-No: NCT02213913
Lenalidomide + Rituximab	CRBN (IRF4) CD20	Ongoing phase II Ongoing phase III	Trial-No: NCT01856192 NCT02128061
Lenalidomide + R-ESHAP	CRBN (IRF4) CD20	Ongoing phase I/II	Trial-No: NCT02340936
Lenalidomide + R-CHOP	CRBN (IRF4) CD20	Ongoing phase III	Trial-No: NCT02285062
Ibrutinib + R-CHOP	BTK CD20	Ongoing phase III	[205, 206] Trial-No: NCT01855750
Everolimus (RAD001) + R-CHOP	mTORC1 CD20	Ongoing phase I	Trial-No: NCT01334502
Carfilzomib + R-CHOP	Proteasome (NF-κB) CD20	Ongoing Phase I/II	Trial-No: NCT02073097
Bortezomib + R-CHOP	Proteasome (NF-κB) CD20	Ongoing phase II	Trial-No: NCT00931918
Bortezomib + R-CHOP	Proteasome (NF-κB) CD20	Ongoing phase III	[206] Trial-No: NCT01324596
Vorinostat + R-CHOP	HDACs CD20	Ongoing phase I/II	[198] Trial-No: NCT00972478
Panobinostat (LBH-589) + R-CHOP	HDACs CD20	Ongoing phase I/II	[198] Trial-No: NCT01238692
Azacytidine (AZA) (CC-486) + R-CHOP	DMNTs CD20	Ongoing phase I/II	[198] Trial-No: NCT01004991
Azacytidine (AZA) (CC-486) + R-CHOP	DMNTs CD20	Ongoing phase I/II	[198] Trial-No:

DLBCL diffuse large B cell lymphoma, *R-CHOP* rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, *DA-EPOCH-R* etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab, *R-ESHAP* etoposide, methylprednisolone, cytosine arabinoside, and

platinum, *IRF4* interferon response factor 4, *BTK* Brutons' tyrosine kinase, *mTORC1* mammalian target of rapamycin (mTOR) complex 1, *NF-κB* nuclear factor-kappa B, *HDAC* histone deacetylase, *DMNT* DNA methyltransferase, *CRBN* cereblon

Table S5:

Experimental clinical studies combining novel experimental agents with conventional (immuno-) chemotherapy (R-CHOP, DHAP) in second-line treatment of relapsed/refractory DLBCL

Treatment	Targets	Age	No. of patients	Response rate	Response duration	Clinical trials	Study
R-CHOP(-21)	CD20	61 (41-86) 61 (19-88) 62 (21-92) 70 (59-80) 70 (60-90) years	87 422 215 267 234	ORR: ≤ 90% CR/CRu: ≤55 % PR: ≤ 30% ORR: ≤86 % CR/CRu: ≤75 % PR: ≤10 %	2y-PFS: ≤75% 2y-OS: ≤82% 3y-PFS: ≤62% 3y-F/EFS: ≤60% 3y-OS: ≤72%	Phase II Phase III	Historical Control cohorts [7, 207, 208] [209, 210]
Ibrutinib + R-CHOP	BTK CD20	61.5 (22-81) years	23	ORR: 95% CR: 72% PR: 21%	NA	Phase Ib	[205] Trial-No: NCT01569750
Ibrutinib + Rituximab + Bendamustine	BTK CD20	62 (23-84) years		ORR: 37% CR: 31% PR: 6%	NA	Phase I/Ib	[211] Trial-No: NCT01479842
Lenalidomide + R-CHOP	CRBN (IRF4) CD20	58 (24-77) years	27	ORR: 96% CR/CRu: 74% PR: 22%	2y-PFS: 80% 2y-EFS: 70% 2y-OS: 90%	Phase Ib	[212] Trial-No: NCT00901615
Lenalidomide + R-CHOP21	CRBN (IRF4) CD20	65 (22-87) years	64	ORR: 98% CR: 80% PR: 18%	1y-E/PFS: 70% 2y-E/PFS: 59% 1y-OS: 90% 2y-OS: 78%	Phase II	[207] Trial-No: NCT00670358
Lenalidomide + R-CHOP21	CRBN (IRF4) CD20	69 (64-71) years	45	ORR: 92% CR: 86% PR: 6%	2y-PFS: 80% 2y-EFS: 70% 2y-OS: 90%	Phase II	[213] Trial-No: NCT00907348
Lenalidomide + R-ICE (as a salvage regimen)	CRBN (IRF4) CD20	61.5 (41-75) years	15	ORR: 73% CR: 60% PR: 13%	NA	Phase I/II	[203] Trial-No: NCT01241734
CC-122 + Obinutuzumab (GA101)	CRBN (Aiolos, Ikaros, IRF4) CD20	64 (estimated)	NA	NA	NA	Ongoing phase Ib	[56] Trial-No: NCT02417285
CC-122 + Rituximab	CRBN (Aiolos, Ikaros, IRF4) CD20	NA	NA	NA	NA	Ongoing phase Ib	[56] Trial-No: NCT02031419
Epratuzumab + R-CHOP	CD22 CD20	58 (21-82) years	107 (81)	ORR: 96% CR/CRu: 74% PR: 22%	2y-PFS: 77% 2y-EFS: 70% 2y-OS: 80%	Phase II	[7] Trial-No: NCT00301821
Epratuzumab + Rituximab	CD22 CD20	56 (24-78) years	15	ORR: 47% CR/CRu: 33% PR: 22%	DOR: 6 m 1y-PFS: 13.5%	Phase II	[214]
Bortezomib	Proteasome	56	40 (35)	ORR: 88%	2y-PFS: 64%	Phase II	[215]

+ R-CHOP	(NF-κB) CD20	(20-87) years		CR/CRu: 75% PR: 13%	2y-OS: 70%		Trial-No: NCT00151320
Bortezomib + R-CHOP	Proteasome (NF-κB) CD20	50	NA	NA	NA	Phase II	Trial-No: NCT00379574
Bortezomib + R-CHOP	Proteasome (NF-κB) CD20	170 (estimated)	NA	NA	NA	Phase II	Trial-No: NCT01040871
Bortezomib + R-ICE	Proteasome (NF-κB) CD20	NA	NA	NA	NA	Ongoing phase I	Trial-No: NCT01226849
Bortezomib + DICE	Proteasome (NF-κB)	NA	NA	NA	NA	Ongoing phase II	Trial-No: NCT00504751
Bortezomib + R-CHOP	Proteasome (NF-κB) CD20	NA	NA	NA	NA	Ongoing phase IIII	Trial-No: NCT01324596
Bortezomib + R-DHAP With ASCT.	Proteasome (NF-κB) CD20	NA	NA	NA	NA	Ongoing phase II/III	Trial-No: NCT01805557
Carfilzomib + Rituximab + Ifosfamide/Carboplatin/ Etoposide	Proteasome (NF-κB) CD20	NA	NA	NA	NA	Ongoing Phase I/II	Trial-No: NCT01959698
Everolimus (RAD001) + Rituximab	mTORC1 CD20	65 (33-87) years	24	ORR: 37.5 % CR: 12.5% PR: 25% SD: 8% PD: 54%	DOR: 8.1 m 1y-PFS: 22% 1y-OS: 37%	Phase II	[216] Trial-No: NCT00869999
Temsirolimus + R-DHAP	mTORC1 CD20	NA	NA	NA	NA	Ongoing phase II	[71, 217, 218] Trial-No: NCT01653067 (STORM)
Vorinostat + R-CHOP	HDACs (HDAC (2)3/4) CD20	NA	NA	NA	NA	Ongoing Phase I/II	[198] Trial-No: NCT00667615
Vorinostat + High-Dose Gemcitabine, Busulfan, Melphalan with ASCT	HDACs (HDAC (2)3/4)	44 (12-65) years	52 (28)	ORR: 96% CR: 73%	2y-EFS: 61.5% 2y-OS: 73%	Phase I	[219] Trial-No: NCT01421173
Alemtuzumab (anti CD52 antibody)	CD52 CD20	NA	NA	NA	NA	Ongoing phase II	Trial-No: NCT01030900

+ Rituximab + DA-EPOCH							
ABT-199 + Bendamustine + Rituximab	BCL2 CD20	NA	NA	NA	NA	Ongoing phase I/II	Trial-No: NCT01594229
CPI-613 (novel tumor-specific anti-mitochondrial agent) + Bendamustine + Rituximab	Mitochondrial metabolism CD20	NA	NA	NA	NA	Ongoing phase I	[220] Trial-No: NCT02168907

DLBCL diffuse large B cell lymphoma, *ABC* activated B cell-like, *GCB* germinal center B cell-like, *ORR* overall response rate, *PR* partial response, *CR* complete response, *CRu* unconfirmed CR, *SD* stable disease, *PD* progressive disease, *DOR* median duration of response, *OS* median overall survival, *PFS* median progression-free survival, *EFS* median event-free survival, *FFS* median failure-free survival; *NA* not available/not applicable, *m* months, *y* year, *ASCT* autologous stem-cell transplantation, *R-CHOP* rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, *DHAP* dexamethasone, cytarabine, and cisplatinum, *DA-EPOCH-R* etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab, *R-ICE* rituximab, ifosfamide, carboplatin and etoposide, *D-ICE* dexamethasone, ifosfamide, carboplatin, etoposide, *IRF4* interferon response factor 4, *BTK* Brutons' tyrosine kinase, *NF-κB* nuclear factor-kappa B, *mTORC1* mammalian target of rapamycin (mTOR) complex 1, *HDAC* histone deacetylase, *DMNT* DNA methyltransferase, *CRBN* cereblon

Table S6

Ongoing clinical experimental studies with JAK/STAT inhibitors in aggressive B-cell lymphoma including DLBCL and relapsed/refractory DLBCL

Treatment	Targets	Patient characteristics	Relapsed/ refractory DLBCL	Clinical trial	Study
Pacritinib (SB1518) Oral JAK2/ FLT3 inhibitor	JAK2/JAK2(V617F FLT3 kinase (STAT1, STAT3, STAT5)	Patient No.: 5 Age: 18 to 65 y;	No	Completed phase I	[221] Trial-No: NCT00741871
INCB039110 Oral JAK1 inhibitor	JAK1 (STAT1, STAT3)	Patient No.: NA Age: 18 -	Yes	Ongoing phase I	Trial-No: NCT01905813
Ruxolitinib (INCB18424) Oral JAK1/JAK2 inhibitor	JAK1/JAK2 (STAT1, STAT3)	Patient No.: NA Age: 19-	Yes	Ongoing phase II	[222] Trial-No: NCT01431209

DLBCL diffuse large B cell lymphoma, *JAK* Janus kinase, *STAT* signal transducer and activator of transcription, *FLT3* fms-related tyrosine kinase 3

Table S7: Experimental clinical studies evaluating antibody-drug conjugates (ACD) as front-line or second-line treatment in DLBCL (as single agent or in combination)

Treatment	Type of Treatment	Age	No. of DLBCL patients	Response rate	Response duration	Clinical trial	Study
Brentuximab Vedotin	Second-line	62 (17-85) years	50 (49)	ORR: 44% CR: 17% PR: 27% SD: 23% PD: 33%	DOR: 5.8m DOR (CR): 16.6m PFS: 4m OS: NA	Completed phase II	[18, 223] Trial-No: NCT01421667
Brentuximab Vedotin + Rituximab	Second-line	62 (22-78) years	16	ORR: 46% CR: 15% PR: 31%	NA	Completed phase II	[18, 223] Trial-No: NCT01421667
Brentuximab Vedotin +/- Lenalidomide	Second-line	NA	NA	NA	NA	Ongoing Phase 1	Trial-No: NCT02086604
Brentuximab-Vedotin +/- R-CHOP or R-CHP	Front-line	NA	NA	NA	NA	Ongoing phase II	Trial-No: NCT01925612
Inotuzumab ozogamicin (INO) + Rituximab	Second-line	72 (33-85) years	67	ORR: 74% CR: 50% PR: 25%	Relapsed: 1y-PFS: 55% 2y-PFS: 42% 1y-OS: 80% 2y-OS: 69% Refractory: 2y-PFS: 10%	Completed phase I/II	[20] Trial-No: NCT00299494
Inotuzumab Ozogamicin (CMC-544) +/- Rituximab	Second-line	60 (19-75) years	63	ORR: 40% CR: 21% PR: 26%	1y-PFS: 28.9% 2y-PFS: 25.3%	Completed phase II	[224] Trial-No: NCT00867087
Inotuzumab Ozogamicin (CMC-544) +/- R-GEMOX	Second-line	NA	NA	NA	NA	Ongoing phaseI/II	Trial-No: NCT01562990
Inotuzumab Ozogamicin +/- R-CVP	Front-line	NA	154 (estimated)	NA	NA	Ongoing phase II	Trial-No: NCT01679119
Inotuzumab ozogamicin (INO) + Rituximab	Second-line	NA	NA	NA	NA	Ongoing phase II	Trial-No: EudraCT 2008-007802-12
SAR3419	Second-line	66 (41-80) years	5 (39)	Reduced tumors: 76%	NA	Completed Phase I	[11] Trial-No: NCT00549185
SAR3419	Second-line	67 (36-82) 70 (37-85)	25 16 (week.) 9 (optim.)	ORR: 30% Reduced tumors: 64%	8 weeks (NA)	Completed Phase I	[12]

		years					
SAR3419 +/- Rituximab	Second-line	NA	50	NA	NA	Completed Phase II	Trial-No: NCT01470456
SAR3419	Second-line	NA	55 (estimated)	NA	NA	Ongoing Phase II	[12] Trial-No: NCT01472887
SGN-CD19A	Second-line	NA	45	ORR: 35% CR: 20% PR: 16% Relapsed ORR: 55% CR: 35% PR: 23% (preliminary data)	NA	Ongoing Phase I	[225, 226] Trial-No: NCT01786135
MEDI-551 (anti CD19 ADC) + Rituximab + ICE or DHAP	Second-line	NA	NA	NA	NA	Ongoing phase II	Trial-No: NCT01453205
Pinatuzumab Vedotin (DCDT2980S) + Rituximab or Obinutuzumab	Second-line	NA	28	ORR: 43% CR: 18% PR: 25% SD: 14% PD: 43%	DOR: 6m	Completed phase I	[15, 227] Trial-No: NCT01209130 (ROMULUS)
Moxetumomab Pasudotox (HA22, anti CD22 ADC)	Second-line	NA	87 (estimated)	NA	NA	Completed Phase I/II	Trial-No: NCT01030536
Polatuzumab Vedotin (DCDS4501A) + Rituximab	Second-line	67 (20–81) years	27	ORR: 56% CR: 14.8% PR: 37% SD: 37% PD: 14.8%	DOR (CR): 5.2 m DOR (PFS): 5 m	Completed phase I	[15, 227, 228] Trial-No: NCT01290549 (ROMULUS)
Polatuzumab Vedotin (DCDS4501A) + Rituximab + Cyclophosphamide, Doxorubicin and Prednisone	First-line	NA	NA	NA	NA	Ongoing phase I	[228] Trial-No: NCT01992653
Polatuzumab Vedotin (DCDS4501A) + Rituximab	Second-line	NA	NA	NA	NA	Ongoing phase II	Trial-No: NCT01691898
Polatuzumab Vedotin (DCDS4501A)	Second-line	NA	NA	NA	NA	Ongoing phase II	Trial-No: NCT02257567

+ Rituximab or Obinutuzumab + Bendamustine							

DLBCL diffuse large B cell lymphoma, *ORR* overall response rate, *PR* partial response, *CR* complete response, *CRu* unconfirmed CR, *SD* stable disease, *PD* progressive disease, *DOR* median duration of response, *OS* median overall survival, *PFS* median progression-free survival, *EFS* median event-free survival, *FFS* median failure-free survival, *NA* not available/not applicable, *m* months, *y* year, *ASCT* autologous stem-cell transplantation, *R-CHOP* rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, DHAP dexamethasone, cytarabine, and cisplatinum, *R-GEMOX* rituximab, gemcitabine and oxaliplatin.

Brentuximab-Vedotin is an affinity-optimized monoclonal anti-CD30 antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE). Vedotin is the commercial name for the microtubule disrupting agent monomethyl auristatin E (MMAE), Inotuzumab ozogamicin is an affinity-optimized monoclonal anti-CD22 antibody linked to the DNA damaging toxin N-acetyl-γ-calicheamicin dimethyl hydrazide (CalichDMH). Moxetumomab Pasudotox (HA22/ BL22) is an affinity-optimized monoclonal anti-CD22 antibody linked to a mono-ADP-ribosylating Pseudomonas Exotoxin. SAR3419 is an affinity-optimized monoclonal anti-CD19 antibody linked to the cytotoxine Maytansine. SGN-CD19A is an affinity-optimized monoclonal anti-CD19 antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE). MEDI-551 is an affinity-optimized and afucosylated monoclonal anti CD19 antibody with enhanced antibody-dependent cellular cytotoxicity. Pinatuzumab-Vedotin is an affinity-optimized monoclonal anti-CD22 antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE). Polatuzumab Vedotin is an affinity-optimized monoclonal anti-CD79B antibody linked to the microtubule disrupting agent monomethyl auristatin E (MMAE).

Table S8:

Experimental clinical studies evaluating anti-CD19 or anti-CD20 Chimeric Antigen Receptor T cells as second-line treatment in relapsed/refractory DLBCL

Inhibitor or Agent	Target or Agent mechanism	No. of patients	Response rate (DLBCL Subtype)	Response duration	Clinical trials	Study
Anti-CD19 CAR T cells	CD19 (T cells expressing anti-CD19 CARs recognize and kill CD19+ target cells)	7	CR/CRu: 57.1% PR: 28.5% SD: 14.3% (preliminary data)	Not yet available	Ongoing phase I	[5, 6] Trial-No: NCT00924326
Anti-CD19 CAR T cells	CD19+ target cells	12	ORR: 50% CR/Cru: 45% (preliminary data)	6m-PFS: 37% (preliminary data)	Ongoing phase II	[229] Trial-No: NCT02030834
Anti-CD19 CAR T cells	CD19+ target cells	NA	NA	NA	Ongoing phase II	Trial-No: NCT02445248
Anti-CD19 CAR T cells	CD19+ target cells	NA	NA	NA	Ongoing phase I	Trial-No: NCT01840566
Anti-CD19 CAR T cells	CD19+ target cells	NA	NA	NA	Ongoing phase I/II	Trial-No: NCT01865617
Anti-CD19 CAR T cells	CD19+ target cells	NA	NA	NA	Ongoing phase I/II	Trial-No: NCT01475058
Anti-CD19 CAR T cells	CD19+ target cells	NA	NA	NA	Ongoing phase I/II	Trial-No: NCT02431988
Anti-CD19 CAR T cells	CD19+ target cells	NA	NA	NA	Ongoing phase I/II	Trial-No: NCT02348216
Anti-CD20 CAR T cells	CD20 (T cells expressing anti-CD19 CARs recognize and kill CD20+ target cells)	NA	NA	NA	Ongoing pilot study	[230] Trial-No: NCT01735604

DLBCL diffuse large B cell lymphoma, *ORR* overall response rate, *PR* partial response, *CR* complete response, *CRu* unconfirmed CR, *SD* stable disease, *PFS* median progression-free survival, *NA* not available, *m* month,

Table S9

Ongoing clinical experimental studies with ARTD/PARP inhibitors in aggressive B-cell lymphoma including DLBCL and relapsed/refractory DLBCL

Treatment	Targets	Patient characteristics	Relapsed/ refractory DLBCL	Clinical trial	Study
Veliparib (ABT-888) + Cyclophosphamide	ARTD1-3 (PIM1?, CDK9?)	Patient No.: NA Age: 18 -	Yes	Ongoing phase I/II	Trial-No: NCT00810966
Veliparib (ABT-888) + Bendamustine + Rituximab	ARTD1-3 (PIM1?, CDK9?) CD20	Patient No.: NA Age: 18 -	Yes	Ongoing phase I/II	Trial-No: NCT01326702
Veliparib (ABT-888) + Cyclophosphamide + Doxorubicin	ARTD1-3 (PIM1?, CDK9?)	Patient No.: NA Age: 18 -	Yes	Ongoing phase I	Trial-No: NCT00740805

DLBCL diffuse large B cell lymphoma, *ARTD* ADP-ribosyltransferase diphteria toxin like, *PARP* poly-ADP-ribose-polymerase, *PIM1* (Proviral Integration site for the Moloney murine leukemia virus) kinase 1, *CDK9* cyclin-dependent kinase 9

Table S10

Pre-clinical multi-targeted combinatorial experimental treatments for DLBCL-NOS

Treatment Combination	**Targets**	**DLBCL subtype(s) where effect was observed**	**Effects in refractory DLBCL *in vitro* or *in vivo*?**	***In vivo* effects in xenograft or B-cell lymphoma mice models**	**Study**
JAKi1/2 + MLN120B	STAT3 IKKβ/ NF-κB	ABC, (n.c.i.)	NA	NA	[28]
Bortezomib/ carfilzomib + ABT737/ Obatoclax	Proteasome (NF-κB) BCL2	GCB, ABC	Yes; carfilzomib/obatoclax regimen potently induced apoptosis in bortezomib-resistant GCB and ABC cell lines *in vitro*	Obatoclax strongly potentiated carfilzomib-induced growth suppression of GCB tumors in xenograft models	[26, 78]
Bortezomib + Thiostrepton	Proteasome (NF-κB) FoxM1	GCB, (n.c.i.)	NA	NA	[174]
Ibrutinib + Bortezomib/ Carfilzomib	BTK Proteasome (NF-κB)	GCB, ABC (BCR signature)	Yes; Ibrutinib/borte-zomib regimen potently induced apoptosis in highly bortezomib-resistant GCB and ABC cell lines *in vitro*	NA	[27, 68]
Ibrutinib + GDC-0980/ Everolimus	BTK mTORC1	ABC, (BCR signature)	NA	NA	[68]
Ibrutinib + Idelalisib (GS-1101, CAL-101)/ BKM-120	BTK PI3K isoforms	ABC, (BCR signature)	NA	NA	[68]
Ibrutinib + MK-2206	BTK AKT	ABC, (BCR signature)	NA	NA	[68]
Ibrutinib + PRT-060318	BTK SYK	ABC, (BCR signature)	NA	NA	[68]
Ibrutinib + Navitoclax (ABT-263)/ ABT-199	BTK BCL2	ABC, (BCR signature)	NA	NA	[68]
Ibrutinib + Lenalidomide	BTK IRF4	ABC, (BCR signature)	NA	Lenalidomide synergized strongly with ibrutinib in suppression of the growth of ABC tumors in xenograft models	[52]
Ibrutinib +	BTK mTORC1/2	ABC, (BCR	NA	Ibrutinib synergized strongly with AZD2014 in tumor	[68, 73]

AZD2014		signature)		regression of ABC tumors in xenograft models	
Ibrutinib + NVP-BEZ-235	BTK mTORC1/2 PI3K, (DNA-PK)	ABC, (BCR signature)	NA	NA	[68]
Ibrutinib + CPI203 and JQ1	BTK NF-κB BRD2/4 (c-Myc?)	ABC, (BCR signature)	NA	Ibrutinib, synergized strongly with BET inhibitors in killing ABC tumors in xenograft models	[122]
Ibrutinib + SP600125	BTK JNKs	ABC, (BCR signature?) (n.c.i.)	NA	NA	[155]
Ibrutinib + OTX015	BTK NF-κB BRD2/4 (c-Myc?)	ABC, (BCR signature)	NA	NA	[130]
OTX015 + Rituximab,	BRD2/4 (c-Myc?) CD20	ABC, GCB, type-3 (strongest effect in ABC) (n.c.i.)	NA	NA	[130]
OTX015 + lenalidomide	BRD2/4 (c-Myc?) CRBN (IRF4)	ABC, GCB, type-3 (strongest effect in ABC) (n.c.i.)	NA	NA	[130]
OTX015 + Idelalisib	BRD2/4 (c-Myc?) PI3Kδ	ABC, GCB, type-3 (strongest effect in ABC) (n.c.i.)	NA	NA	[130]
OTX015 + Everolimus	BRD2/4 (c-Myc?) mTORC1	ABC, GCB, type-3 (n.c.i.)	NA	NA	[130]
OTX015 + Decitabine	BRD2/4 (c-Myc?) DMNTs	ABC, GCB, type-3 (n.c.i.)	NA	NA	[130]
OTX015 + Vorinostat	BRD2/4 (c-Myc?) HDACs	ABC, GCB, type-3 (n.c.i.)	NA	NA	[130]
U73122 + Enzastaurin/pp2	PLCγ2 PKCβ/SRC	ABC, GCB (n.c.i.)	NA	NA	[64]
Ricolinostat (ACY-1215) + Carfilzomib (CFZ)	HDAC6 Proteasome (NF-κB)	GCB, ABC (n.c.i.)	NA	NA	[146]
Ricolinostat (ACY-1215)	HDAC6 Proteasome	ABC, GCB (n.c.i.)	NA	Combination treatment demonstrated significant	[231]

+ Bortezomib	(NF-κB)			tumor growth delay and prolonged overall survival in xenograft mouse model of DLBCL	
Vorinostat + Carfilzomib (CFZ)	HDACs Proteasome (NF-κB)	GCB, ABC (n.c.i.)	Yes; Vorinostat / CFZ regimen potently induced apoptosis in partially bortezomib-resistant GCB and ABC cell lines *in vitro*	Subeffective vorinostat doses synergized strongly with CFZ in tumor growth suppression and apoptosis of ABC tumors in xenograft models	[25]
Vorinostat + Niacinamide	HDACs Sirtuins	ABC, GCB, type3 (n.c.i.)	Niacinamide /Vorinostat combination showed some effects in patients with relapsed or refractory DLBCL in a phase 1 proof-of-principle clinical trial	Niacinamide /Vorinostat combination treatment synergistically produced remissions in a spontaneous aggressive B-cell lymphoma mouse model expressing Bcl6	[145]
Vorinostat + ABT-737	HDACs BCL2	GCB, (n.c.i.)	NA	NA	[79]
Vorinostat + Enzastaurin	HDACs PKCβ	GCB, ABC (n.c.i.)	NA	NA	[232]
Vorinostat / Panobinostat (LBH-589) + Decitabine	HDACs DMNTs	GCB (strong effects) ABC (weak effects) (n.c.i.)	NA	Vorinostat/ Decitabine combination treatment synergistically inhibited the growth of GCB tumors in xenograft models	[233]
Vorinostat / Panobinostat (LBH-589) + JQ1/ RVX2135	HDACs BRD2-4	NA	NA	Vorinostat / RVX2135 combination treatment synergistically produced remissions in a murine model of aggressive MYC driven B Cell lymphoma	[234]
Panobinostat (LBH-589) + Rapamycin	HDACs (HDAC3/4) mTORC1	GCB, (n.c.i.)	NA	NA	[74]
Panobinostat (LBH-589) + NVP-BEZ235	HDACs (HDAC3/4) mTORC1/2 PI3K (DNA-PK)	ABC, GCB, type3 (incl. BCL/ c-MYC double-hit DLBCL) (n.c.i.)	NA	BEZ235/panobinostat combination treatment synergistically inhibited the growth of GCB tumors in xenograft models and combined treatment increased animal survival compared with single agents.	[235]
ABT-263 + Rapamycin	BCL2 mTORC1	GCB, (n.c.i.)	NA	ABT-263/ Rapamycin combination treatment synergistically induced tumor regression, with GCB tumors	[236]

				showing 100% ORR in xenograft models	
ABT-737 + Cyclopamine-KAAD	BCL2 SMO	GCB, (ABC? n.c.i.)	NA	NA	[237]
ABT-199 + Dinaciclib	BCL2 CDK1, CDK2, CDK5, CDK9, (MCL1)	GCB, (ABC? n.c.i.)	NA	ABT-199/ dinaciclib combination treatment synergistically induced tumor regression, in xenografts and in a genetically accurate murine model of MYC-BCL2 double-hit lymphoma	[89]
AG490 or STA-21 + YM155	STAT3 (?) (STAT1?) Survivin	GCB, (n.c.i.)	NA	NA	[91]
YM155 + Rituximab	Survivin CD20	ABC, GCB, (n.c.i.)	NA	YM155/ Rituximab combination treatment synergistically induced tumor growth inhibition and tumor regression in GCB and ABC tumors in xenograft models	[93]
CGS-21680 (AdR agonist) + Trequinsin	Adenosine A2A receptor, Phosphodi-esterases (PDE) 2-4	ABC, GCB, type3 (n.c.i.)	NA	NA	[178]
CGS-21680 / Salmeterol (AdR agonists) + Dexamethasone (GR agonist)	Adenosine A2A receptor, glucocorticoid receptor (GR)	ABC, GCB, type3 (n.c.i.)	NA	NA	[238]
Cyclopamine-KAAD + BAY-11-7082	SMO NF-κB	GCB (ABC? n.c.i.)	NA	NA	[29]
ERK inhibitor 76 + CHK2 inhibitor II	ERK1/2 CHK2	ABC, GCB, type3 (n.c.i.)	NA	Concurrent administration of ERK inhibitor 76 enhanced the antitumour activity of CHK2 inhibitor II in GCB tumors in xenograft models	[149]
Rapamycin + UCN-01	mTORC1 CDK1	GCB (n.c.i.)	NA	NA	[158]
Rapamycin +	mTORC1 AKT	GCB (n.c.i.)	Yes, rapamycin showed synergistic effects with	NA	[69]

Nelfinavir /MK-2206			nelfinavir or MK-2206 in inhibiting cell viability in rapamycin-resistant GCB cell lines		
Everolimus (RAD001) + NVP-BEZ235	mTORC1/2 PI3K (DNA-PK)	GCB (strong effects) ABC (weak effects) (n.c.i.)	NA	NA	[239]
Temsirolimus + Idelalisib	mTORC1 PI3K	GCB, ABC, (additive effects) (n.c.i.)	NA	NA	[240]
Temsirolimus + Ibrutinib	mTORC1 BTK	ABC, (additive effects) (n.c.i.)	NA	NA	[240]
Temsirolimus + Bortezomib	mTORC1 NF-κB	ABC (additive effects) (antagonistic effects in some GCB cells) (n.c.i.)	NA	NA	[240]
NVP-BKM120 + chloroquine/3-methyladenine/Bafilomycin A 1	PI3K Autophagy	GCB, ABC (n.c.i.)	NA	NA	[65]
Bortezomib + chloroquine	Proteasome (NF-κB) Autophagy	ABC, GCB (n.c.i.)	NA	NA	[241]
RI-BPI + SAHA, TSA, or VPA	BCL6 HDACs	GCB, ABC (n.c.i.)	NA	SAHA strongly potentiated RI-BPI mediated growth suppression of GCB tumors in xenograft models	[97]
RI-BPI + 17-DMAG, PU-H71	BCL6 HSP90	GCB, ABC (n.c.i.)	NA	PU-H71 strongly potentiated RI-BPI mediated growth suppression of GCB tumors in xenograft models	[97]
BL22 (anti-CD22 immunotoxin) + Bryostatin 1	CD22 PKCβII	GCB, ABC? (n.c.i.)	NA	NA	[21]

DLBCL diffuse large B cell lymphoma, *ABC* activated B cell-like, *GCB* germinal center B cell-like, *OxPhos* oxidative phosphorylation subtype, *BCR* BCR-activated B-cell (antigen) receptor/proliferation subtype**,** *HR* host response signature subtype, *MD* c-MYC-driven signature subtype, *n.c.i.* not completely investigated, *NA* not available/not analyzed, *type-3* unclassified DLBCL-NOS, *NF-κB* nuclear factor-

kappa B, *STAT* signal transducer and activator of transcription, *IRF4* interferon response factor 4, *IKK* inhibitor of kappa B kinase, *BRD* BET bromodomain protein, *HDACs* histone deacetylases, *DMNT* DNA methyltransferase, *BTK* Brutons' tyrosine kinase, *SMO* smoothened, frizzled class receptor, *CDK* cyclin-dependent kinase, *MCL1* myeloid cell leukemia 1, *mTORC1* mammalian target of rapamycin (mTOR) complex 1, *PI3K* phosphoinositide 3-kinase, *BCL* B-cell lymphoma protein, *HSP* heat shock protein, *FoxM1* forkhead box M1, *CHK1/2* Chk1 protein kinase 1/2, *PKCβ* protein kinase Cβ, *CRBN* cereblon

Table S11: Dual inhibitors currently evaluated in preclinical and/or clinical studies in DLBCL

Dual Inhibitor	Targets	Manufacturer	DLBCL subtype(s) where effect was observed *in vitro* or *in vivo*	*In vivo* effects in xenograft or B-cell lymphoma mice models	Clinical trial	Study
OSI-027	mTORC1/2	OSI Pharmaceuticals	(n.c.i.)	OSI-027 markedly diminished proliferation and induced apoptosis in a variety of lymphoid cell lines and induced tumor regressions in B-cell lymphoma xenograft models	Completed phase I	[242] Trial-No: NCT00698243
CC-223	mTORC1/2	Celgene Corporation	ABC, GCB, type3 (n.c.i.)	NA	Ongoing phase I Ongoing phase I/II	Trial-No: NCT02031419 NCT01177397 [75]
AZD2014	mTORC1/2	AstraZeneca	ABC, (n.c.i.)	AZD2014 treatment inhibited the growth of ABC tumors in xenograft models and increased animal survival.		[73]
NVP-BEZ235	mTORC1/2 PI3Ks (DNA-PK)	Novartis	ABC, GCB, type3 (incl. double-hit DLBCLs) (n.c.i.)	BEZ235 treatment inhibited the growth of GCB tumors in xenograft models and increased animal survival.		[68, 235, 239, 243]
PRT062070 (Cerdulatinib)	SYK JAK1/3	Portola Pharmaceuticals	GCB, (n.c.i.)	NA	Ongoing phase I	[244] Trial-No: NCT01994382
QL-X-138	BTK MNK		ABC, (n.c.i.)	NA		[245]

DLBCL diffuse large B-cell lymphoma, *ABC* activated B cell-like, *GCB* germinal center B cell-like, *type-3* unclassified DLBCL-NOS, *mTORC1/2* mammalian target of rapamycin (mTOR) complex 1/2, *PI3K* phosphoinositide 3-kinase, *DNA-PK* DNA dependent protein kinase, *SYK* spleen tyrosine kinase, *JAK* Janus kinase, *BTK* Brutons' tyrosine kinase, *MNK* mitogen-activated protein kinase interacting kinase 1 and 2 (MNK1/2), *n.c.i.* not completely investigated, *NA* not available/not analyzed

Table S12

Ongoing experimental clinical multi-targeted studies combining novel experimental agents with or without conventional (immuno-)chemotherapy in first-line treatment of newly diagnosed DLBCL

Treatment	Targets	Clinical trial	Study
Sotrastaurin (AEB071) + Everolimus (RAD001) (in patients with CD79-mutant or ABC DLBCL)	PKCβ mTORC1	Ongoing phase Ib/II	Trial-No: NCT01854606

DLBCL diffuse large B-cell lymphoma, *ABC* activated B cell-like, *GCB* germinal center B cell-like, *PKCβ* protein kinase Cβ, *mTORC1/2* mammalian target of rapamycin (mTOR) complex 1/2,

Table S13

Completed experimental clinical multi-targeted studies combining novel experimental agents in relapsed/refractory DLBCL

Inhibitor or Agent	Target or Agent mechanism	No. of patients	Response rate (DLBCL Subtype)	Response duration	Clinical trials	Study
Temsirolimus + Bortezomib	mTORC1 Proteasome (NF-κB)	18	ORR: 16.7% CR: 11.1 % PR: 5.5%	DOR: 11.3 m PFS: 2 m	Phase II	[246] Trial-No: NCT01281917
Decitabine + Vorinostat	DNMT1-3 HDACs	NA	NA	NA	Completed phase I	Trial-No: NCT00275080
Decitabine (DAC) +/- Valproic acid	DNMT1-3 HDACs (HDAC (2)3/4)	NA	NA	NA	Completed phase I	Trial-No: NCT00109824

DLBCL diffuse large B-cell lymphoma, *ORR* overall response rate, *PR* partial response, *CR* complete response, *DOR* median duration of response, *OS* median overall survival, *PFS* median progression-free survival, *NA* not available/not applicable, *m* months, *mTORC1* mammalian target of rapamycin (mTOR) complex 1, *HDACs* histone deacetylases, *DNMTs* DNA methyltransferases, *NF-κB* nuclear factor-kappa B.

Table S14

Ongoing experimental clinical multi-targeted studies combining novel experimental agents with or without conventional (immuno-)chemotherapy in relapsed/refractory DLBCL

Treatment	Targets	Results	Clinical trial	Study
Decitabine + Vorinostat	DNMT1-3 HDACs	NA	Completed phase I	Trial-No: NCT00275080
Decitabine (DAC) +/- Valproic acid	DNMT1-3 HDACs (HDAC (2)3/4)	NA	Completed phase I	Trial-No: NCT00109824
Idelalisib + ONO/GS-4059	PI3Kδ BTK		Ongoing phase I	Trial-No: NCT02457598
Lenalidomide + Ibrutinib	CRBN (IRF4) BTK	NA	Ongoing phase I	Trial-No: NCT01955499
Lenalidomide + Ibrutinib +/- Rituximab	CRBN (IRF4) BTK CD20	NA	Ongoing phase I/II	Trial-No: NCT02077166
Lenalidomide + Ibrutinib + DA-EPOCH-R	CRBN (IRF4) BTK CD20	NA	Ongoing phase I/II	Trial-No: NCT02142049
Lenalidomide + Everolimus (RAD001)	CRBN (IRF4) mTORC1	NA	Ongoing phase I/II	Trial-No: NCT01075321
Lenalidomide + Obinutuzumab (GA101)	CRBN (IRF4) CD20	NA	Ongoing phase Ib/II	Trial-No: NCT01582776
CC-122 + CC-223 +/- Rituximab	CRBN (Aiolos, Ikaros, IRF4) mTORC1/mTORC2 CD20	NA	Ongoing phase Ib	[56] Trial-No: NCT02031419
CC-122 + CC293 +/- Rituximab	CRBN (Aiolos, Ikaros, IRF4) BTK CD20	NA	Ongoing phase Ib	[56] Trial-No: NCT02031419
CC-223 + CC293 +/- Rituximab	mTORC1/mTORC2 BTK CD20	NA	Ongoing phase Ib	[56] Trial-No: NCT02031419
Panobinostat (LBH-589) + Rituximab	HDACs CD20	NA	Ongoing Phase I/II Ongoing Phase II	[198] Trial-No: NCT01238692, NCT01282476
Vorinostat + Azacytidine (AZA)	HDACs (HDAC (2)3/4) DNMT1/2	NA	Ongoing Phase I/II	[198] Trial-No: NCT01120834
Vorinostat + Bortezomib	HDACs (HDAC (2)3/4) Proteasome (NF-κB)	NA	Ongoing Phase II	[198] Trial-No: NCT00703664
Vorinostat + Carfilzomib	HDACs (HDAC (2)3/4) Proteasome (NF-κB)	NA	Ongoing Phase I	Trial-No: NCT01276717

Belinostat (PXD-101) + Carfilzomib	HDACs Proteasome (NF-κB)	NA	Ongoing Phase I	Trial-No: NCT02142530
Idelalisib (GS-1101) + Entospletinib (GS-9973)	PI3K SYK	NA	Ongoing Phase II	[247] Trial-No: NCT01796470
INCB040093 (PI3Kδ inhibitor) + INCB039110 (JAK1 inhibitor)	PI3K JAK1 (STAT1, STAT3)	NA	Ongoing Phase I	Trial-No: NCT01905813
Lenalidomide + Dexamethasone + Rituximab	CRBN (IRF4) CD20 GR	NA	Ongoing phase I/II	[248]
Nivolumab + Ipilimumab	PD-1 CTLA-4	NA	Ongoing phase I	Trial-No: NCT01592370
Nivolumab + Lirilumab	PD-1 KIR	NA	Ongoing phase I	Trial-No: NCT01592370
MPDL3280A (anti-PD-L1 antibody) + Obinutuzumab (GA101)	PD-1 CD20 (Obinutuzumab is a novel humanized Type II anti-CD20 monoclonal antibody)	NA	Ongoing phase I	Trial-No: NCT02220842
MEDI4736 (anti-PD-L1 antibody) + Ibrutinib	PD-1 BTK	NA	Ongoing phase I/II	Trial-No: NCT02401048
Veltuzumab + 90Y-Epratuzumab- Tetraxetan (Radioimmunotherapy)	CD20 CD22 + Radioimmunotherapy (radiolabeled anti CD22 antibody, 90Y-epratuzumab tetraxetan)	NA	Ongoing phase II	[204] Trial-No: NCT01101581

DLBCL diffuse large B-cell lymphoma, *DA-EPOCH-R* etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin plus rituximab, *IRF4* interferon-regulatory factor 4, *mTORC1* mammalian target of rapamycin (mTOR) complex 1, *BTK* Bruton's tyrosine kinase, *HDACs* histone deacetylases, *DNMTs* DNA methyltransferases, *NF-κB* nuclear factor-kappa B, *PI3K* phosphoinositide 3-kinase, *SYK* spleen tyrosine kinase, *JAK* Janus kinase, *STAT* signal transducer and activator of transcription, *GR* glucocorticoid receptor, *PD-1* programmed cell death 1, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *KIR* inwardly rectifying potassium channel, *CRBN* cereblon

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