

Epidemiology and real-world treatment of incident diffuse large B-cell lymphoma (DLBCL): A German claims data analysis

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Supplementary Data

Table S1. Treatments for DLBCL and corresponding ATC/OPS codes

Treatments of interest	Agent/Therapy	ATC Code (outpatient)	OPS Code (inpatient)
Chemotherapy	Instillation of and locoregional therapy with cytotoxic materials and immunomodulators	-	8-541.-
	Non-complex chemotherapy	-	8-542.-
	Moderately complex and intensive block chemotherapy	-	8-543.-
	Highly complex and intensive block chemotherapy	-	8-544.-
	Hyperthermic chemotherapy	-	8-546.-
	Aclarubicin	L01DB04	-
	Bendamustine	L01AA09	-
	Capecitabine	L01BC06	-
	Carboplatin	L01XA02	-
	Carmustine	L01AD01	6-003.3
	Chlorambucil	L01AA02	-
	Cisplatin	L01XA01	-
	Cyclophosphamide	L01AA01	-
	Cytarabine	L01BC01	-
	Cytarabine	L01BC01	6-002.a; 6-00b.6
	Dacarbazine	L01AX04	-
	Doxorubicin	L01DB01	6-001.b; 6-002.8
	Etoposide	L01CB01	-
	Fludarabine	L01BB05	-
	Gemcitabine	L01BC05; H02AB06; H02BX06	-
	Hydroxycarbamide	L01XX05	-
	Ifosfamide	L01AA06	-
	Melphalan	L01AA03	-
	Methotrexate	L01BA01; L04AX03	-
	Mitoxantrone	L01DB07	-
	Oxaliplatin	L01XA03	-
	Procarbazine	L01XB01	-
Vincristine	L01CA02	-	
Vinorelbine	L01CA04	-	
Demethylation agents	Azacitidine	L01BC07	6-005.0
	Decitabine	L01BC08	6-004.4
Histone deacetylase	Panobinostat	L01XH03; L01XX42	6-009.2
Immunomodulators	Lenalidomide	L04AX04	6-003.g
	Pomalidomide	L04AX06	6-007.a
	Thalidomide	L04AX02	-
	Immunotherapy with immunomodulators	-	8-547.2
	Immunosuppression	-	8-547.3
Kinase inhibitors	Ruxolitinib	L01EJ01; L01XE18	6-009.4
	Ibrutinib	L01EL01; L01XE27;	6-007.e

Treatments of interest	Agent/Therapy	ATC Code (outpatient)	OPS Code (inpatient)
		L01XC02	
	Idelalisib	L01EM01; L01XX47	6-007.f
Monoclonal antibodies	Antibodies	L01XC	-
	Belantamab Mafodotin	L01XC39	6-00d.4
	Daratumumab	L01XC24	6-009.a
	Elotuzumab	L01XC23	6-009.d
	Isatuximab	L01XC38	-
	Obinutuzumab	L01XC15	6-007.j
	Ofatumumab	L01XC10	6-006.4
	Polatuzumab vedotin	L01XC37	6-00c.c
	Rituximab	L01XC02	6-001.h; 6-001j
	Tafasitamab	L01FX12	-
	Immunotherapy with unmodified antibodies	-	8-547.0
Immunosuppression	-	8-547.1	
mTOR inhibitors	Temsirolimus	L01EG01; L01XE09	6-004.e
Proteasome inhibitors	Bortezomib	L01XG01; L01XX32	6-001.9
	Carfilzomib	L01XG02; L01XX45	6-008.9
	Ixazomib	L01XG03; L01XX50	6-00a.9
Radiation	Radiation	-	8-52
Supportive care agents	Darbepoetin	B03XA02	-
	Dexamethasone	H02AB02	-
	Mesna	V03AF01	-
	Prednisolone	H02BX02	-
	Prednisone	A07EA03; H02AB07	-
Transplantation procedures	Autologous stem cell transplantation	-	5-411.0, 8-860.-, 8-805.0
	Allogeneic stem cell transplantation	-	5-411.2-5-411.5, 8-863, 8-805.2-8-805.5
	Unspecified transfusion of hematopoietic stem cells	-	8-805.x, 8-805.y
	CAR-T-cell therapy	-	5-936

Table S2. DLBCL treatment algorithm components and definitions

Treatment algorithm component	Definition
Start of LOT1 therapy	<ul style="list-style-type: none"> • First date on which the patient receives a treatment of interest (ATC or OPS code) within the study inclusion period for DLBCL-related treatment. • Supportive care agents (prednisone, prednisolone, dexamethasone, mesna, and/or darbepoetin) do not constitute a therapy line. • In case of combination therapy, all ATC/OPS codes within the first 30 days will comprise a LOT regimen.
End of treatment line	<p>Any of the following:</p> <ul style="list-style-type: none"> • A new ATC/OPS code that is not included in the previous regimen (exceptions: supportive care agents, radiation). • Treatment discontinuation <ul style="list-style-type: none"> • Outpatient: gap in therapy of >60 days from the runout date. <ul style="list-style-type: none"> ▪ The runout date for oral medication is defined as: administration date + days of supply – 1 day; the runout date for medications administered otherwise is defined as: date of administration + 60 days. ▪ All agents (except supportive care agents) of the regimen must be discontinued, unless monotherapy rituximab or lenalidomide following the active LOT. • Inpatient: gap in therapy of >6 months between OPS codes. • Inpatient and outpatient: If OPS codes can be observed before or after outpatient prescriptions, treatment discontinuation is defined as >6 months between OPS codes and outpatient prescriptions. • death, end of the study period, or loss to follow-up.
Start of subsequent treatment line	<p>Any of the following:</p> <ul style="list-style-type: none"> • A new ATC/OPS code >30 days after the start of the preceding therapy line (exceptions: addition of supportive care agents, monotherapy rituximab/lenalidomide, replacement of doxorubicin by etoposide) • Restart of same treatment/regimen as the preceding LOT after treatment discontinuation.
SCT treatment line	<ul style="list-style-type: none"> • Start: date of the cell apheresis (OPS 5-410; ICD Z52.-) within 6 months of SCT date. • End: date of the SCT + six weeks • Pharmaceutical agents prescribed and high-dose chemotherapy started within six months before the SCT are counted as part of the SCT treatment.
CAR-T treatment line	<ul style="list-style-type: none"> • Start: date of cell depletion (OPS 8-544.0) within 3 months of CAR-T date • End: date of hospital discharge after the CAR-T-cell therapy. • Bridging therapy before CAR-T-cell therapy is considered as an individual LOT.
Treatment duration	<ul style="list-style-type: none"> • Outpatient only: Date of first prescription to runout date of the last prescription. • Inpatient and outpatient: Date of first prescription/admission date of first hospitalization to runout date of last prescription/admission date of last hospitalization. • Inpatient only: Treatment duration is not available for inpatient setting only

Table S3. DLBCL treatment regimens under each treatment category

Treatment category	Treatment subcategory	Treatment regimens
Chemotherapy		
CD-20 antibodies + chemotherapy	CD-20 antibodies + chemotherapy (agent or inpatient)	obinituzumab + chemotherapy agent (bendamustine)
		obinituzumab + chemotherapy agent (chlorambucil)
		rituximab + chemotherapy (inpatient)
		rituximab + chemotherapy (inpatient) + chemotherapy agent (cytarabine)
		rituximab + chemotherapy (inpatient) + chemotherapy agent (procarbazine)
		rituximab + chemotherapy (inpatient) + demethylation agent (azacitidine)
		rituximab + chemotherapy (inpatient) + immunomodulator (lenalidomide)
		rituximab + chemotherapy (inpatient) + kinase inhibitor (ibrutinib)
		rituximab + chemotherapy (inpatient) + kinase inhibitors (ibrutinib, idelalisib)
		rituximab + chemotherapy (inpatient) + monoclonal antibodies (ATC code: L01XC)
		rituximab + chemotherapy agent (chlorambucil)
		rituximab + chemotherapy agent (cyclophosphamide, fludarabine, mitoxantrone)
		rituximab + chemotherapy agent (cytarabine)
		rituximab + chemotherapy agent (doxorubicin)
		rituximab + chemotherapy agent (etoposide)
		rituximab + chemotherapy agent (gemcitabine)
		rituximab + chemotherapy agent (hydroxycarbamide)
		rituximab + chemotherapy agent (ifosfamide)
		rituximab + chemotherapy agent (mitoxantrone)
		rituximab + chemotherapy agent (vincristine)
	rituximab + chemotherapy agent (procarbazine, vincristine)	
	BO	bendamustine + obinituzumab
	BR	bendamustine + rituximab
		bendamustine + rituximab + mTOR inhibitor (temsirolimus)
		bendamustine + rituximab + chemotherapy agent (cisplatin, gemcitabine)
		bendamustine + rituximab + chemotherapy agent (cyclophosphamide, doxorubicin)
		bendamustine + rituximab + chemotherapy agent (doxorubicin)
		bendamustine + rituximab + chemotherapy agent (etoposide)
		bendamustine + rituximab + chemotherapy agent (gemcitabine)
		bendamustine + rituximab + chemotherapy agent (gemcitabine) + chemotherapy agent (oxaliplatin)
		bendamustine + rituximab + chemotherapy agent (gemcitabine) + kinase inhibitor (idelalisib)
	bendamustine + rituximab + chemotherapy agent (vincristine)	
	O-CHOP (like)	obinituzumab + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone/prednisone)
Pola-R + B/chemotherapy	Pola-R + bendamustine (polatuzumab vedotin, bendamustine, rituximab)	

Treatment category	Treatment subcategory	Treatment regimens
		Pola-R + bendamustine + chemotherapy agent (cyclophosphamide)
		Pola-R + bendamustine + chemotherapy agent (doxorubicin)
		Pola-R + bendamustine + immunomodulator (lenalidomide) + monoclonal antibodies (tafasitamab)
		Pola-R + chemotherapy (inpatient) – inpatient only
	R-CHOEP (like)	R-CHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone/prednisone)
		R-CHOEP - prednisolone/prednisone
		R-CHOEP + chemotherapy agent (cytarabine)
		R-CHOEP + chemotherapy agent (ifosfamide)
		R-CHOEP + chemotherapy agent (gemcitabine)
	R-CHOP (like)	R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone/prednisone)
		R-CHOP - cyclophosphamide - doxorubicin
		R-CHOP - cyclophosphamide - vincristine
		R-CHOP - doxorubicin
		R-CHOP - doxorubicin + chemotherapy agent (mitoxantrone)
		R-CHOP - prednisolone/prednisone
		R-CHOP - vincristine
		R-CHOP - vincristine
		R-CHOP + bendamustine ¹
		R-CHOP + chemotherapy agent (bendamustine)
		R-CHOP + monoclonal antibodies (polatuzumab vedotin)
	R-CHOP + proteasome inhibitor (bortezomib)	
	R-GemOx (like)	R-GemOx (rituximab, gemcitabine, oxaliplatin)
		R-GemOx + kinase inhibitor (ibrutinib)
Chemotherapy	Chemotherapy (with or without other treatments of interest)	chemotherapy (inpatient)
		chemotherapy (inpatient) + immunomodulator (lenalidomide)
		chemotherapy (inpatient) + immunomodulator (lenalidomide) + monoclonal antibodies (daratumumab) + proteasome inhibitor (carfilzomib)
		chemotherapy (inpatient) + immunomodulator (lenalidomide) + monoclonal antibodies (tafasitamab)
		chemotherapy (inpatient) + kinase inhibitor (ibrutinib)
		chemotherapy (inpatient) + kinase inhibitor (ruxolitinib)
		chemotherapy (inpatient) + monoclonal antibodies (ATC code: L01XC)
		chemotherapy (inpatient) + monoclonal antibodies (daratumumab)
		chemotherapy (inpatient) + monoclonal antibodies (daratumumab) + proteasome inhibitor (bortezomib)
		chemotherapy (inpatient) + mTOR inhibitor (temsirolimus)
		chemotherapy (inpatient) + proteasome inhibitor (bortezomib)
		chemotherapy agent (bendamustine)
		chemotherapy agent (bendamustine) + immunomodulator (lenalidomide) + monoclonal antibodies (tafasitamab)
		chemotherapy agent (bendamustine, gemcitabine, oxaliplatin)
		chemotherapy agent (bendamustine, vincristine)
		chemotherapy agent (capecitabine)
		chemotherapy agent (capecitabine, cisplatin)
chemotherapy agent (carboplatin)		

Treatment category	Treatment subcategory	Treatment regimens	
		chemotherapy agent (carboplatin, etoposide)	
		chemotherapy agent (chlorambucil)	
		chemotherapy agent (cisplatin, cytarabine)	
		chemotherapy agent (cisplatin, etoposide)	
		chemotherapy agent (cisplatin, gemcitabine)	
		chemotherapy agent (cisplatin, vinorelbine)	
		chemotherapy agent (cyclophosphamide)	
		chemotherapy agent (cyclophosphamide) + proteasome inhibitor (bortezomib)	
		chemotherapy agent (cyclophosphamide, dacarbazine, etoposide)	
		chemotherapy agent (cyclophosphamide, fludarabine)	
		chemotherapy agent (cytarabine)	
		chemotherapy agent (doxorubicin)	
		chemotherapy agent (etoposide)	
		chemotherapy agent (fludarabine)	
		chemotherapy agent (gemcitabine)	
		chemotherapy agent (hydroxycarbamide)	
		chemotherapy agent (melphalan) + monoclonal antibodies (daratumumab)	
		chemotherapy agent (mitoxantrone)	
		chemotherapy agent (oxaliplatin)	
		chemotherapy agent (oxaliplatin) + monoclonal antibodies (ATC code: L01XC)	
		chemotherapy agent (procarbazine)	
		chemotherapy agent (vincristine)	
		chemotherapy agent (vinorelbine)	
		chemotherapy agent (vinorelbine) + monoclonal antibodies (ATC code: L01XC)	
		CHOP (like)	CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone/prednisone)
			CHOP - doxorubicin
		CHOP - prednisolone/prednisone	
	CHOP + chemotherapy agent (bendamustine)		
	CHOP + chemotherapy agent (dacarbazine, etoposide)		
	CHOP + chemotherapy agent (darbepoetin, etoposide)		
	CHOP + chemotherapy agent (etoposide, procarbazine)		
	CHOP + chemotherapy agent (gemcitabine)		
Non-chemotherapy			
CD-20 antibodies	CD-20 antibodies	obinituzumab	
		obinituzumab + kinase inhibitor (ruxolitinib)	
		obinituzumab + proteasome inhibitor (bortezomib)	
		obinituzumab + mTOR inhibitor (temsirolimus)	
		rituximab	
		rituximab + immunomodulator (lenalidomide) + proteasome inhibitor (bortezomib)	
		rituximab + kinase inhibitor (ibrutinib)	
		rituximab + monoclonal antibodies (polatuzumab vedotin)	
		Inpatient immunotherapy with unmodified antibodies (including rituximab in patients with lymphomas)	
Immunomodulators	Immunomodulators	lenalidomide	
		lenalidomide + kinase inhibitor (ibrutinib)	

Treatment category	Treatment subcategory	Treatment regimens
		Inpatient immunotherapy with modified antibodies
		Inpatient Immunosuppression
Kinase inhibitors	Kinase inhibitors	ibrutinib
		idelalisib
		ruxolitinib
mTOR/proteasome inhibitors	mTOR/proteasome inhibitors	bortezomib
		carfilzomib
Other inpatient treatments		
CAR-T	CAR-T	As defined in treatment algorithm
SCT	SCT	As defined in treatment algorithm
Radiation	Radiation	Radiation alone

Table S4. Prevalent and incident patients per calendar year of the inclusion period

Calendar year	Main Cohort (n = 2633)		Patients with treatments of interest (n = 2119)	
	Prevalent patients per calendar year n (%)	Incident patients per calendar year n (%)	Prevalent patients per calendar year n (%)	Incident patients per calendar year n (%)
2012	308 (11.7)	308 (11.7)	240 (11.3)	240 (11.3)
2013	490 (18.6)	316 (12.0)	400 (18.9)	239 (11.3)
2014	581 (22.1)	295 (11.2)	502 (23.7)	237 (11.2)
2015	670 (25.4)	291 (11.1)	591 (27.9)	241 (11.4)
2016	727 (27.6)	284 (10.8)	649 (30.6)	236 (11.1)
2017	787 (29.9)	289 (11.0)	706 (33.3)	245 (11.6)
2018	824 (31.3)	269 (10.2)	739 (34.9)	216 (10.2)
2019	892 (33.9)	301 (11.4)	798 (37.7)	243 (11.5)
2020	910 (34.6)	280 (10.6)	817 (38.6)	222 (10.5)

Table S5. Detailed DLBCL treatment categories and treatment duration (LOT1-LOT3+)

Treatment categories, n (%)	LOT 1				LOT2				LOT3+		
	All n=2119	Outpatient only n=343	Inpatient/ outpatient n=756	Inpatient only n=1020	All n=403	Outpatient only n=156	Inpatient/ outpatient n=40	Inpatient only n=207	All n=136	Outpatient only + inpatient/ outpatient ¹ n=87	Inpatient only n=49
Chemotherapy regimens	1922 (90.7)	270 (78.7)	742 (98.1)	910 (89.2)	225 (55.8)	101 (64.7)	(≈58.0) ²	101 (48.8)	74 (54.4)	48 (55.2)	(≈55.0) ²
Chemotherapy + CD-20 antibodies (all)	1530 (72.2)	243 (70.8)	723 (95.6)	564 (55.3)	183 (45.4)	80 (51.3)	(≈48.0) ²	84 (40.6)	54 (39.7)	35 (40.2)	(≈40.0) ²
Chemotherapy (agent or inpatient) + CD-20 antibodies	913 (43.1)	<10	(≈45.0) ²	564 (55.3)	95 (23.6)	<10	<10	(≈40.0) ²	23 (16.9)	<10	18 (36.7) ²
R-CHOP	509 (24.0)	192 (56.0)	317 (41.9)	-	23 (5.7)	20 (12.8)	<10	-	<10	<10	<10
BR	90 (4.2)	41 (12.0)	49 (6.5)	-	42 (10.4)	39 (25.0)	<10	-	10 (7.4) ¹	<10	<10
BO	<10	<10	<10	-	-	-	-	-	<10	<10	<10
O-CHOP	<10	<10	<10	-	-	-	-	-	<10	<10	<10
Pola-R + B/chemo	<10	<10	<10	-	12 (3.0)	<10	<10	<10	<10	<10	<10
R-CHOEP	<10	<10	<10	-	<10	-	<10	-	<10	<10	<10
R-GemOx	<10	<10	<10	-	10 (2.5)	<10	<10	-	<10	<10	<10
BR or R-GemOx	(≈5.0) ²	(≈13.0) ²	(≈7.0) ²	-	52 (12.9)	(≈30.0) ²	<10	-	16 (11.8)	16 (18.3)	<10
Chemotherapy ³	392 (18.5)	27 (7.9)	19 (2.5)	346 (33.9)	43 (10.7)	(≈14.0) ²	<10	(≈8.0) ²	20 (14.7)		
Non-chemotherapy regimens	137 (6.5)	73 (21.3)	13 (1.7)	51 (5.0)	69 (17.1)	(≈35.0) ²	<10	10 (4.8)	45 (33.1)	36 (41.4)	<10
CD-20 antibodies	116 (5.5)	64 (18.7)	12 (1.6)	40 (3.9)	42 (10.4)	(≈20.0) ²	<10	<10	14 (10.3)	<10	<10
Immunomodulators ⁴	12 (0.6)	<10	<10	(≈1.0) ²	<10	<10	<10	<10	12 (8.8)	<10	<10
Kinase inhibitors ⁴	<10	<10	<10	<10	18 (4.5)	(≈11.0) ²	<10	<10	18 (13.2)	18 (20.7)	<10
mTOR/proteasome inhibitor ⁴	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10	<10
SCT or CAR-T	<10	-	<10	<10	100 (24.8%)	-	13 (32.5%)	87 (42.0)	<10	<10	<10
Radiation	51 (2.4)	-	-	51 (5.0)	<10	-	-	<10	<10	-	<10
Treatment duration, median (IQR)	-	172.0 (102.0–223.8)	191.0 (157.0–243.0)	-	-	171.0 (98.5–229.5)	132.5 (57.8–210.5)	-	-	130.0 (67.0–227.0)	-

¹Treatment lines in outpatient settings (outpatient only: n=65, 47.8%; inpatient/outpatient: n=22, 16.3%) were combined due to limited number of LOT3+ treatment lines

²Percentage of patients approximated to preserve patient anonymity

³Includes regimens of inpatient chemotherapy, chemotherapy agents, demethylation agents, alkylating agents, CHOP, or similar

⁴Includes regimens with and without CD-20 antibodies

Table S6. Treatment duration of DLBCL by treatment category

Treatment categories ¹	Outpatient only			Inpatient/outpatient		
	n (%)	Therapy only	With monotherapy rituximab/ lenalidomide	n (%)	Therapy only	With monotherapy rituximab/ lenalidomide
LOT1	n=343			n=756		
Chemotherapy	270 (78.7)	174.0 (132.0-224.8)	213.0 (150.3-265.5)	742 (98.1)	192.0 (159.0-243.0)	221.0 (178.0-283.8)
Chemotherapy + CD-20 antibodies	243 (70.8)	178.0 (144.5-226.5)	217.0 (174.5-265.5)	723 (95.6)	193.0 (161.5-243.0)	221.0 (178.5-284.5)
Chemotherapy	27 (7.9)	68.0 (59.0-133.6)	68.0 (59.0-154.6)	19 (2.5)	151.0 (90.5-237.5)	151.0 (90.5-237.5)
Non-chemotherapy	73 (21.3)	88.0 (59.0-198.0)	150.0 (67.0-275.0)	13 (1.7)	80.0 (67.0-106.0)	91.0 (67.0-180.0)
CD-20 antibodies	64 (18.7)	87.0 (59.0-176.8)	143.0 (64.5-245.0)	12 (1.6)	74.5 (66.3-94.8)	83.0 (66.3-124.5)
LOT2	n=156			n=40		
Chemotherapy	101 (64.7)	126.0 (57.0-276.0)	164.0 (63.0-293.0)	22 (55.0) ²	126.0 (91.0-180.4)	135.0 (110.5-184.4)
Chemotherapy + CD-20 antibodies	80 (51.3)	169.5 (72.8-292.0)	209.0 (84.8-325.5)	18 (45.0) ²	175.0 (122.5-224.5)	182.9 (149.5-244.5)
Chemotherapy	21 (13.5)	82.0 (48.0-156.0)	82.0 (48.0-156.0)	<10	-	-
Non-chemotherapy	55 (35.3)	241.6 (85.0-348.0)	241.6 (96.0-499.0)	<10	-	-
CD-20 antibodies	32 (20.5)	71.5 (52.5-268.0)	164.5 (71.5-346.3)	<10	-	-
Kinase inhibitors	17 (10.9)	291.0 (85.0-768.0)	291.0 (85.0-768.0)	<10	-	-
SCT or CAR-T	<10	-	-	13 (32.5)	111.0 (105.0-126.0)	111.0 (105.0-126.0)
LOT3+	n=65			n=22		
Chemotherapy	34 (52.3)	101.0 (46.0-200.5)	105.8 (46.0-217.0)	14 (63.6) ²	207.0 (110.0-308.0)	278.5 (12.3-327.0)
Chemotherapy + CD-20 antibodies	23 (35.4)	130.0 (66.5-225.5)	165.0 (66.5-230.0)	12 (54.5) ²	207.0 (152.0-300.8)	278.5 (182.8-319.0)
Chemotherapy	11 (16.9)	67.0 (23.0-105.3)	67.0 (23.0-105.3)	<10	-	-
Non-chemotherapy	31 (47.0)	145.0 (63.5-236.5)	158.7 (83.5-335.3)	<10	-	-
Kinase inhibitors	16 (24.2)	179.8 (77.8-358.8)	179.8 (77.8-358.8)	<10	-	-

¹Only treatment categories for each LOT with >10 patients in outpatient only or inpatient/outpatient settings are shown

²Values approximated to preserve patient anonymity

Figure S1. Kaplan-Meier OS analysis after start of LOT1 (n=2119)

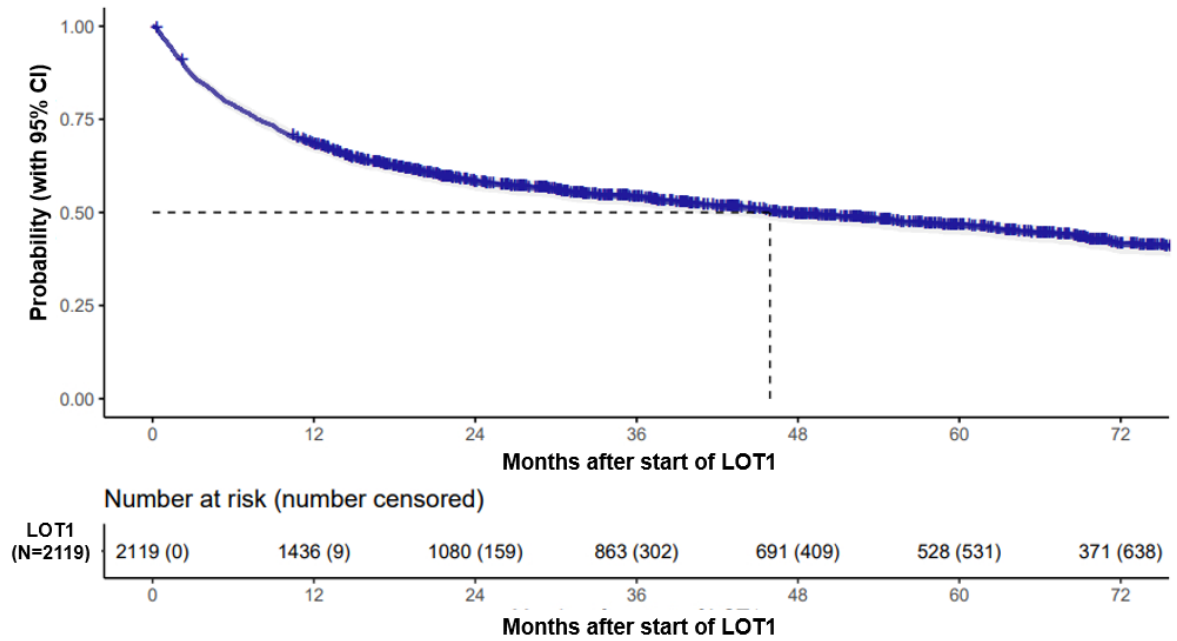


Figure S2. Kaplan-Meier OS analysis after start of LOT2 (n=403)

