LYMPHOME FOLLICULAIRE R/R

IHE-NANCY

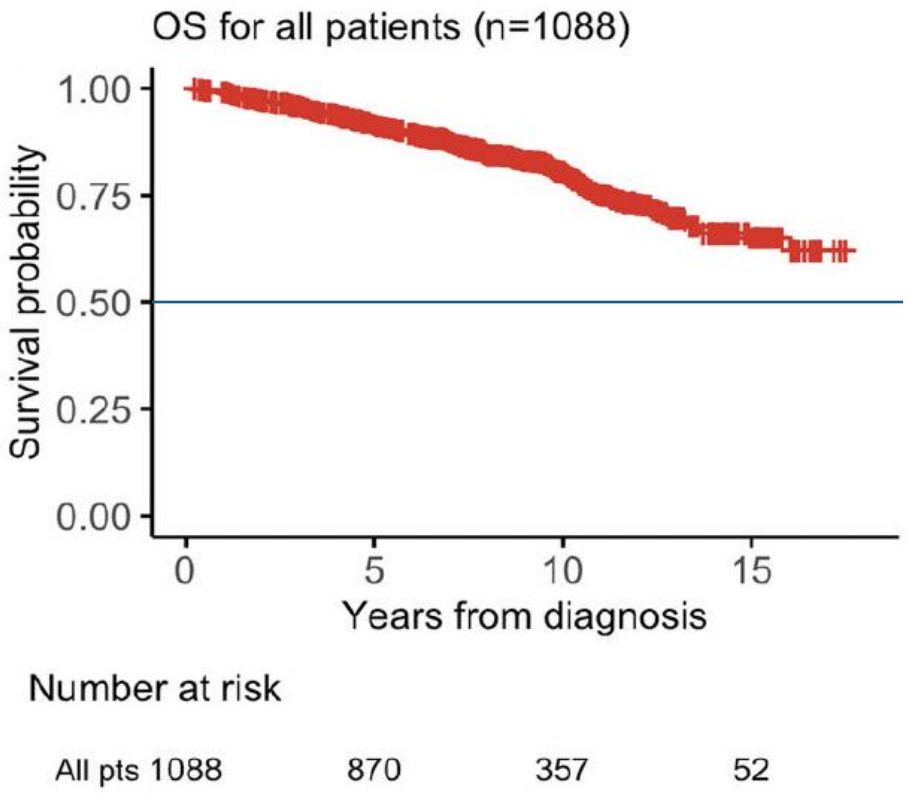
04 octobre 2025

Prof. Cédric Rossi

CHU Dijon Bourgogne

Disease course & medical needs in FL

1998-2009
MSKCC cohort



Median overall survival expected to be longer than 20 years for all newly diagnosed FL

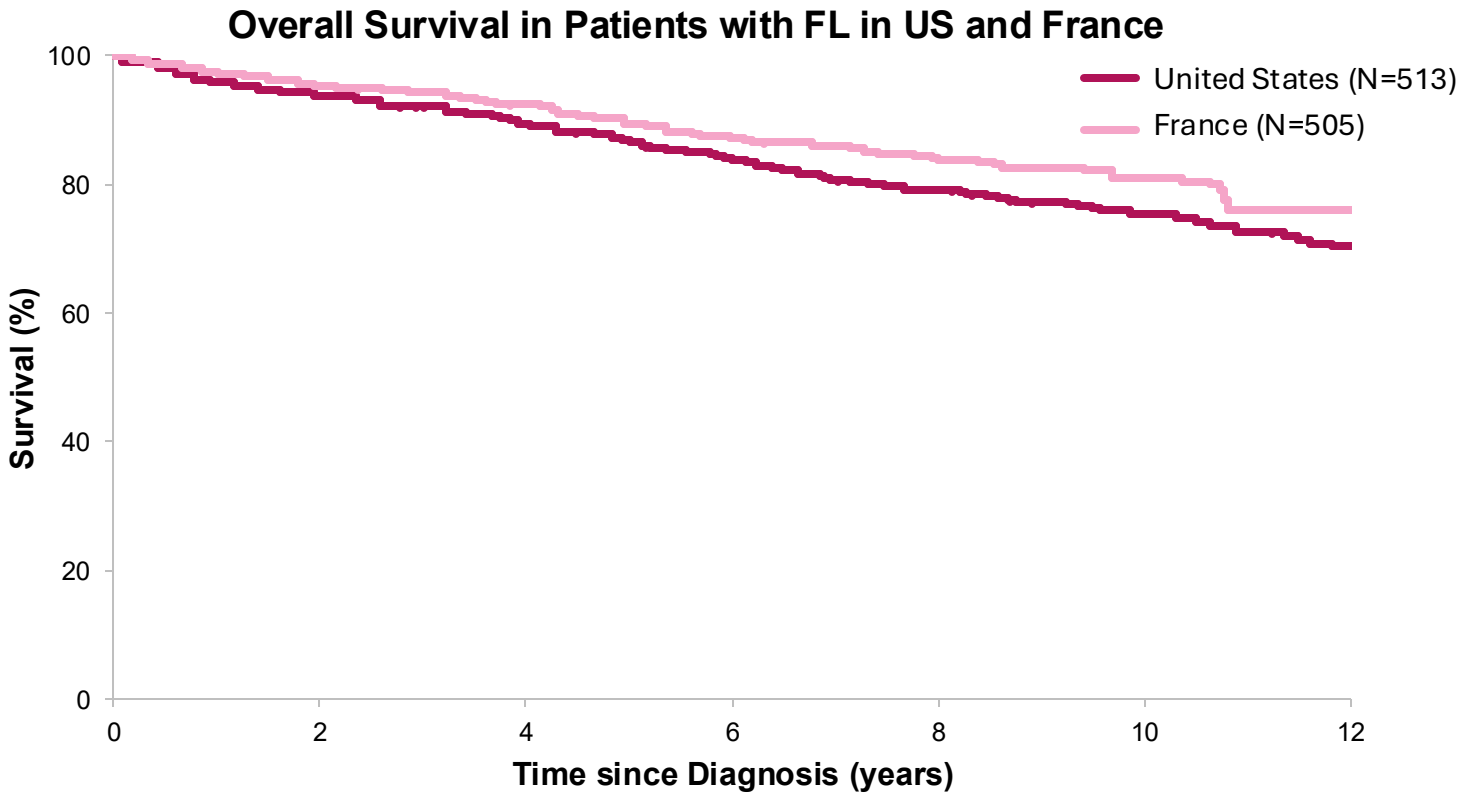
Batlevi et al. Blood Cancer Journal 2020

Follicular Lymphoma: One of the Most Common NHL Subtypes

Follicular lymphoma is:

...an indolent disease

with ~80% survival at 10y after diagnosis



Period patients treatment 2001-2013

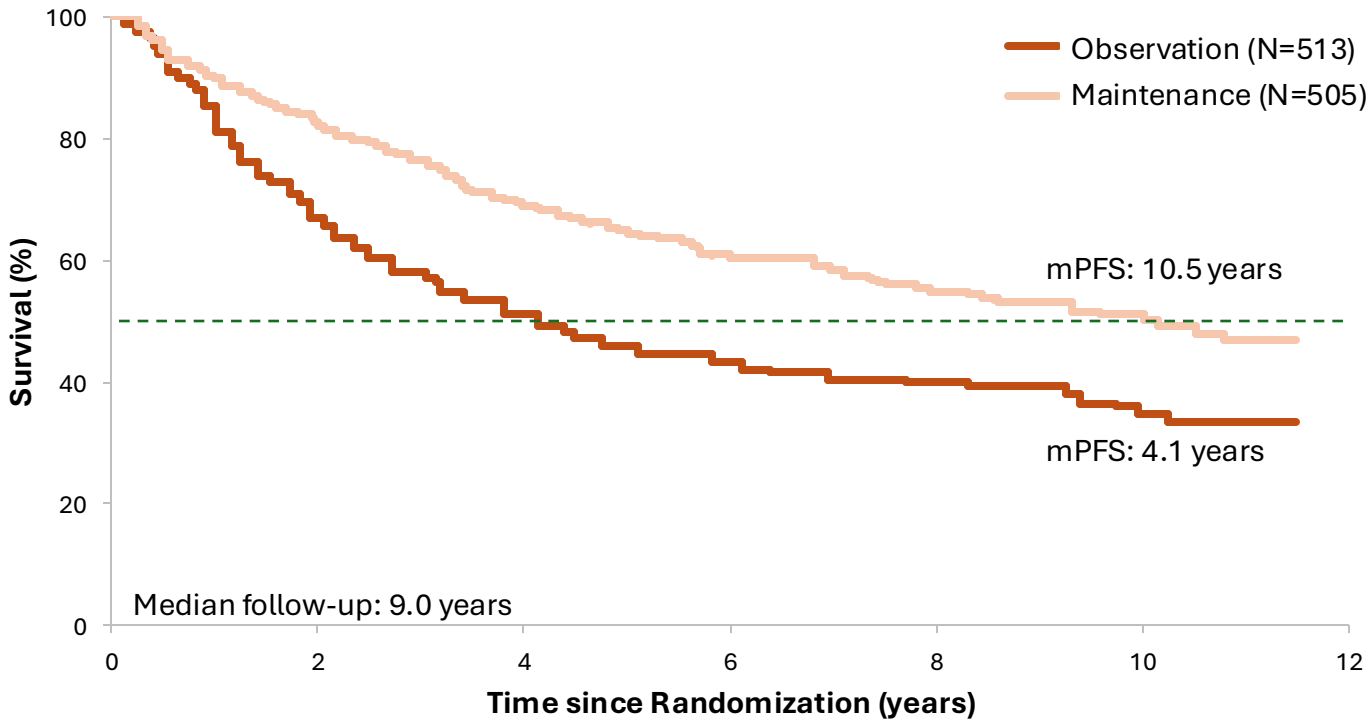
Sarkozy et al, *JCO*. 2019 Jan 10;37(2):144-152.

Follicular lymphoma is:

...an incurable disease

with a continuous pattern of relapse

Phase 3 PRIMA Study: Long-term Progression-free Survival in Patients Receiving Rituximab Maintenance after 1L Treatment

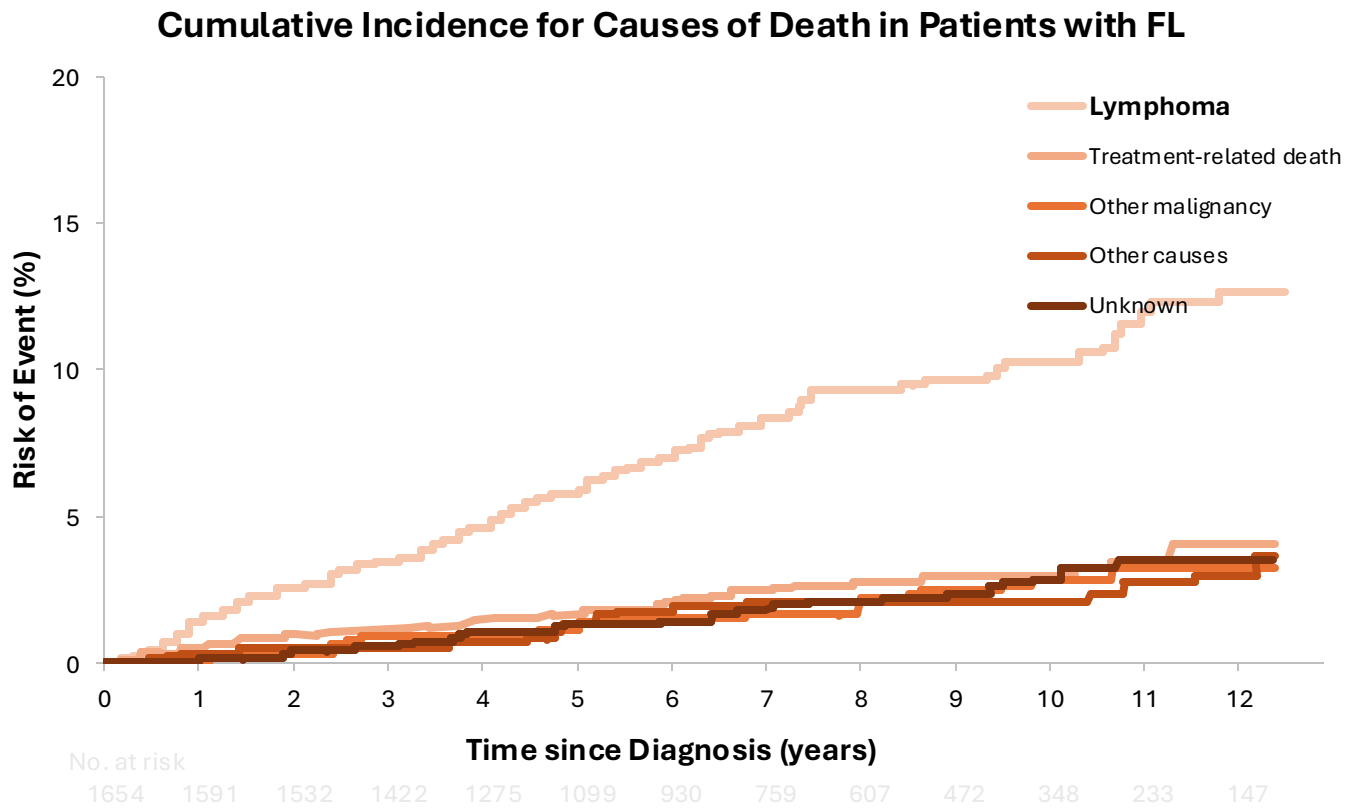


Bachy et al, *JCO*. 2019 Nov 1;37(31):2815-2824.

Follicular Lymphoma: One of the Most Common NHL Subtypes

Follicular lymphoma is:

… the leading cause of death amongst patients with FL



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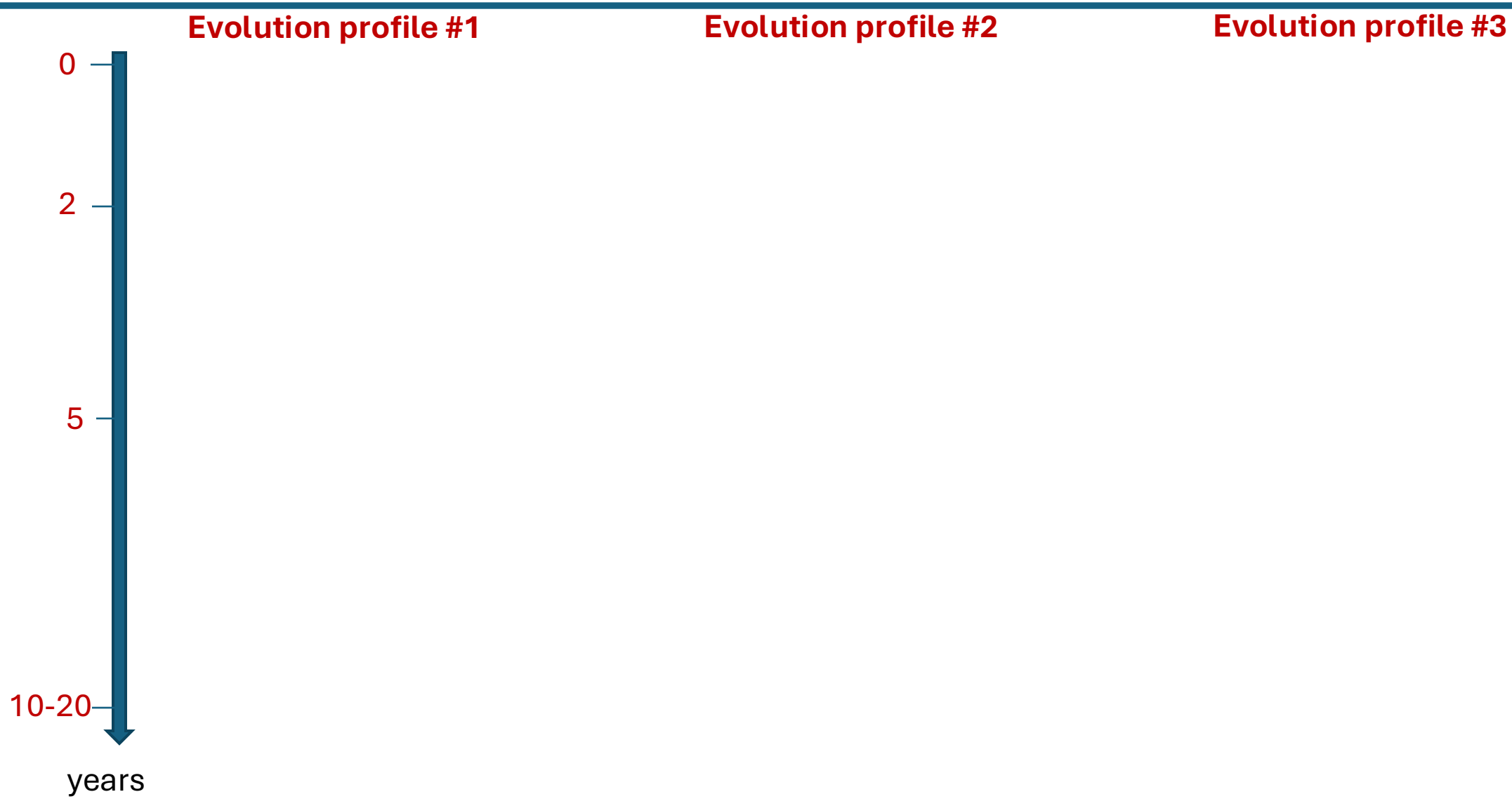
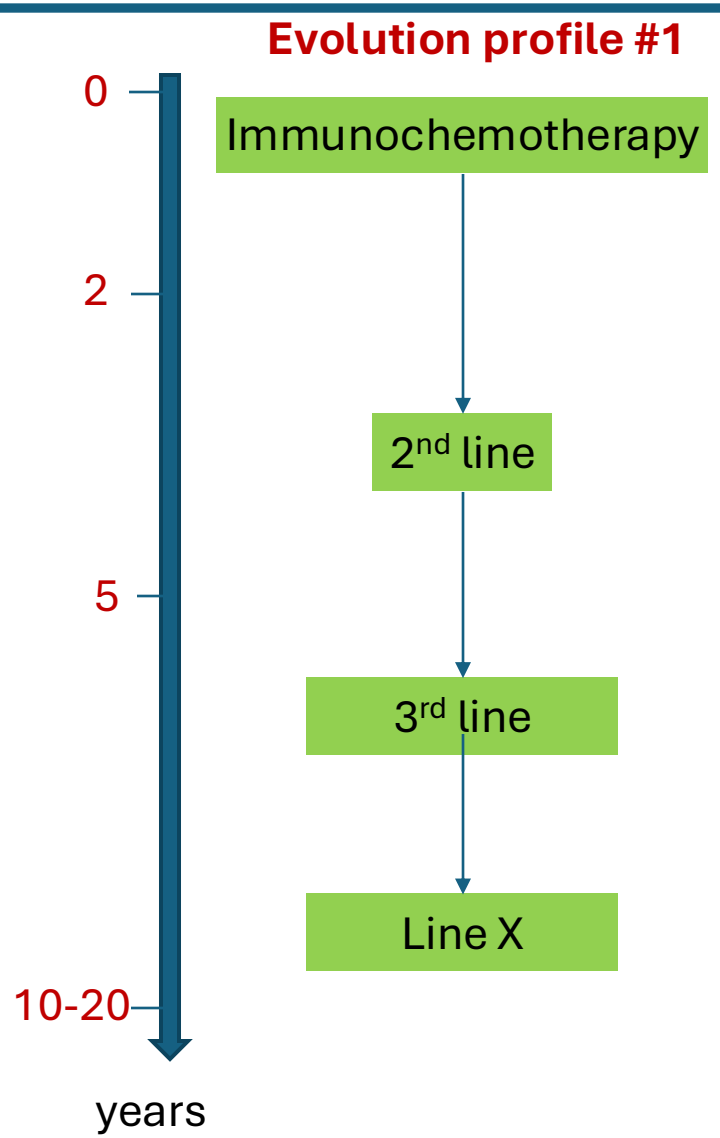
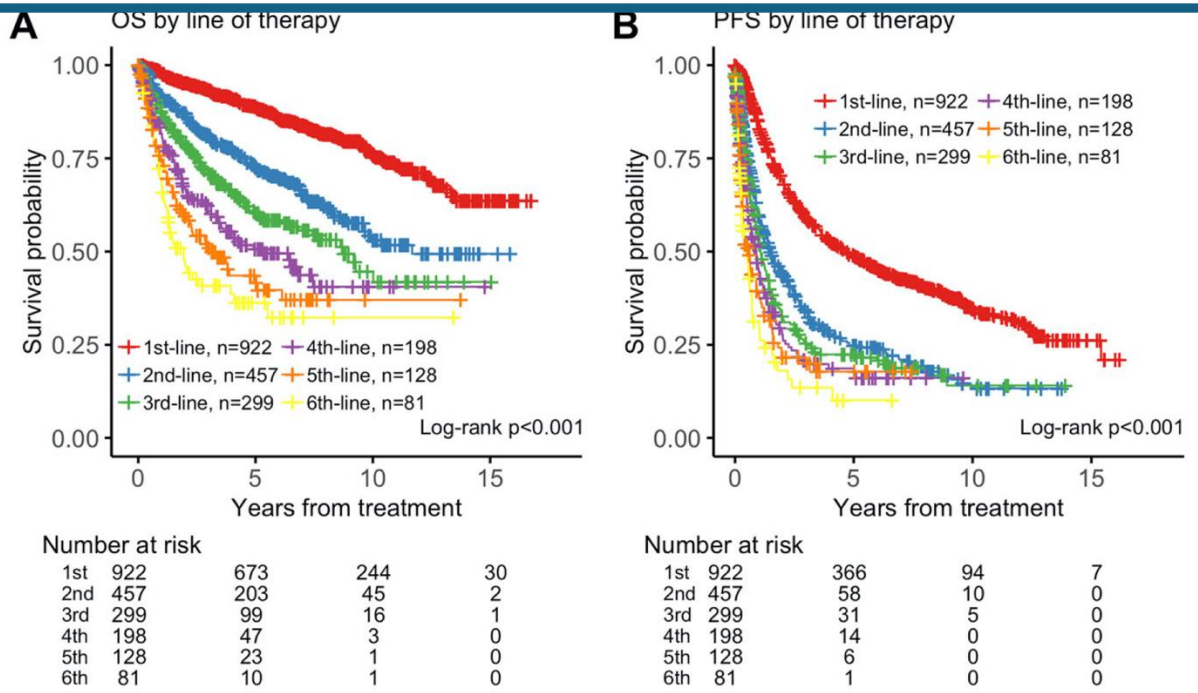
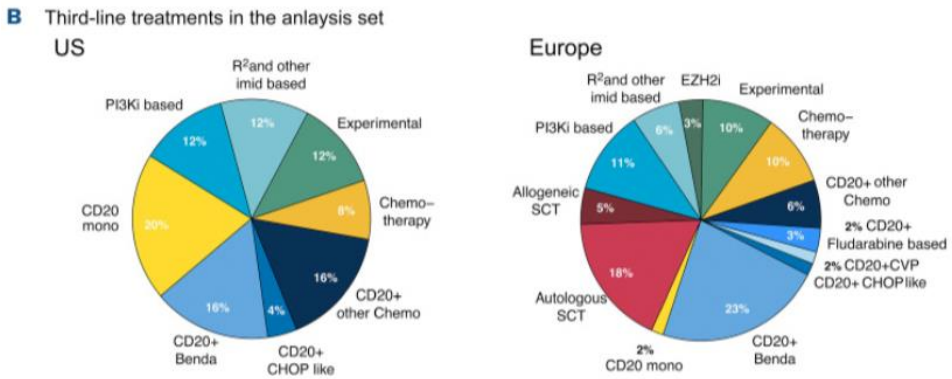
Disease course & medical needs in FL



Disease course & medical needs in FL







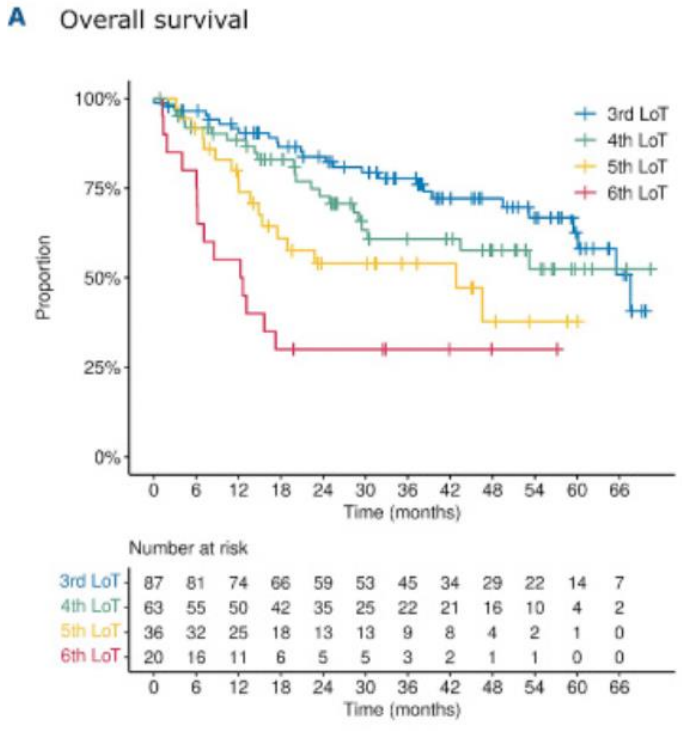
Courtesy of Pr. Bachy

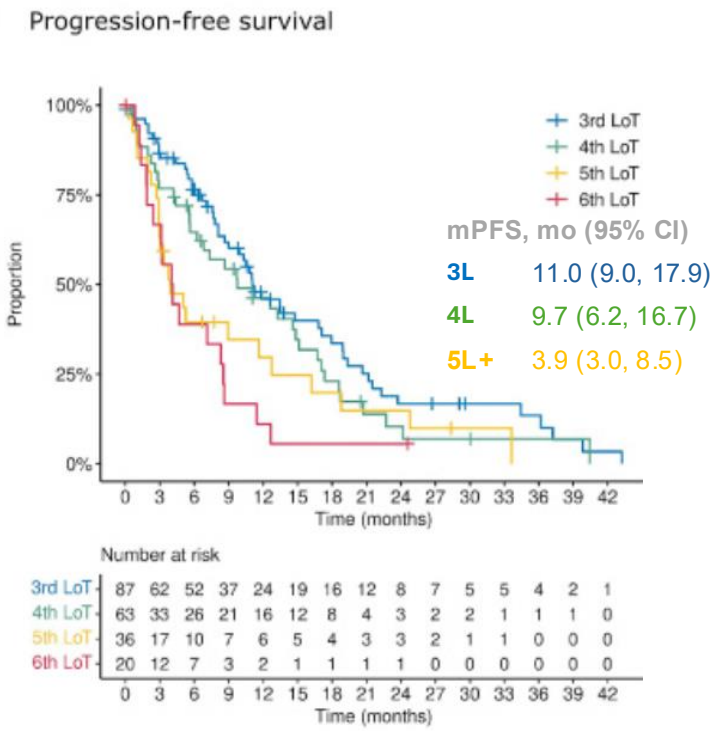
Batlevi et al. Blood Cancer Journal 2020

SCHOLAR-5

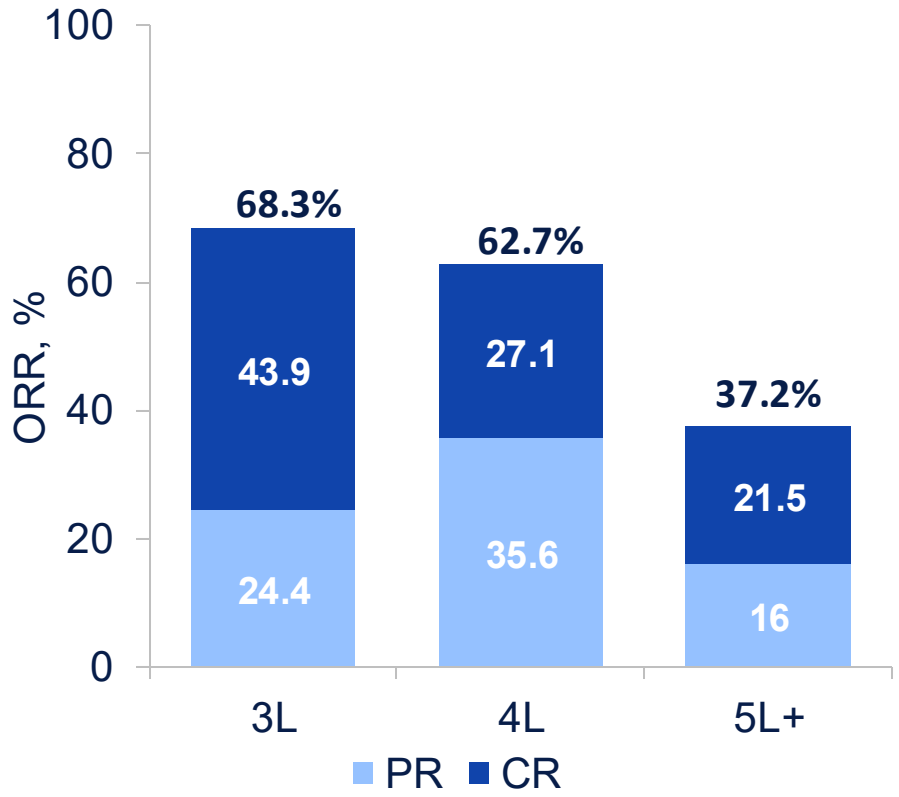
Historic Response and Survival Rates in R/R FL

Progression-Free Survival





Overall Response Rate

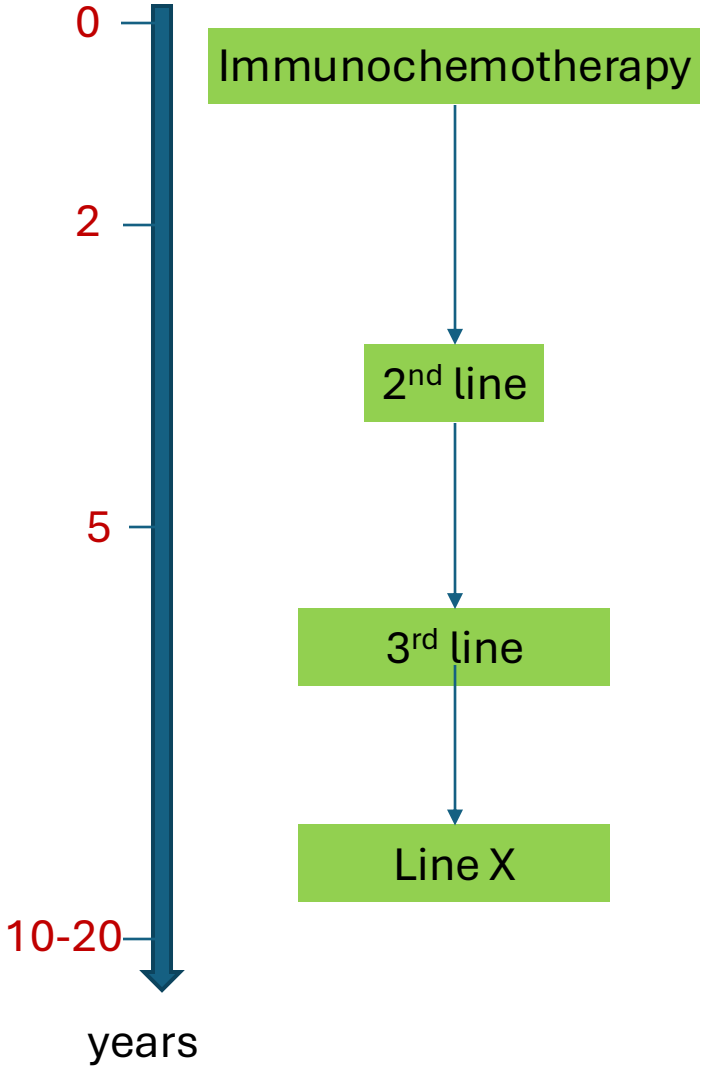


Cohorts = US/Europe-treated after 2014

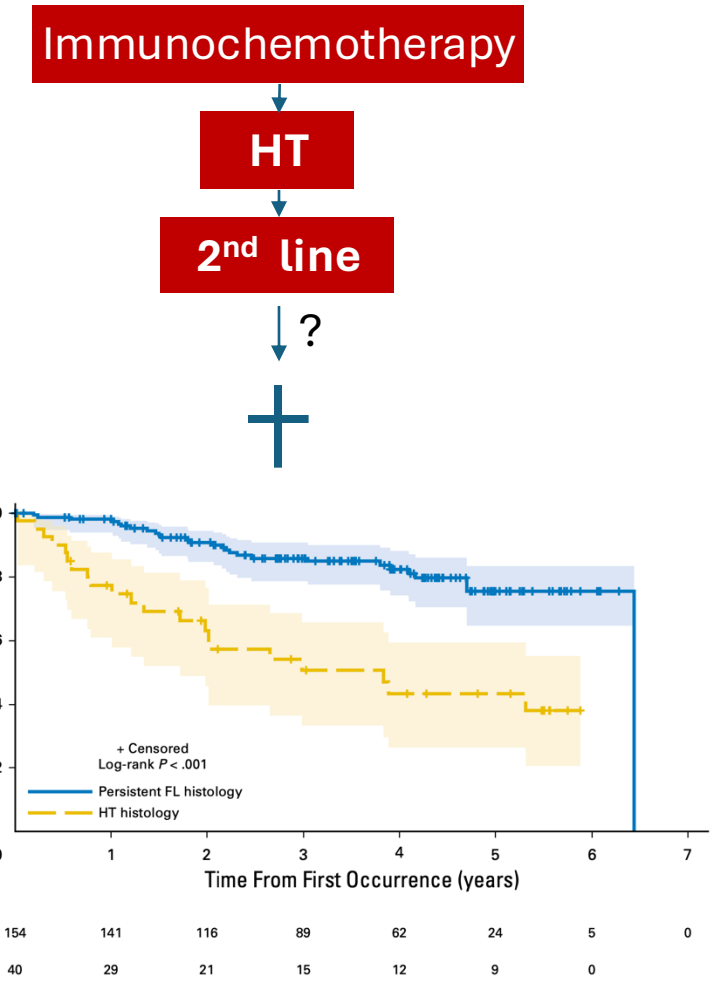
Adapted from Ghione P, et al. Haematologica. 2023 Mar 1;108(3):822-832.

Disease course & medical needs in FL

Evolution profile #1



Evolution profile #2



Sarkozy, JCO 2016

Courtesy of Pr. Bachy

Disease course & medical needs in FL

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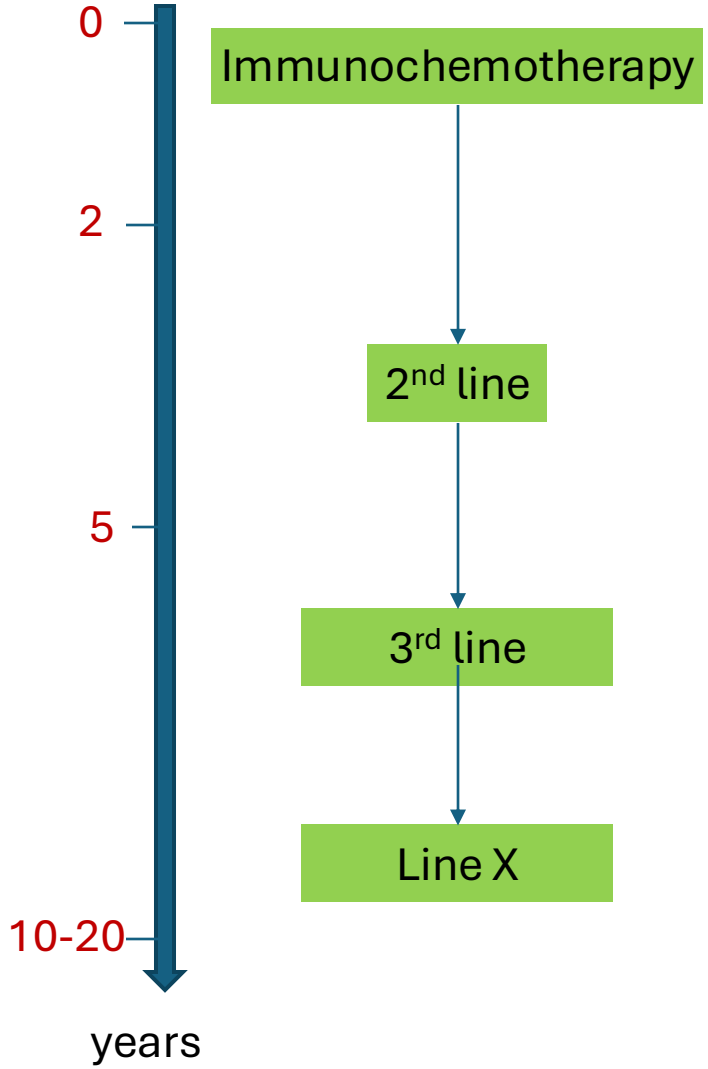
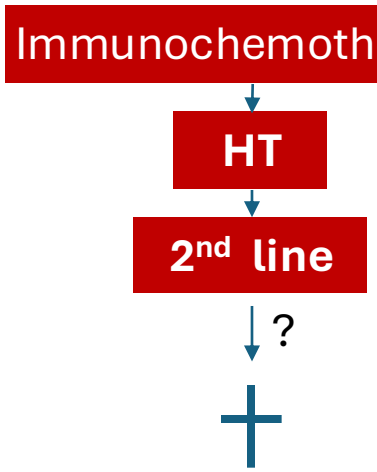
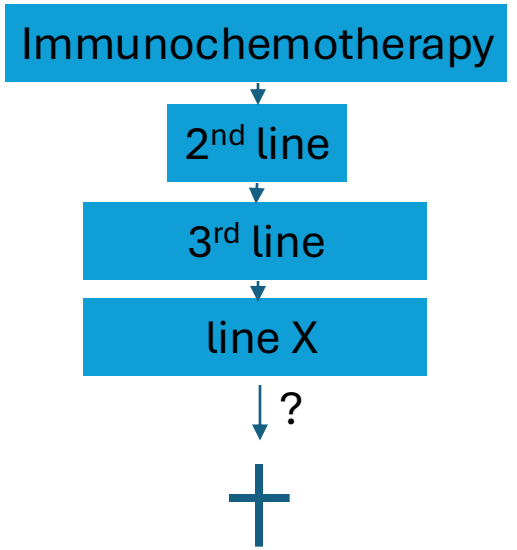
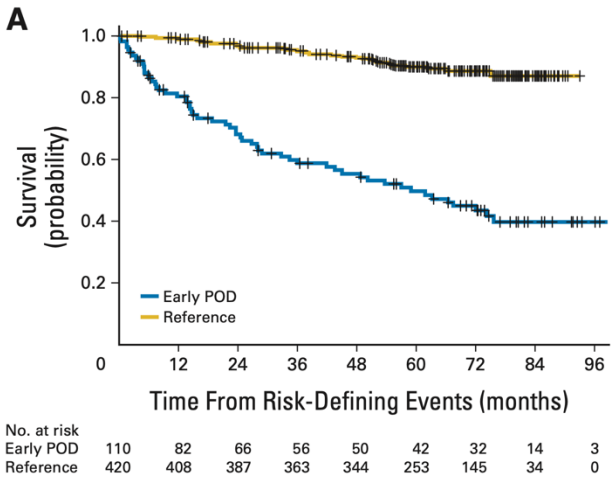


Evolution profile #2



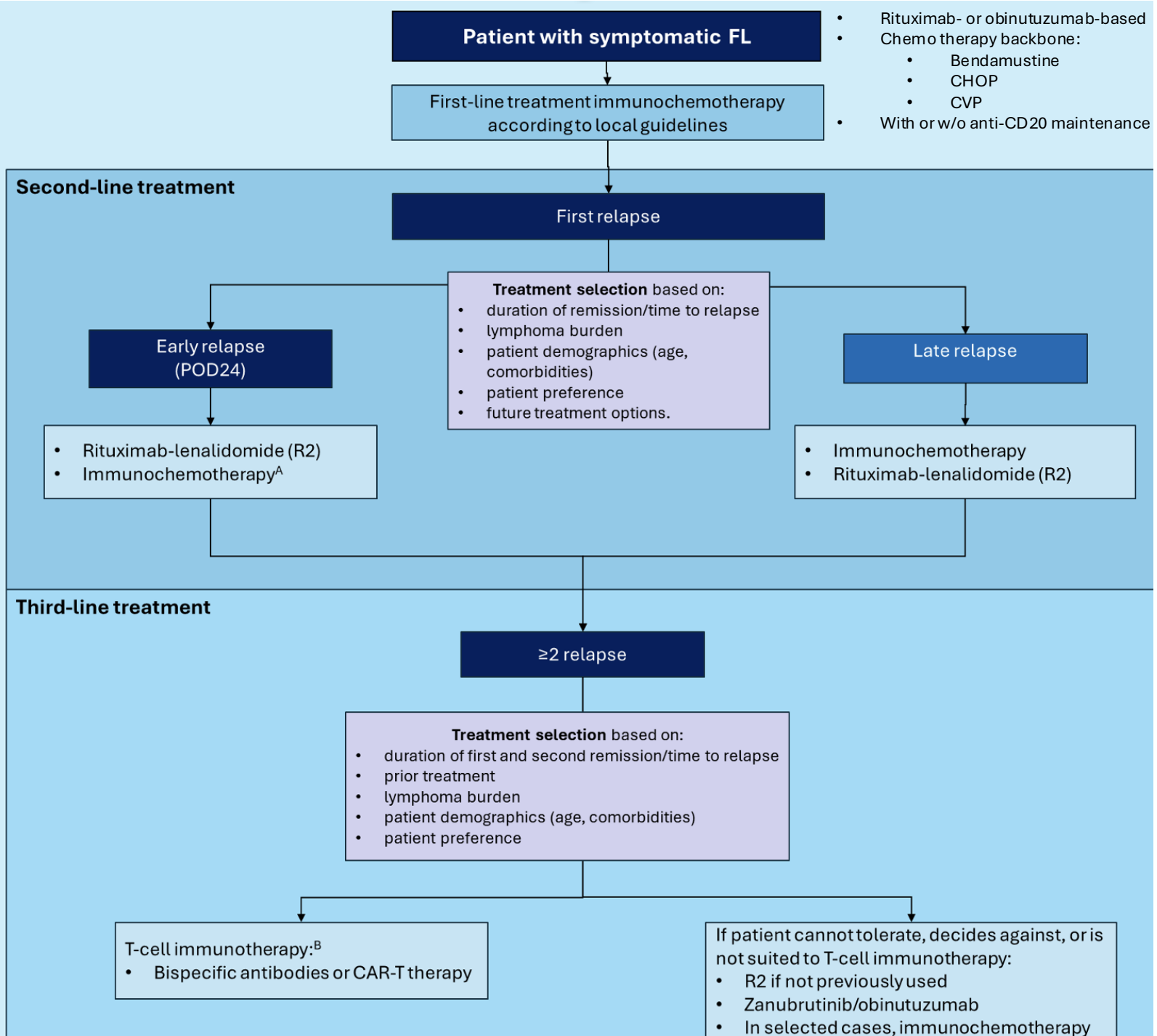
Evolution profile #3





Casulo, JCO 2015

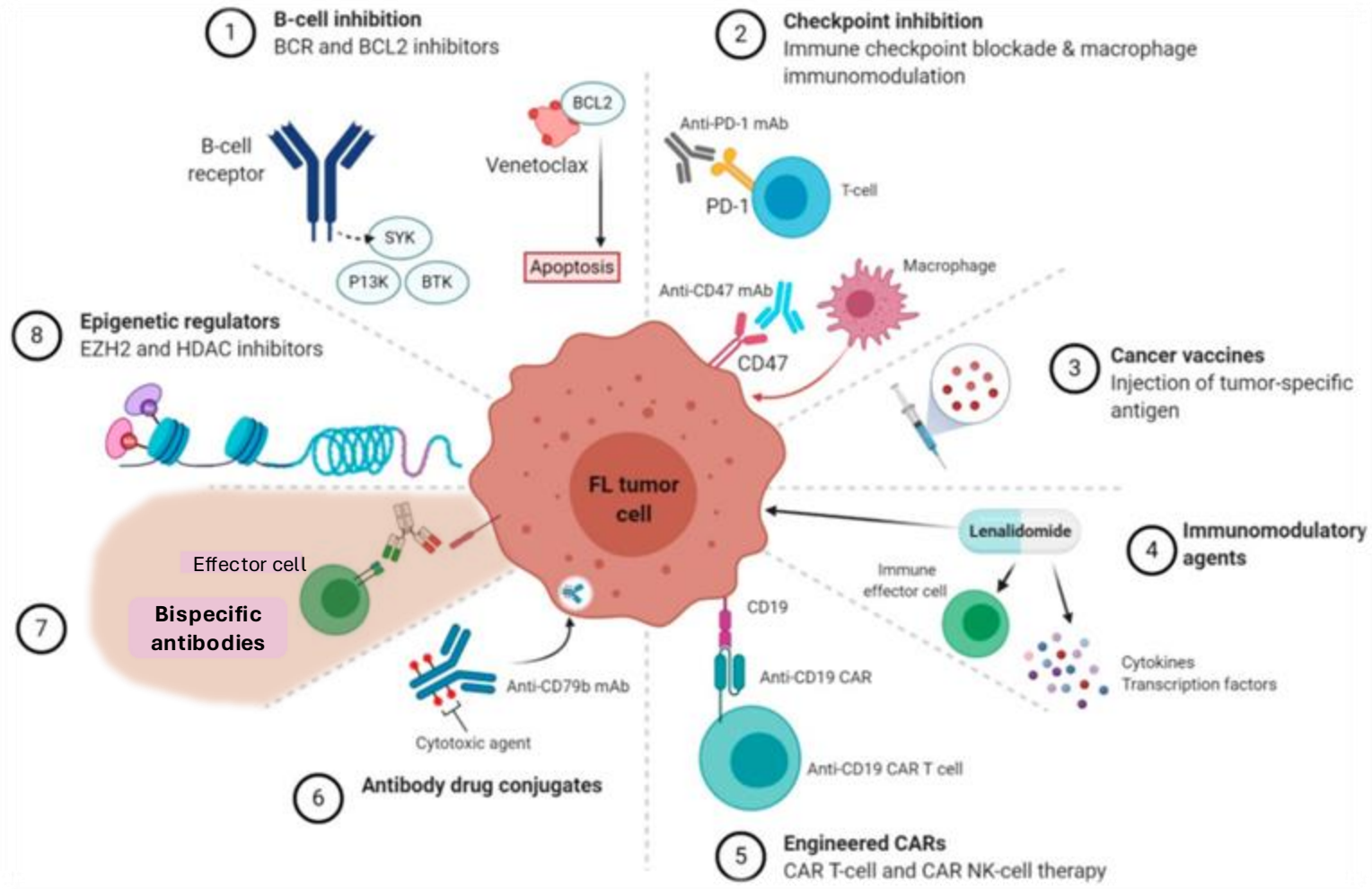
Courtesy of Pr. Bachy



Treatment options in R/R FL

- Medscape, WebMD UK
- Dreyling, Iacoboni, Bachy, Zinzani

Therapeutic Innovation in FL

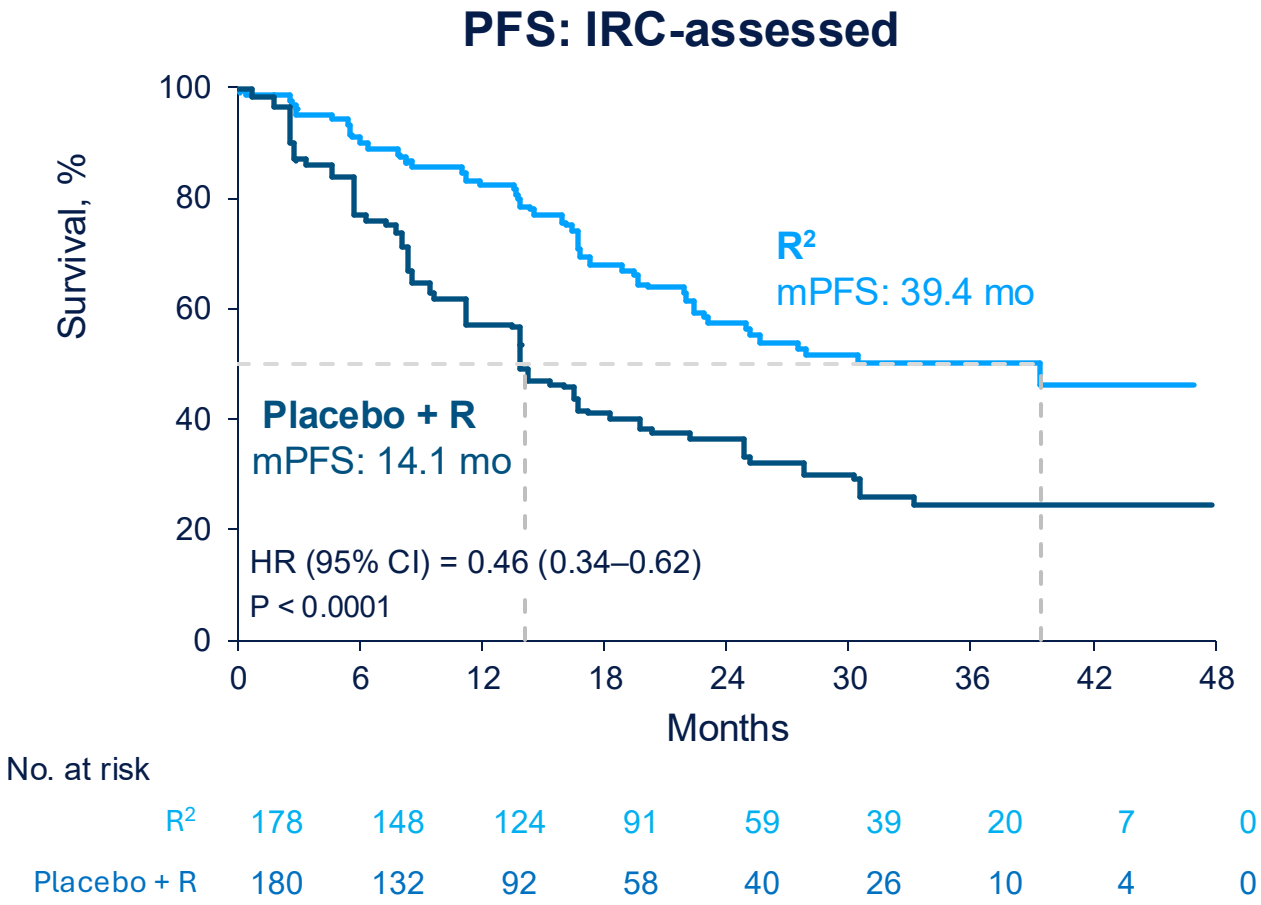


Adapted from:
Nath K and Gandhi. *J Pers Med*. 2021 Feb 22;11(2):152.

R²: AUGMENT Trial

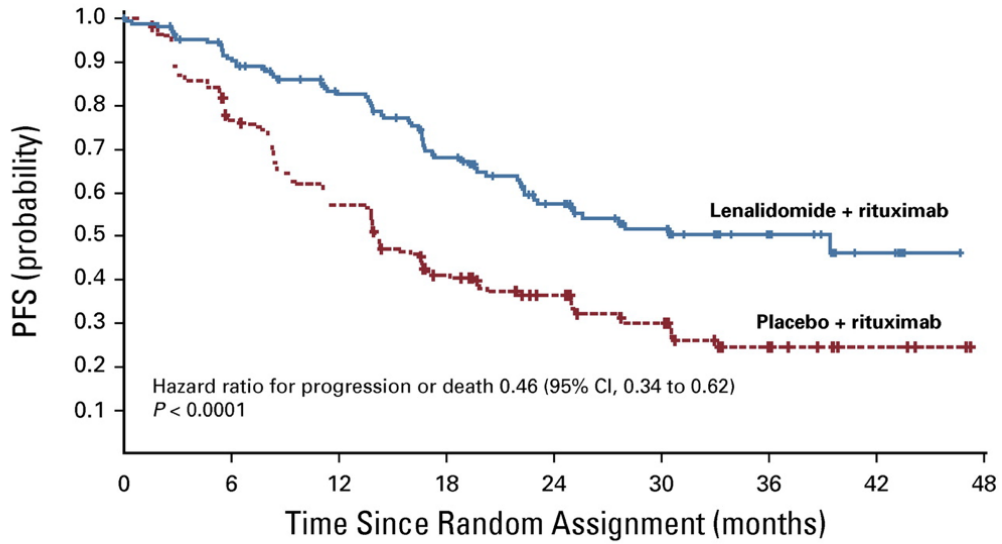
Outcomes	R² (N=178)	Placebo + R (N=180)
ORR by IRC, n (%)	138 (78)	96 (53)
CR	60 (34)	33 (18)
PR	78 (44)	63 (35)
mDOR, months [range]	36.60 [22.9 to NR]	21.7 [12.8 to 27.6]
mOS, months [range]	NR [NR to NR]	NR [NR to NR]

AEs Gr 3+, ≥ 5%, all Gr (Gr 3+)	R² (N=178)	Placebo + R (N=180)
Neutropenia*	58% (50%)	22% (13%)
Leukopenia	20% (7%)	9% (2%)
Anemia	16% (5%)	4% (1%)
Serious TEAE	26%	14%



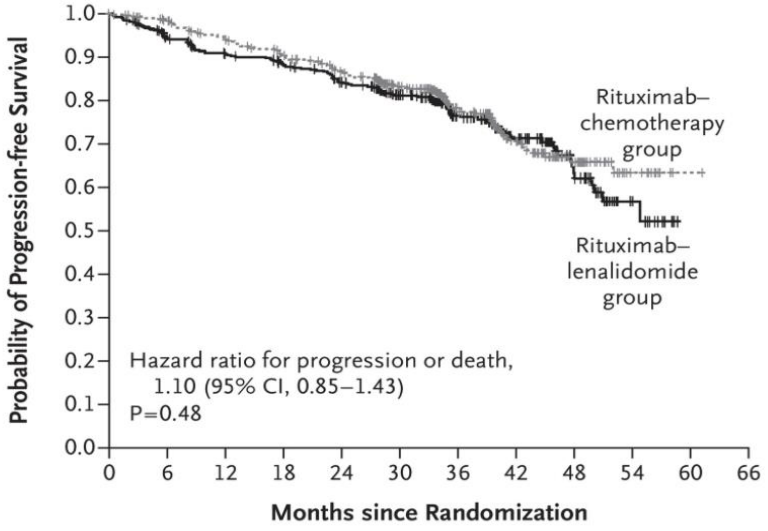
Adapted from Leonard JP, et al. J Clin Oncol. 2019;37(14):1188-1199.

AUGMENT trial : R^2 v rituximab



No. at risk:									
Lenalidomide + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0

Leonard et al, JCO, 2019



No. at Risk												
Rituximab–lenalidomide group	513	435	409	393	364	282	174	107	49	13	0	
Rituximab–chemotherapy group	517	474	446	417	387	287	175	109	51	14	1	0

Morschhauser et al, NEJM, 2018

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Efficacy of R^2 vs PBO + R by POD24 Status[2]

	R^2 (N=147)			Placebo + R (N=148)		
	All FL Patients (n = 147)	POD24 (n = 56)	No POD24 (n = 89)	All FL Patients (n = 148)	POD24 (n = 57)	No POD24 (n = 89)
Median PFS, mo (95% CI)	39.4 (23.1, NR)	30.4 (16.8, NR)	39.4 (22, NR)	13.9 (11.2, 16.0)	13.8 (6.7, 16.9)	13.9 (11.2, 16.6)
ORR, %	80	80	80	55	51	58
CR, %	35	30	37	20	18	21

Adapted from: 1. Leonard JP, et al. J Clin Oncol. 2019;37(14):1188-1199.
2. Leonard JP, et al. Abstract 069. 15th International Conference on Malignant Lymphoma 2019.

Treatment options at relapse: the past and present

Treatments options							
Treatment	Trial	Patients with FL, n	ORR,* %	**CR,* %**	**Median PFS,* months**	Most common AEs (overall population)	AE leading to discontinuations (overall population), %
Lenalidomide + rituximab (R2)	**MAGNIFY** (Phase IIIb in R/R iNHL)	148	70	**42**	**–**	Fatigue (47%), neutropenia (43%), diarrhea (37%)	14
	AUGMENT (Phase III in R/R iNHL)	147	80	**35**	**39.4**	Neutropenia (58%), diarrhea (31%), constipation (26%)	9
Obinutuzumab + bendamustine	**GADOLIN** (Phase III in rituximab-refractory iNHL)	164	68	**9†**	**24.1**	IRR (63%), nausea (52%), fatigue (40%), neutropenia (38%)	20
Rituximab monotherapy	**AUGMENT** (Phase III in R/R iNHL)	148	55	**20**	**13.8**	Diarrhea (23%), neutropenia (22%), fatigue (18%)	5
Idelalisib	**DELTA** (Phase II in rituximab-refractory iNHL)	72	56	**17**	**11.0**	Diarrhea (43%), nausea (30%), fatigue (30%)	28
Obinutuzumab + zanubrutinib	**ROSEWOOD** (Phase II in R/R FL)	143	69	**39**	**28.0**	Thrombocytopenia (36%), neutropenia (29%), dirrhea (18%)	16

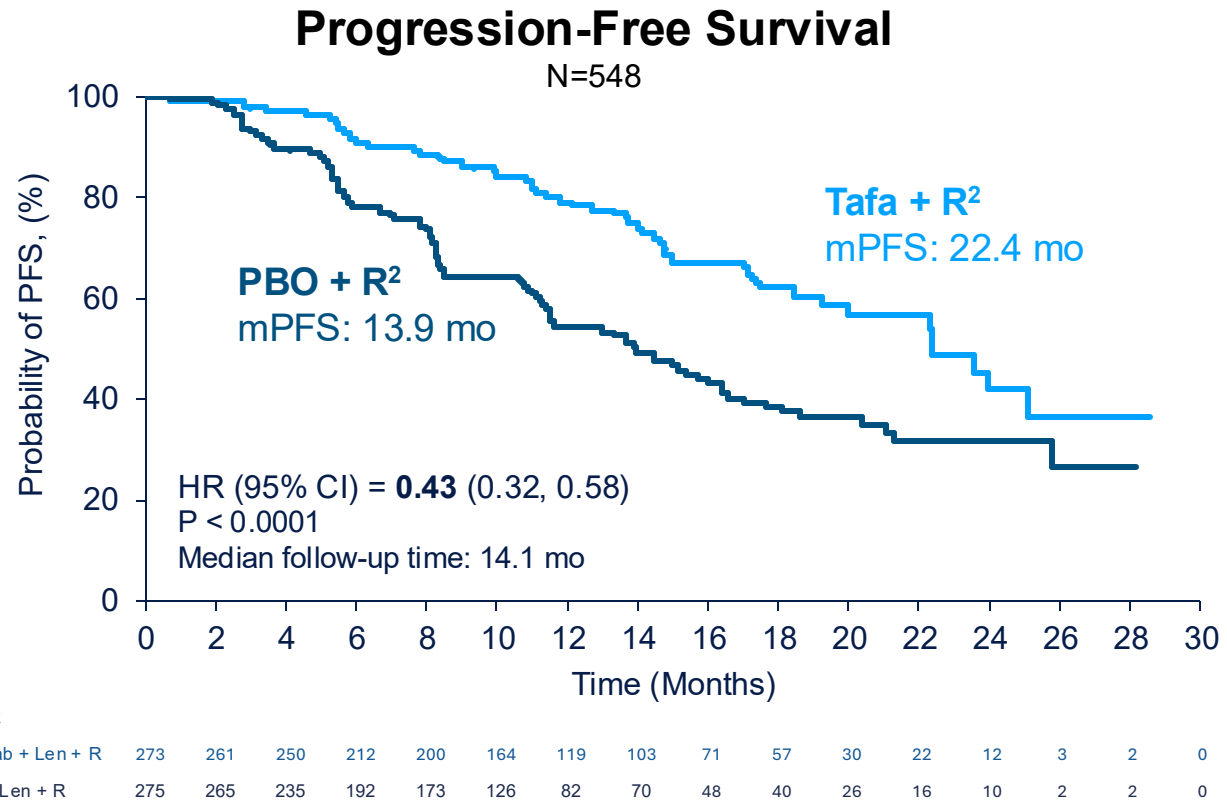
Treatment options are limited by low CR rates

Phase 3 inMIND

Tafasitamab + R^2 in 2L+ FL

Demographics, n (%)	**Tafa+Len+R** (n=273)	**PBO + Len + R** (n=275)
Median age, years (range)	64.0 (36,88)	64.0 (31, 85)
ECOG PS 1-2	92 (33.7)	83 (30.2)
FLIPI score 3-5	137 (50.2)	150 (54.5)
mPLOT, range	1 (1, 7)	1 (1, 10)
POD24	85 (31.1)	88 (32.0)

Safety, n (%)	**Tafa+Len+R** (n=274)	**Placebo + Len R** (n=272)
Neutropenia	109 (39.8)	102 (37.5)
Pneumonia	23 (8.4)	14 (5.1)
Thrombocytopenia	17 (6.2)	20 (7.4)
Neutrophil count decrease	16 (5.8)	18 (6.6)
Anemia	12 (4.4)	16 (5.9)
COVID-19	16 (5.8)	6(2.2)
COVID-19 pneumonia	13 (4.7)	3 (1.1)



Adapted from Sehn L, et al. Abstract LBA-2. ASH Annual Meeting 2024.

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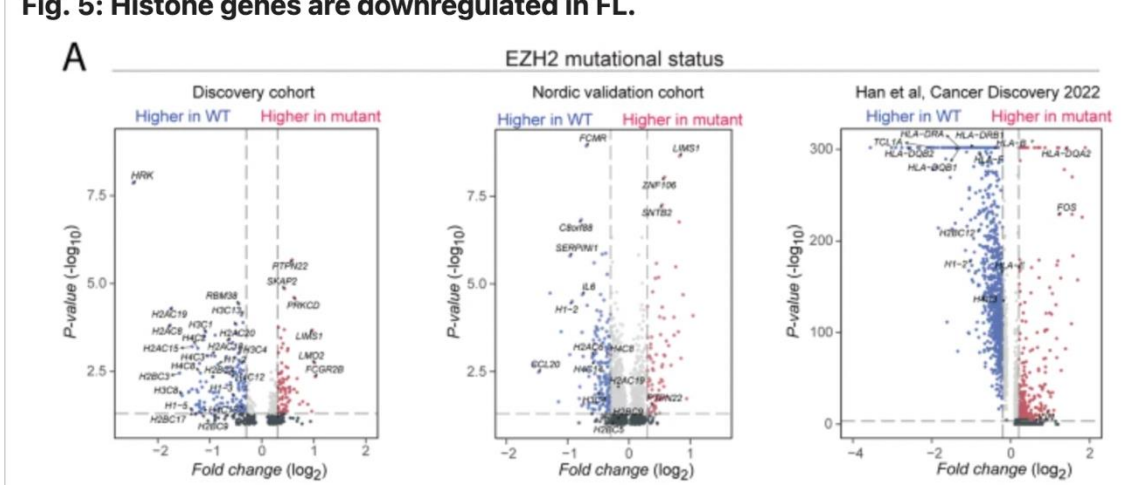
Anemia	12 (4.4)	16 (5.9)
COVID-19	16 (5.8)	6(2.2)
COVID-19 pneumonia	13 (4.7)	3 (1.1)

Efficacy Endpoints by POD24 Status[2]

Variable (95% CI)	POD24 Positive		POD24 Negative	
	Tafa + R^2 (n=121)	Pbo + R^2 (n=128)	Tafa + R^2 (n=142)	Pbo + R^2 (n=140)
Median PFS, mo	19.2 (14.8, NE)	11.5 (8.5, 13.9)	24.0 (22.3, NE)	18.2 (14.4, NE)
HR (95% CI)	0.4 (0.3, 0.7)		0.5 (0.3, 0.7)	
PET-CR, %*	43.2 (33.9, 53.0)	31.4 (23.1, 40.5)	55.0 (46.0, 63.7)	49.2 (40.4, 58.1)
OR (95% CI)	1.7 (1.0, 2.8)		1.3 (0.8, 2.2)	
ORR, %	79.3 (71.0, 86.2)	64.8 (55.9, 73.1)	87.3 (80.7, 92.3)	80.7 (73.2, 86.9)
OR (95% CI)	2.1 (1.2, 3.7)		1.8 (0.9, 3.5)	
Median TTNT, mo†	NR (NE, NE)	17.9 (13.6, NE)	NR (NE, NE)	NR (NE, NE)
HR (95% CI)	0.5 (0.3, 0.8)		0.4 (0.2, 0.8)	

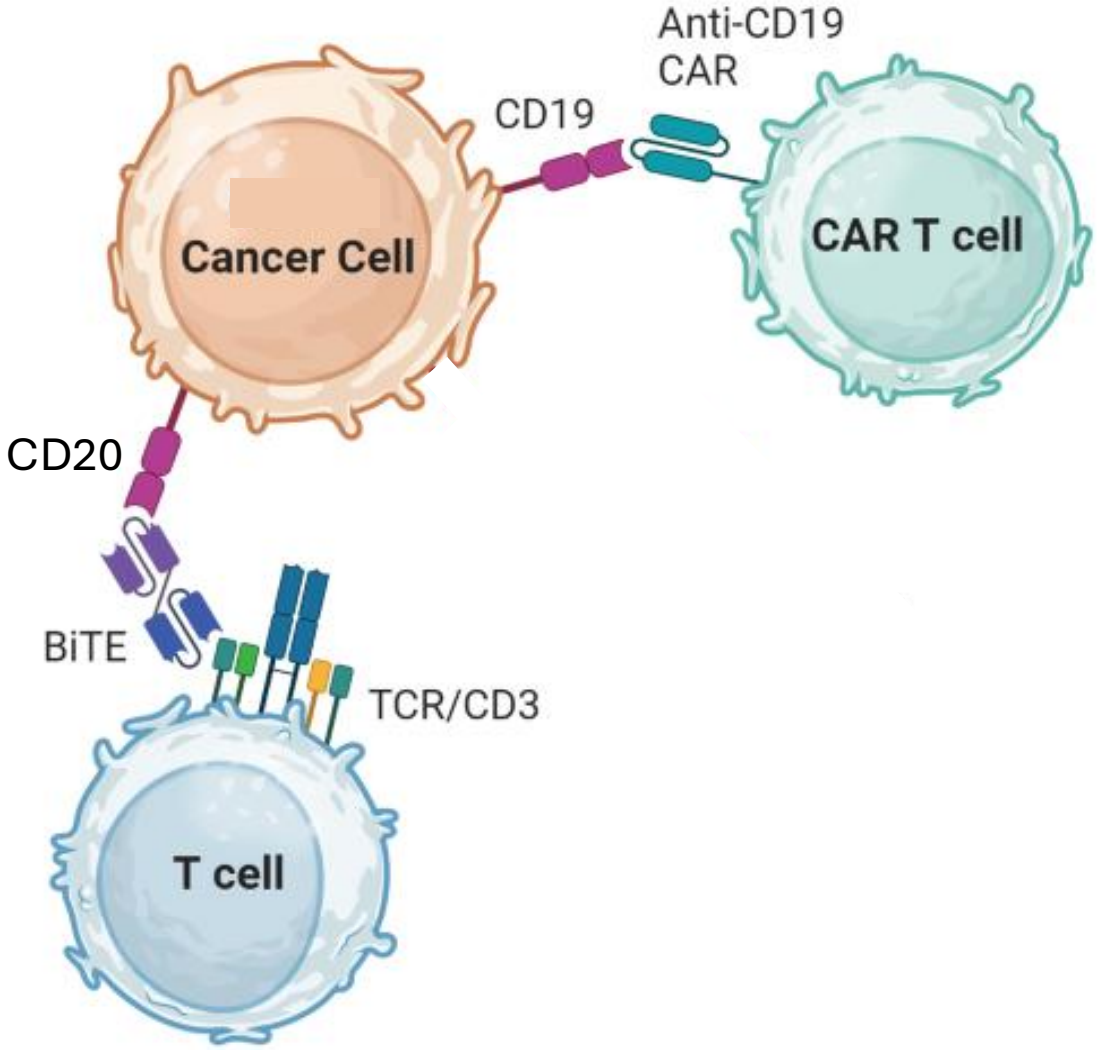
Adapted from: 1. Sehn L, et al. Abstract LBA-2. ASH Annual Meeting 2024.
2. Tmeny M, et al. PS1877. EHA. June 12-15, 2025. Milan, Italy.

Targeting EZH2



- Tazemetostat is a first-in-class oral EZH2 inhibitor that is approved by the FDA for adult patients with R/R FL whose tumors are positive for an *EZH2* mutation and who have received ≥2 prior systemic therapies or who have no satisfactory alternative treatment options.
- Approval of tazemetostat was based on the phase II E7438-G000-101 trial (NCT01897571) in patients with both mutated and wild-type *EZH2*. (Morshhauser et al, Lancet oncol. 2020)
- At data cutoff, with a median follow-up of 22.0 months for the mutated *EZH* cohort and 35.9 months for the wild-type *EZH2* cohort, key efficacy data from this trial include:
  - In patients with mutated *EZH2* (n = 45), overall response rate (ORR) was 69% and complete response rate (CRR) was 13%.
  - In patients with wild-type *EZH2* (n = 54), ORR was 35% and CRR was 4%.
  - Progression-free survival was similar between both groups (13.8 months for mutated *EZH2* and 11.1 months for wild-type *EZH2*).
  - The duration of response was 10.9 months in patients with a mutated *EZH2* and 13 months in patients with wild-type *EZH2*.
  - Tazemetostat benefited both patients with mutated and wild-type *EZH2*, even though patients with mutated *EZH2* have notably better prognostic factors.

Treatment options at relapse: the present and future



Response Rates and Outcomes

Key CAR T-cell Therapies in FL

	Ph2 ZUMA-5 Axi-cel[1]	Ph2 TRANSCEND-FL Liso-cel[2,3]	Ph2 ELARA Tisa-cel[4,5]
N	127	114	97
Median Follow-Up	65.7 mo*	29.5 mo (for OS)**	53 mo
ORR	**94%***	**97%**	**86%**
CR	79%*	94%	69%

1. Neelapu SS, et al. Abstract 864. ASH Annual Meeting 2024. 2. Nastoupil, et al. Abstract 4387, ASH Annual Meeting 2024. 3. Morschhauser F, et al. Nat Med. 2024; 30:2199-2207.
4. Thieblemont, et al. Abstract 3034, ASH Annual Meeting 2024. 5. Fowler NH, et al. Nat Med. 2022 Feb;28(2):325-332.

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Median Follow-Up	65.7 mo*	29.5 mo (for OS)**	53 mo
ORR	**94%***	**97%**	**86%**
CR	79%*	94%	69%
Median DOR	60.4 mo*	24-mo rate: 74.6%**	24-mo rate: 66.4%
TTNT	NR; 60-mo rate: **54.0%***	NR; 24-mo rate: **80.1%****	NR; 24-mo rate: **69.7%**
Median OS	NR; 60-mo rate: 68.9%*	NR, 24-mo rate: 88.2%**	NR; 24-mo rate: 87.7%
Median PFS	**57.3 mo***	NR; 24-mo rate: **72.5%****	**53.3 mo**

1. Neelapu SS, et al. Abstract 864. ASH Annual Meeting 2024. 2. Nastoupil, et al. Abstract 4387, ASH Annual Meeting 2024. 3. Morschhauser F, et al. Nat Med. 2024; 30:2199-2207.
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TTNT	NR; 60-mo rate: **54.0%***	NR; 24-mo rate: **80.1%****	NR; 24-mo rate: **69.7%**
Median OS	NR; 60-mo rate: 68.9%*	NR, 24-mo rate: 88.2%**	NR; 24-mo rate: 87.7%
Median PFS	**57.3 mo***	NR; 24-mo rate: **72.5%****	**53.3 mo**
CRS (grade ≥3)	78% (6%)	58% (1%)	49% (0%)
ICANS (grade ≥3)	56% (18%)	15% (2%)	23% (1%)

1. Neelapu SS, et al. Abstract 864. ASH Annual Meeting 2024. 2. Nastoupil, et al. Abstract 4387, ASH Annual Meeting 2024. 3. Morschhauser F, et al. Nat Med. 2024; 30:2199-2207.
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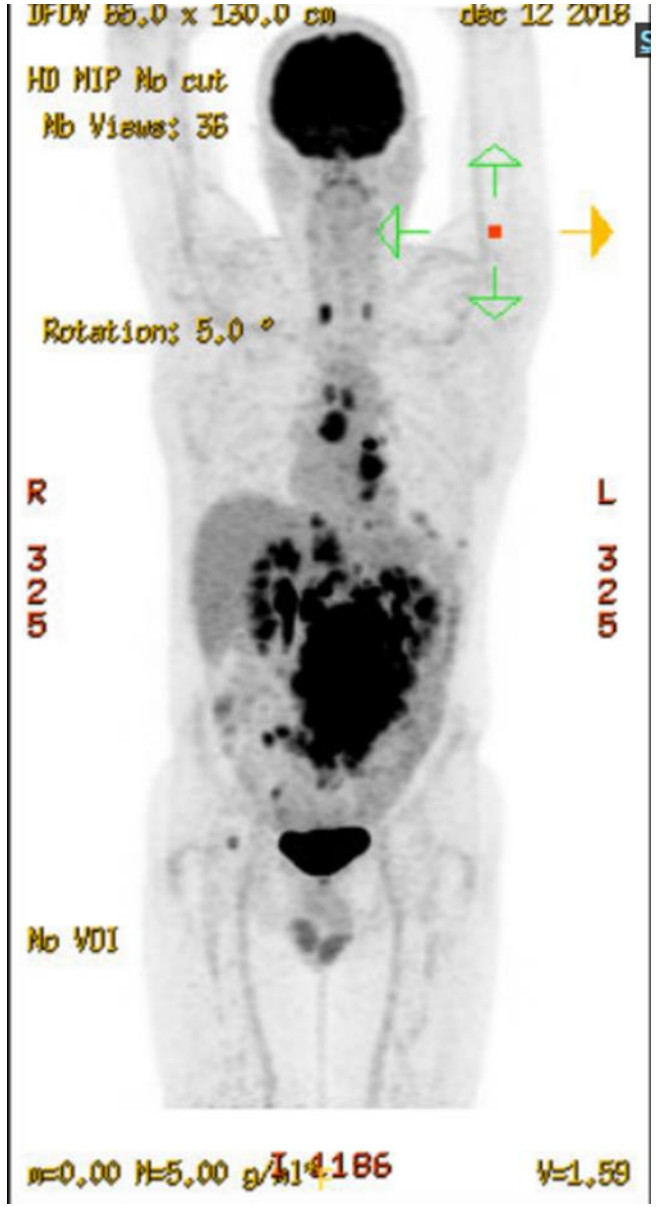
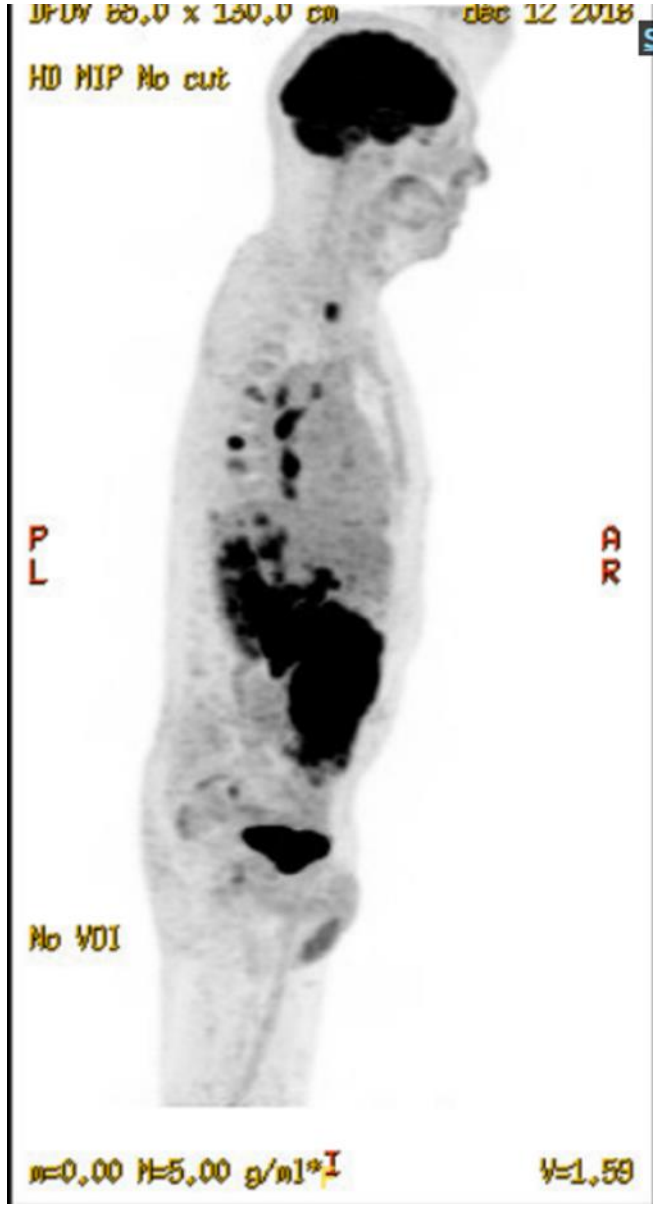
53 ans à la PEC pr les CAR T

lymphome folliculaire multitraité réfractaire

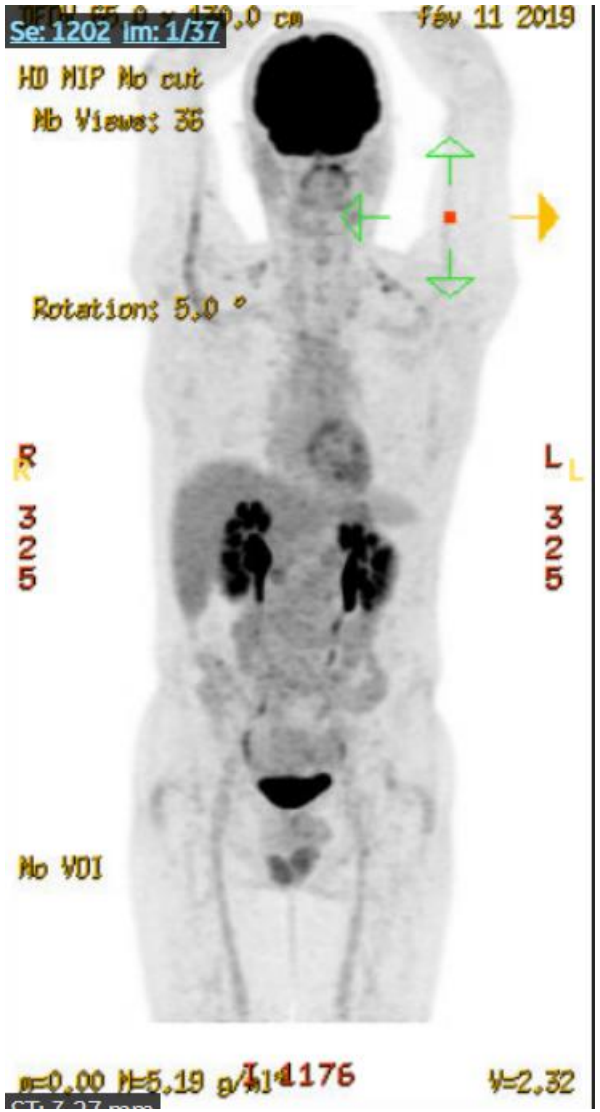
- L1 R-CHOP
- L2 R-DHAOX IBRUTINIB (essai BIBLOS)
- L3 GA 101 REVLIMID
- L4 GA 101 BENDAMUSTINE
- L5 ICE
- L6 Idelalisib
- L7 R-Gemox

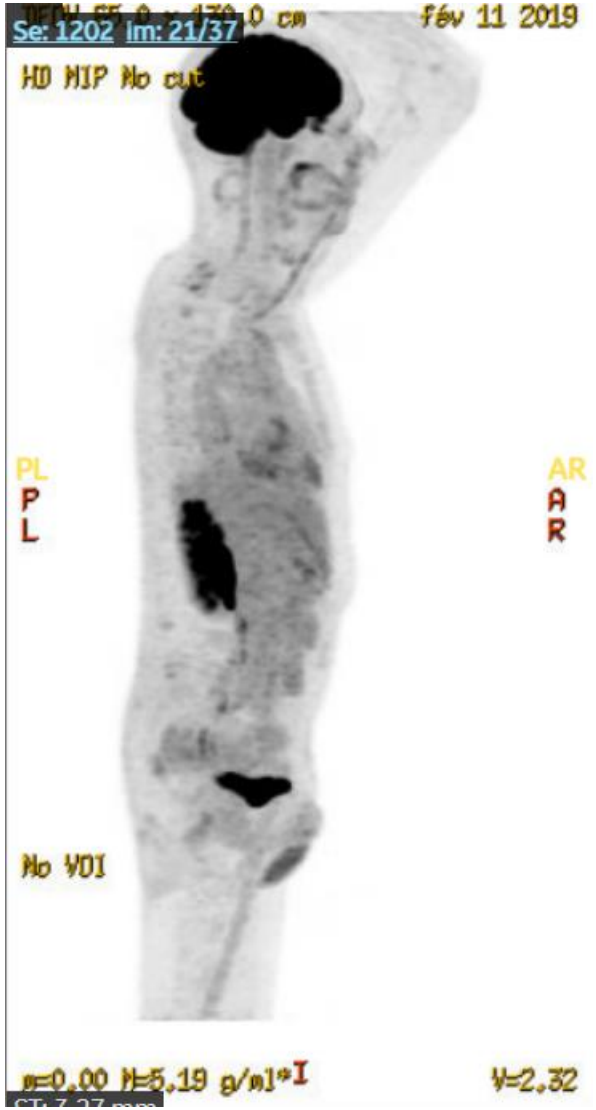




Tep pré CAR T 12/12/2018

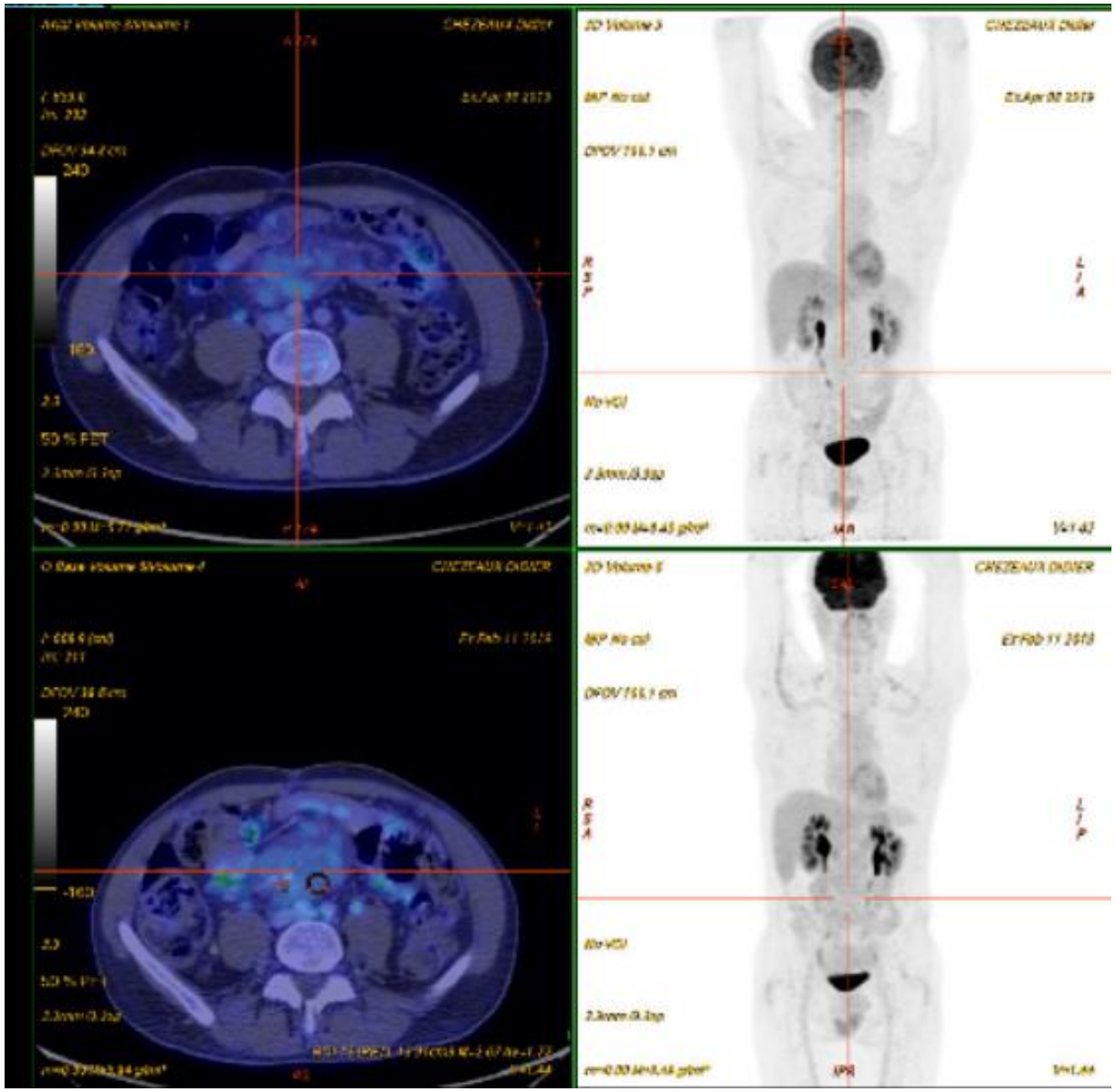
LD 09-11/01/19
J0= 14/01/19





TEP M1 11/02/19

Réponse métabolique et morphologique quasi-complète en sus diaphragmatique. En sousdiaphragmatique il persiste une réponse morphologique de l'ordre de 75% avec persistance d'un hypermétabolisme modéré pour un SUV max à 2,54.
Deauville 3

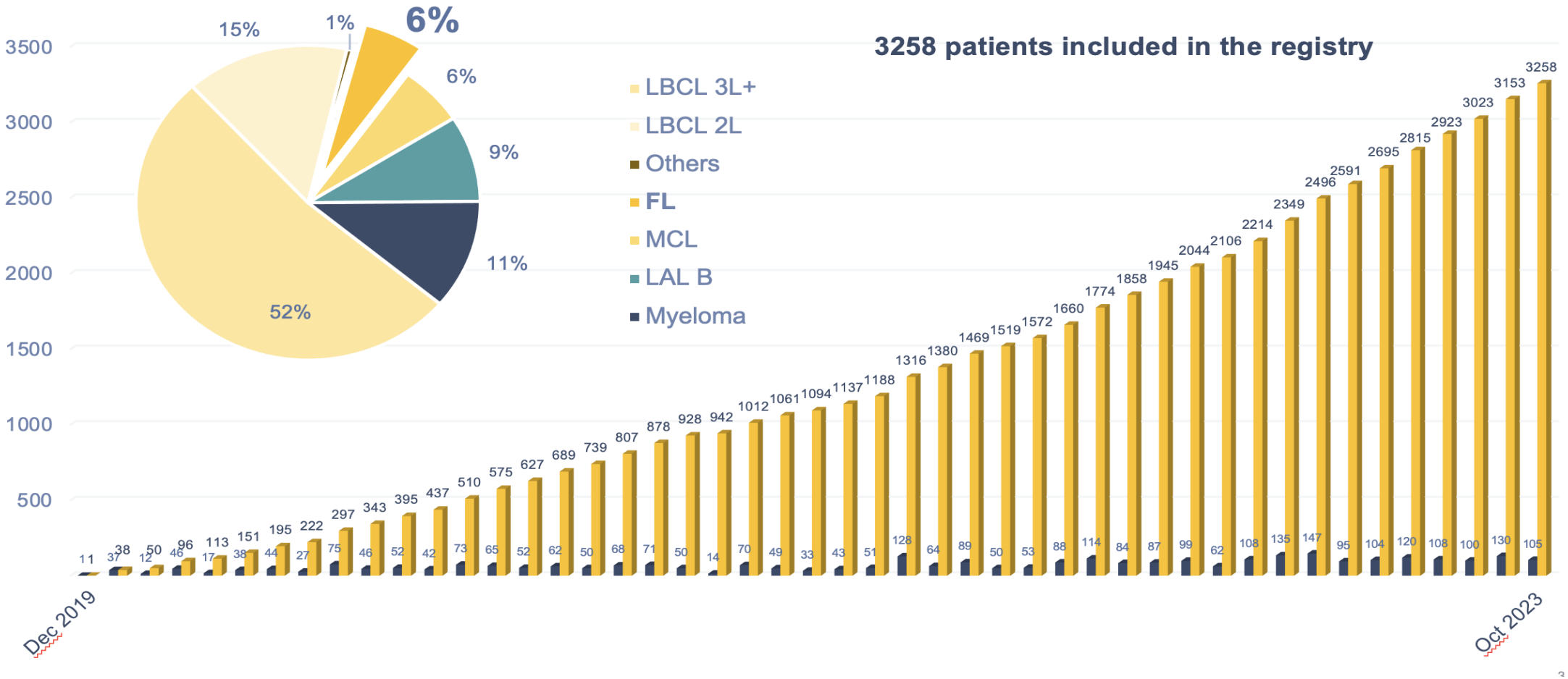


TEP M3 08/04/19

aspect de réponse métabolique complète Deauville 2, morphologique partielle mais avec poursuite d'une régression morphologique de l'atteinte mésentérique (72*39 mm de diamètre axial versus 80*45 précédemment, SUVmax 2.27 versus 2.67)

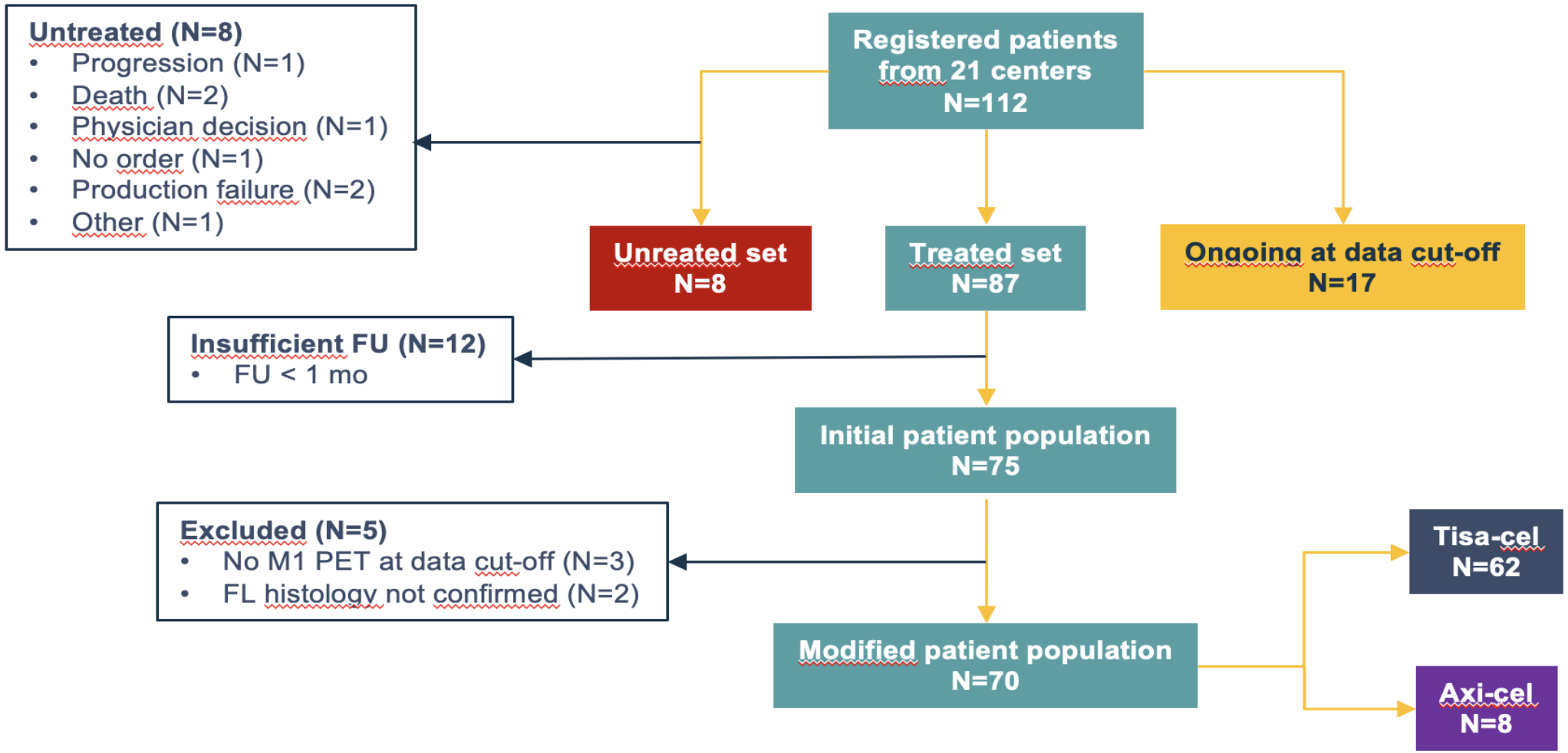
- Dernière visite de suivi= 04/11/24= 5 ans
- Sera vu le 03/11/25

CAR T in FL : real world evidence data (DESCART registry)



Bachy et al, ASH 2023

CAR T in FL : real world evidence data (DESCART registry)

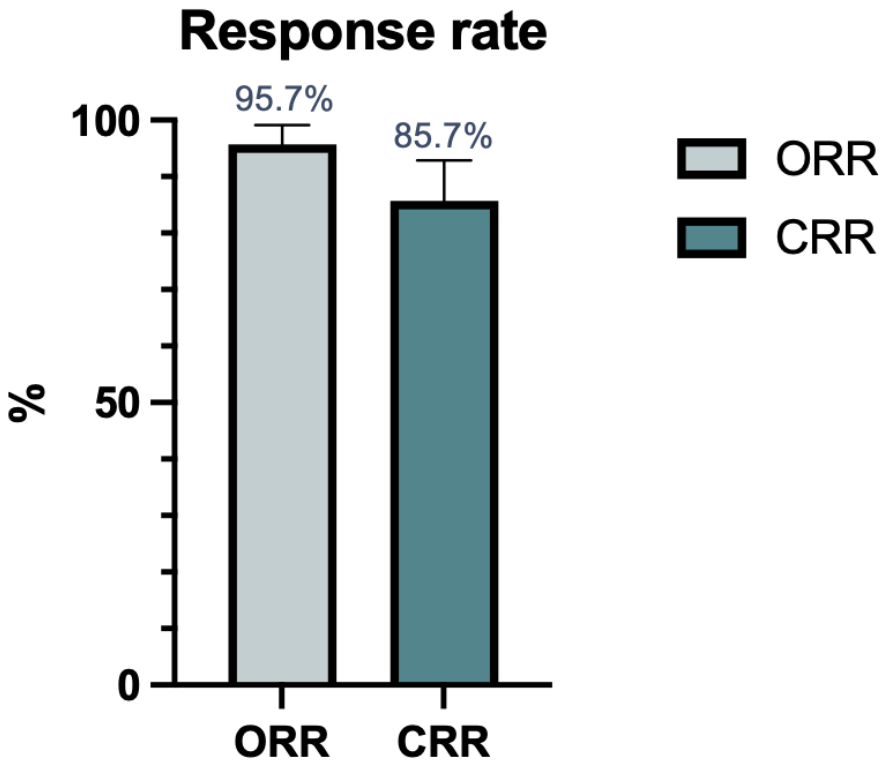


Bachy et al, ASH 2023

CAR T in FL : real world evidence data (DESCART registry)

	Patient population	
	N=70	
Best ORR		
Best ORR (CR/PR)	67	(95.7%)
95% CI	[88.0% ; 99.1%]	
Best CRR		
Best CRR	60	(85.7%)
95% CI	[75.3% ; 92.9%]	

*defined as the best response according to the Lugano 2024 classification at 1, 3 or 6 months



Turning point in FL therapy

Bachy et al, ASH 2023

Baseline Characteristics

Key Bispecific Antibody Studies in FL: 3L+ Monotherapy

	Ph 1/2 EPCORE NHL-1 Epcoritamab[1]	Ph 2 GO29781 Mosunetuzumab[2,3]	Ph 2 ELM-2 Odronextamab[4]
N	128	90	128
Median Follow-Up	17.4 mo	49.4 mo	20.1 mo
Median age, years (range)	65 (55–72)	60 (29-90)	61.0 (22-84)
Ann Arbor stage III-IV	85%	77%	85%
FLIPI 3-5	61%	--	58%
Bulky disease	26%	34%	14%
POD24	52%	52%	49%
Median prior LOT (range)	3 (2-4)	3 (2-10)	3 (2-13)
Refractory to last systemic tx	69%	69%	72%
Refractory to prior anti-CD20 tx	79%	79%	74%
Double refractory	70%	53%	41%

.

1. Linton KM, et al. Lancet Haematol. 2024 Aug;11(8):e593-e605. 2. Shadman M, et al. Abstract 4407. ASH Annual Meeting 2024. 3. Sehn LH, et al. Blood. 2025 Feb 13;145(7):708-719.
4. Kim TM, et al. Ann Oncol. 2024 Nov;35(11):1039-1047.

Key Bispecific Antibody Studies in FL: 3L+ Monotherapy

	Ph 1/2 EPCORE NHL-1 Epcoritamab[1]	Ph 2 GO29781 Mosunetuzumab[2,3]	Ph 2 ELM-2 Odronextamab[4]
N	128	90	128
Median Follow-Up	17.4 mo	49.4 mo	20.1 mo
ORR	82%	78%	80%
CR	62%	60%	73%
Median PFS	15.4 months	24 months	20.7 months
CRS grades 3-4	2%	1%	2%
ICANS grade 3-4	0%	0%	3%

.

1. Linton KM, et al. Lancet Haematol. 2024 Aug;11(8):e593-e605. 2. Shadman M, et al. Abstract 4407. ASH Annual Meeting 2024. 3. Sehn LH, et al. Blood. 2025 Feb 13;145(7):708-719.
4. Kim TM, et al. Ann Oncol. 2024 Nov;35(11):1039-1047.

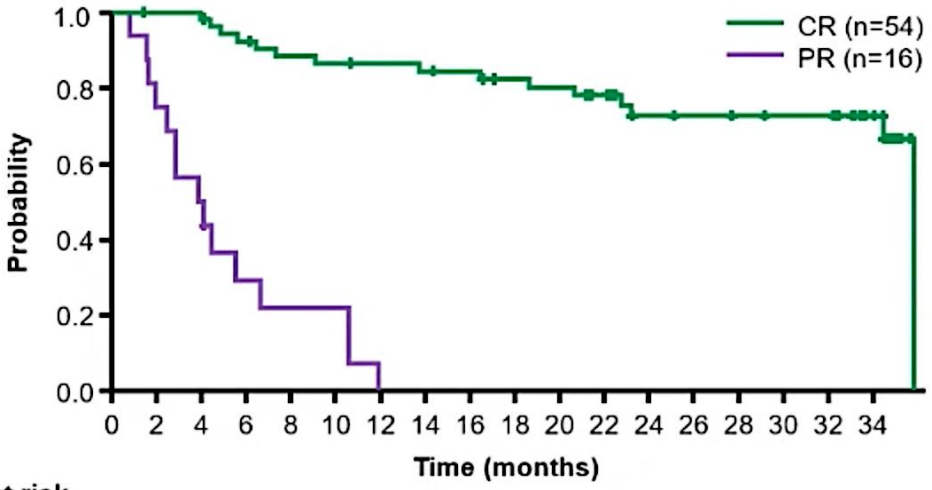
Treatment options at relapse: cell therapy and cell engagers

	Mosunetuzumab (n=90)[1]	Epcoritamab (n=128)[2]	Odronextamab (n=128)[3]	Axi-cel (n=124)[4]	Tisa-cel (n=97)[5]	Liso-cel (n=107 3L+)[6]
Age (IQR or range)	60 (IQR=53-67)	65 (IQR=55-72)	61 (range=22-84)	60 (IQR=53-67)	57 (range=29-73)	62 (range=23-80)
Female	39%	38%	47%	41%	34%	38%
ECOG 1 (v 0)	41%	40% (5%=2)	48% (1%=2)	37%	43%	39%
Stage III/IV	77%	85%	85%	85%	86%	89%
FLIPI 3/4/5	**44%**	**61%**	**58%**	**44%**	**60%**	**57%**
GELF criteria	NA	NA	NA	52%	**>64% (bulk)**	**53% (modified)**
Median previous lines	3 (IQR=2-4)	3 (IQR=2-4)	3 (range=2-13)	3 (IQR=2-4)	**4 (range=2-13)**	3 (range=2-10)
Prior transplant	21%	NA	30%	24%	36%	31%
Refractory last line	69%	69%	72%	68%	78%	65%
POD24 (from therapy initiation)	**52%**	**42%**	**49%**	**55%**	**63%**	**54%**
Bridging	NA	NA	NA	3% (not allowed)	**45%**	38%
Longest follow-up (months)	**18**	**17**	**20**	**53**	**41**	**17**
ORR	**80%**	**82%**	**80%**	**94%**	**86%**	**97%**
CRR	**60%**	**62%**	**73%**	**79%**	**69%**	**94%**
TTR (median in months)	1.4	1.4	2.6	1	3 (1st assessment)	1
PFS (median in months)	**18**	**24**	**21**	**57**	**37**	**NR**
1-yr PFS	58%	60%	66%	78%	67%	81%
CRS (grade 3+)	**42% (2%)**	**67% (2%)**	**56% (2-6%)**	**78% (6%)**	**48% (0%)**	**59% (1%)**
ICANS (grade 3+)	**5% (0%)**	**0% (0%)**	**1% (0%)**	**56% (15%)**	**4% (1%)**	**15% (2%)**
Cytopenia of grade 3+ after D30 for CAR T	NA	NA	NA	33%	NA	24%

[1]Budde et al., Lancet Oncol, 2022, [2]Linton et al., Lancet Haematol 2024, [3]Unpublished (accepted for publication in Ann Oncol), [4]Jacobson et al., Lancet Oncol, 2021 (and Neelapu et al., ASH 2024), [5]Fowler et al., Nat Med, 2021 (and Dreyling et al., EHA 2024), [6]Morschhauser et al., Nat Med 2024

Prognostic value of response quality

mosunetuzumab

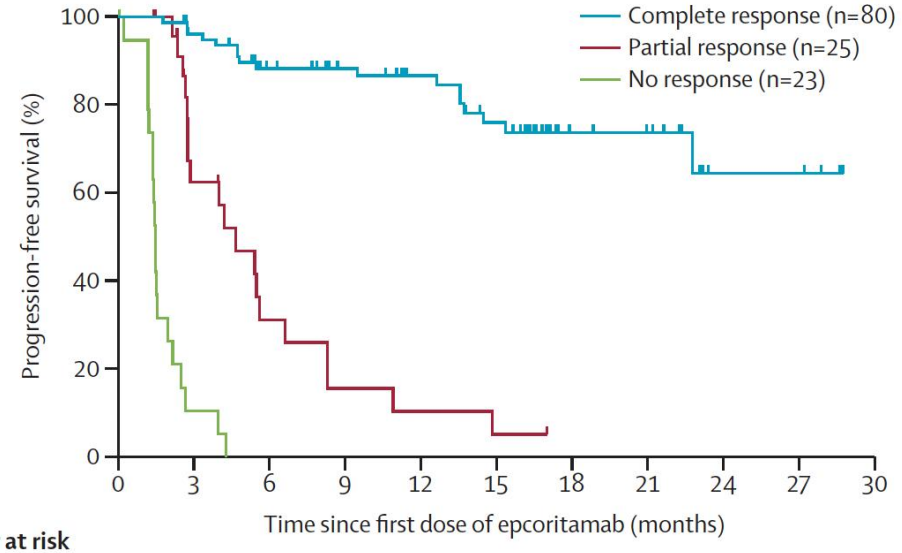


Patients at risk

CR	54	53	52	48	45	44	43	42	41	38	37	34	26	25	24	23	23	15
PR	16	12	8	4	3	3	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Schuster et al, ASH 2023

epcoritamab



Number at risk (number censored)											
Complete response	80	75	61	54	41	34	14	12	4	4	0
	(0)	(2)	(10)	(17)	(29)	(31)	(50)	(52)	(59)	(59)	(63)
Partial response	25	13	6	3	2	1	0	0	0	0	0
	(0)	(4)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(6)
No response	23	2	0	0	0	0	0	0	0	0	0
	(0)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

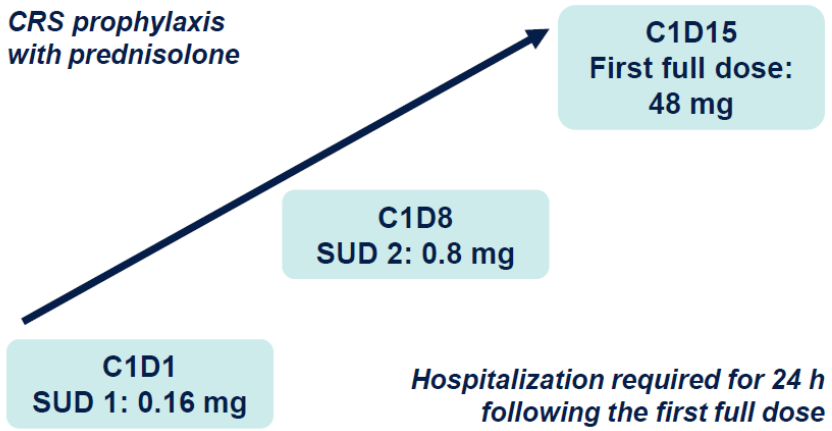
Linton et al., Lancet Haematol 2024

First C1 OPT–Focused Data Disclosure From EPCORE® NHL-1

Key inclusion criteria

- R/R CD20+ FL grade 1–3A
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 regimen with an anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide
- FDG-avid disease by PET/CT
- Prior CAR T allowed

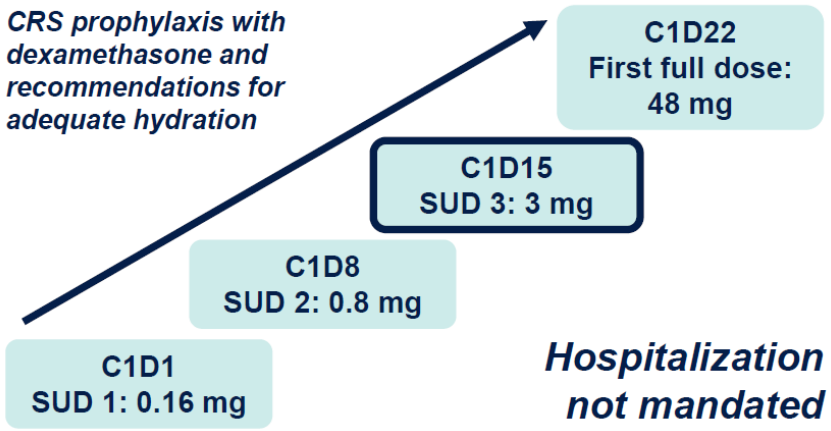
Pivotal[a]



Primary objective: ORR by independent review committee

Data cutoff: April 21, 2023
Median follow-up: 17.4 mo

C1 optimization[a]



Primary objective: Assess incidence and severity of CRS

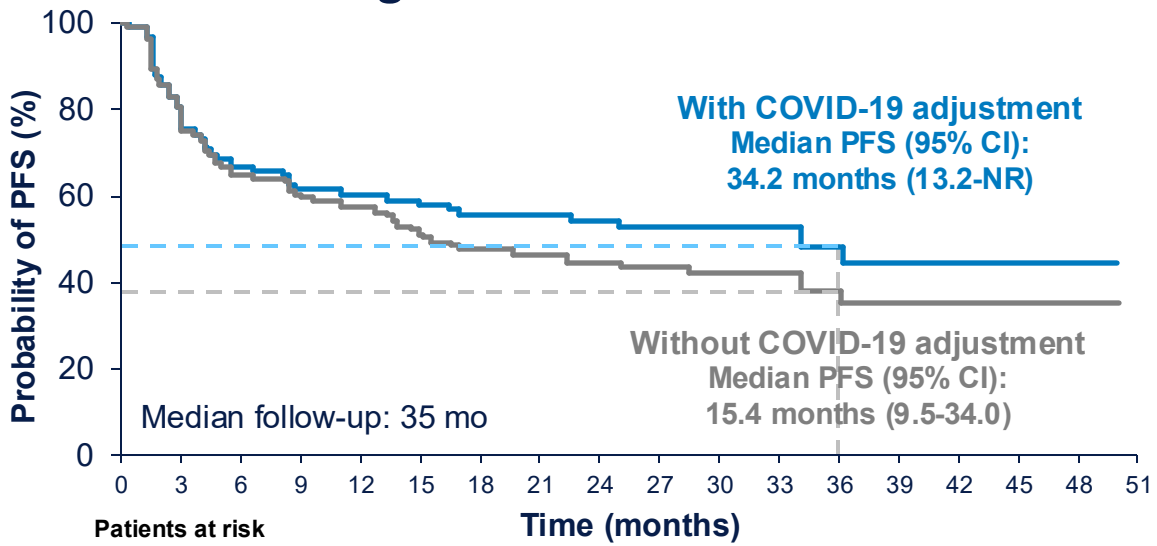
Data cutoff: January 8, 2024
Median follow-up: 5.7 mo

Phase 1/2 trial. C, cycle; CAR T, chimeric antigen receptor T-cell therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; MRD, minimum residual disease; OPT, optimization; ORR, overall response rate; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SUD, step-up dose. [a]Patients received subcutaneous epcoritamab QW C1–3, Q2W C4–9, and Q4W C≥10 until progressive disease (≥2 measurable [by CT/MRI] and FDG PET–positive lesions) or unacceptable toxicity. Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. MRD was assessed in peripheral blood using the clonoSEQ® (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001748-36.

Epcoritamab Monotherapy in 3L+ FL

Phase 1/2 EPCORE NHL-1

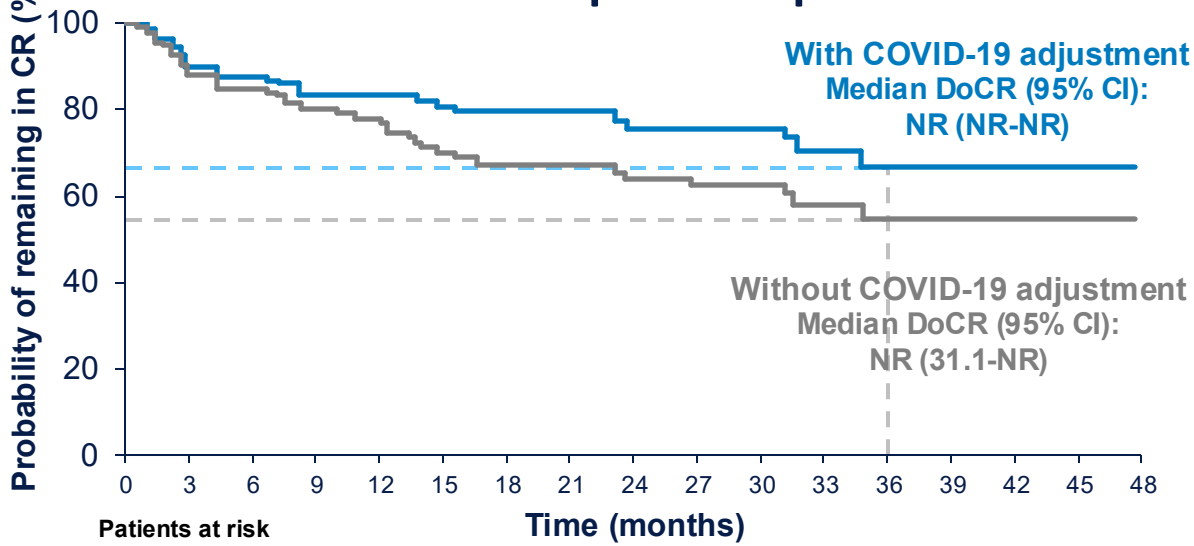
Progression-free Survival



Patients at risk

w/out COVID-19 adj:	128	89	76	70	66	58	51	49	39	38	26	25	15	10	6	1	1	0
w/ COVID-19 adj:	128	88	74	68	59	56	49	48	38	37	26	25	15	10	6	1	1	0

Duration of Complete Response



Patients at risk

	100	85	82	76	72	62	56	50	45	36	31	20	16	7	3	1	0	
	100	84	80	72	66	60	56	50	44	36	31	20	16	7	3	1	0	

Outcome	**N=149**
ORR	**85%**
CR	67%
mDoR, months (with COVID-19 adj.)	**NR**
without COVID-19 adj.	31.6 mo

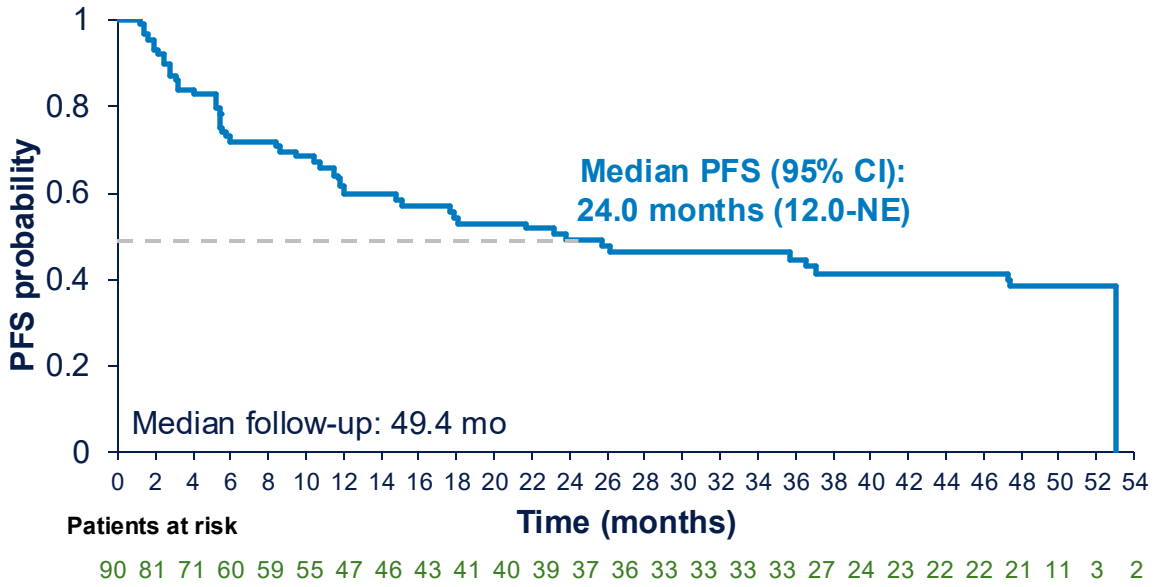
Most Common AEs, All Grades	**N=149**
CRS (with Opt. SUD)	70%
Injection-site reaction	42%
COVID-19	36%
Fatigue	30%
CRS	**Opt. SUD, N=86**
All Grades	49%
Grade 3-4	0

Epcoritamab is not approved for the treatment of FL in Switzerland.
Median follow-up: 35 months (for cycle 1 optimization cohort, median follow-up was 15.5 months)
AE, adverse event; CR, complete response; CRS, cytokine release syndrome; DoCR, duration of complete response; DoR, duration of response; FL, follicular lymphoma; L, line; m, median; NR, not reached; Opt. SUD, optimized step-up dose; ORR, overall response rate; PFS, progression-free survival.
Adapted from Vitolo U. et al. Abstract PF881. EHA Congress 2025, Milan.

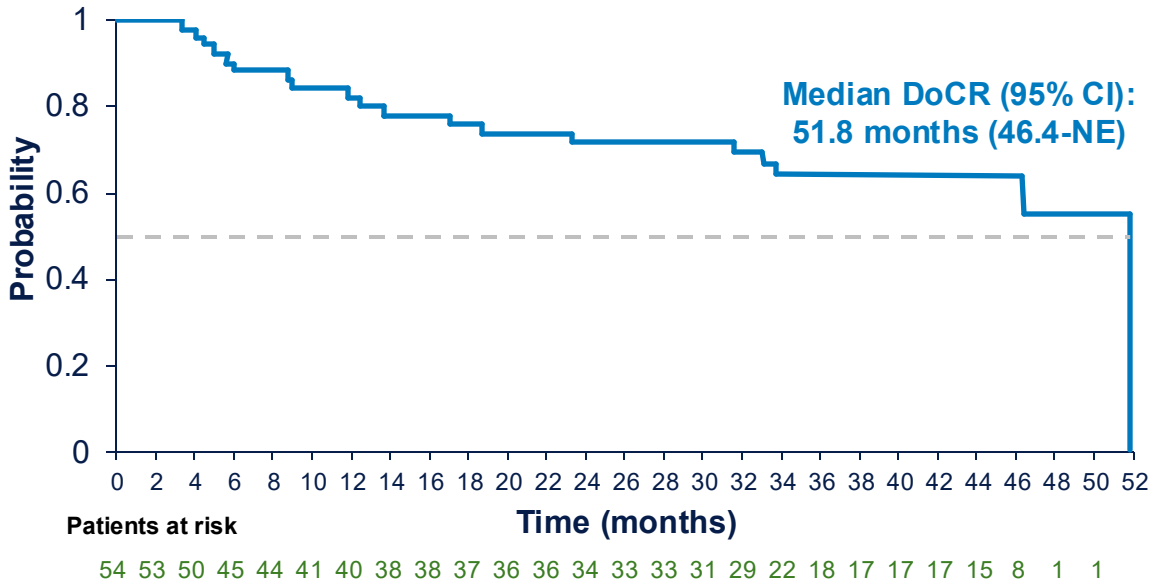
Mosunetuzumab Monotherapy in 3L+ FL

Phase 1/2 GO29781

Progression-free Survival[1]



Duration of Complete Response[1]



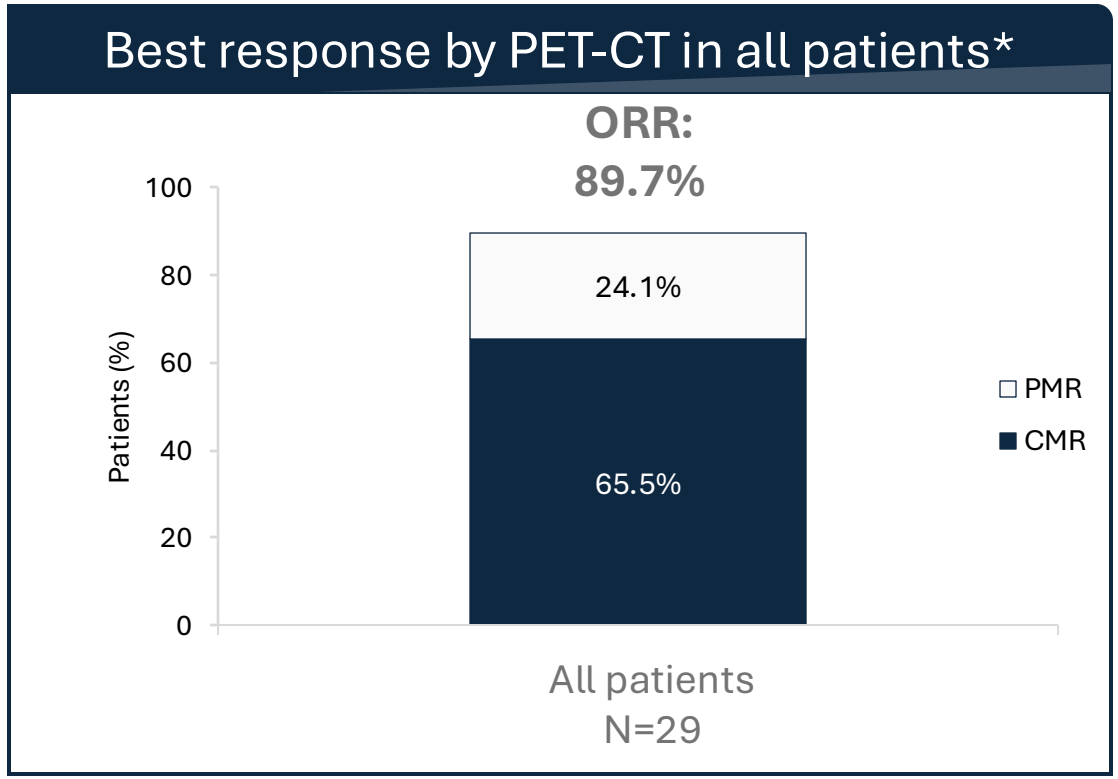
Outcome[2]	N=90
ORR	**80%**
CR	60%
mDoR, months	46.4

Most Common AEs, All Grades[3]	N=90
CRS (Grade 3-4)	44% (2%)
Fatigue	44%
Rash	42%
Headache	39%
Pyrexia	32%

1. Shadman M, et al. Abstract 4407. ASH Annual Meeting. Dec. 7-11, 2024. 2. Schuster, et al. Oral #603. ASH Annual Meeting. Dec. 8-12, 2023. 3. Budde E, et al. Lancet Oncol. 2022 Aug;23(8):1055-1065.

IMiDs and bispecifics in FL

Mosu-len



Morschhauser et al., ASH 2021

Epco-len

n (%)	Total N=30
Evaluable pts	27
Overall response	27 (100)
Complete metabolic response (CMR)	25 (93)
Partial metabolic response	2 (7)
Stable disease	0
Progressive disease	0

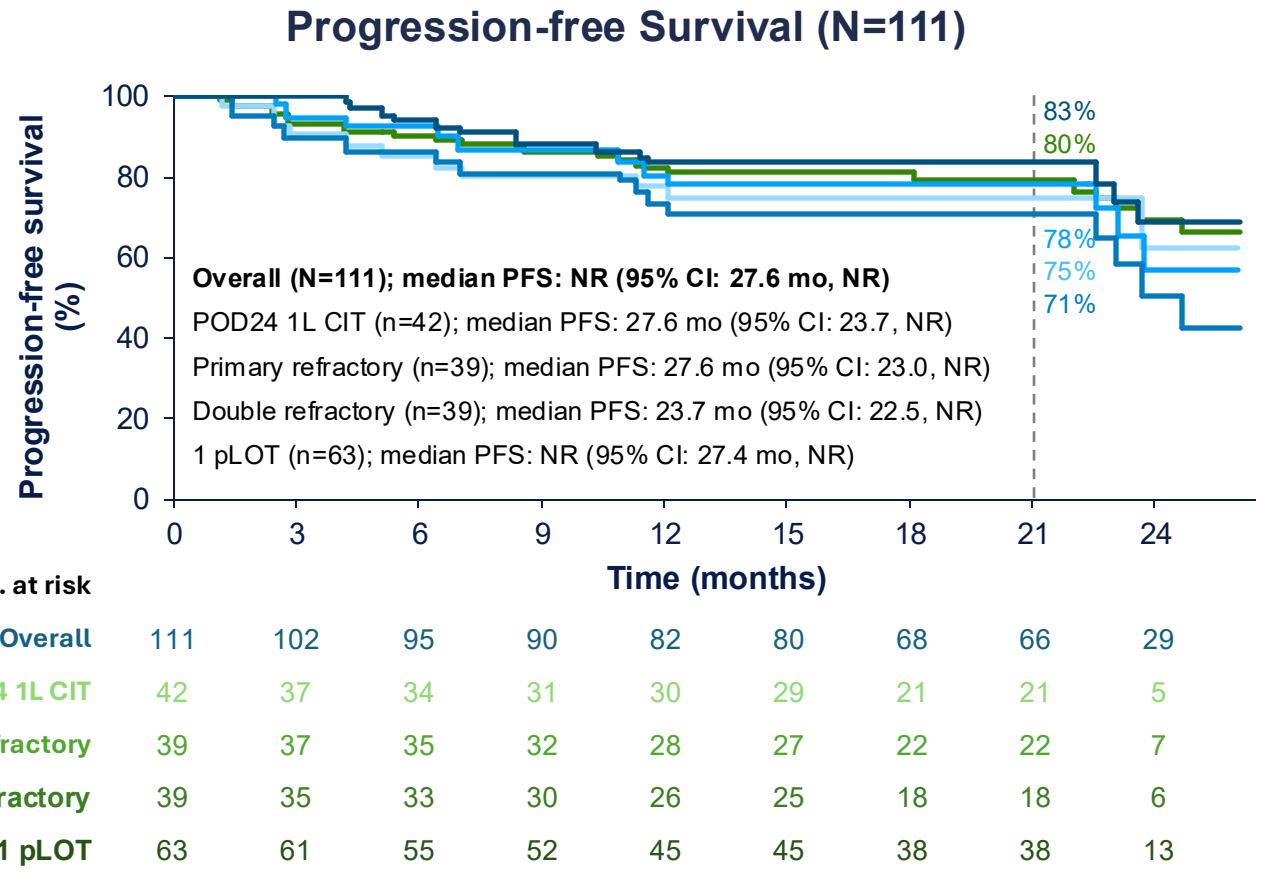
Falchi et al., ASCO 2022

Phase 2 EPCORE NHL-2 Arm 2

Epcoritamab + R^2 in 2L FL

Outcomes, n (%)	Epcor + R^2 (N=111)
ORR	96%
CR	87%
MRD-negativity, any time	88%
Median DOCR, months	NR

Common TEAEs, All Grades | Gr ≥3	Epcor + R^2 (N=111)
Neutropenia[a]	62% | 53%
COVID-19[b]	57% | 24%
CRS	52% | 2%
Diarrhea	46% | 4%
ISR[c]	44% | 0%
Fatigue	39% | 3%
Constipation	36% | 1%

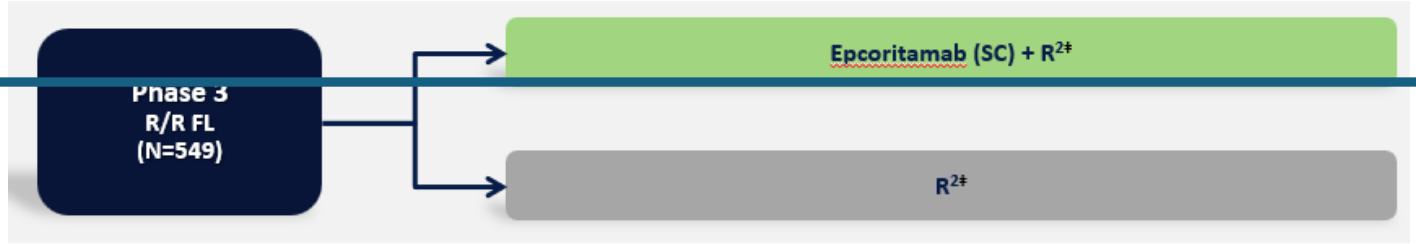


No. at risk									
Overall	111	102	95	90	82	80	68	66	29
POD24 1L CIT	42	37	34	31	30	29	21	21	5
Primary refractory	39	37	35	32	28	27	22	22	7
Double refractory	39	35	33	30	26	25	18	18	6
1 pLOT	63	61	55	52	45	45	38	38	13

Adapted from Falchi L, et al. Abstract 342. ASH Annual Meeting 2024.

Phase 3

EPCORE FL-1



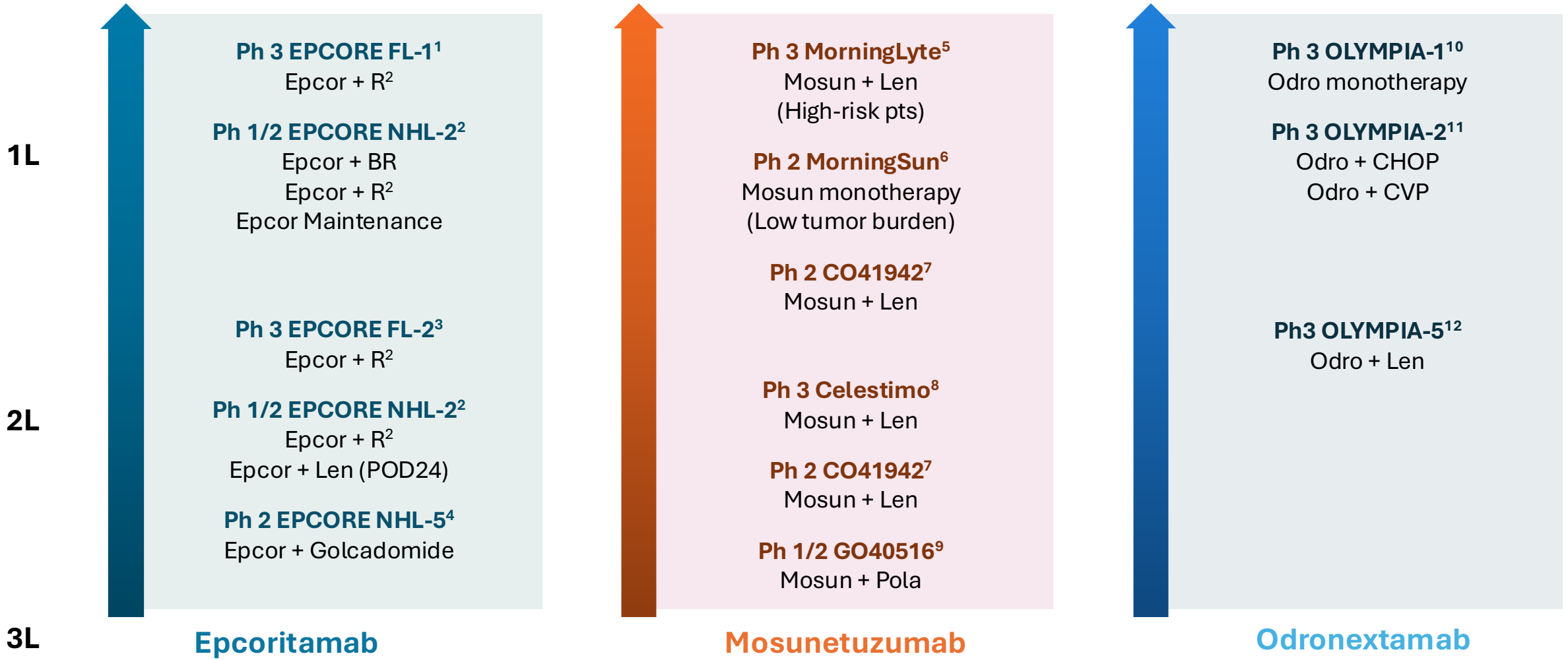
Genmab Announces Phase 3 EPCORE® FL-1 Clinical Trial Met Dual Primary Endpoints in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

Aug 7, 2025 at 4:30 PM CEST

- **Epcoritamab in combination with rituximab and lenalidomide (R^2) demonstrated statistically significant improvement in Overall Response Rate (ORR; 95.7%, p < 0.0001) and Progression-Free Survival (HR 0.21, p-value <0.0001) versus R^2 alone in patients with relapsed/refractory (R/R) Follicular Lymphoma (FL)**
- **Results from EPCORE FL-1 form the basis of global regulatory submissions**
- **U.S. FDA has accepted for priority review new supplemental Biologics License Application (sBLA) for epcoritamab plus R^2, with action date of November 30, 2025**
- **If approved, epcoritamab plus R^2 would be the first bispecific antibody combination regimen available as a second-line treatment option for patients with R/R FL**

https://ir.genmab.com/news-releases/news-release-details/genmab-announces-phase-3-epcorer-fl-1-clinical-trial-met-dual/

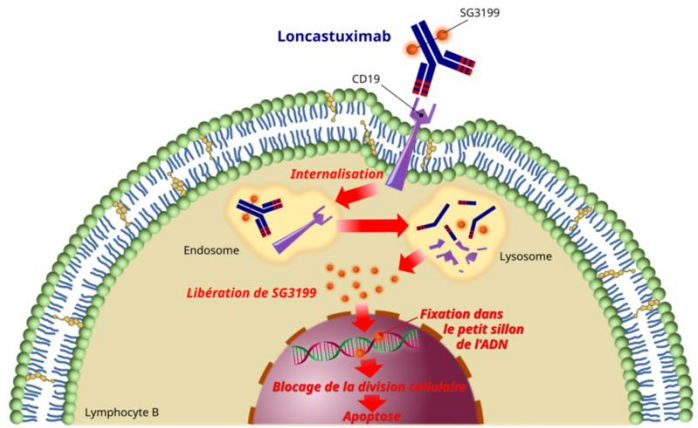
Bispecific Development in FL



BR, bendamustine + rituximab; Epcor, epcoritamab; FL, follicular lymphoma; L, line; Len, lenalidomide; Mosun, mosunetuzumab; Odro, odronextamab; Ph, phase; POD24, Progression of Disease within the first 24 months; Pola, polatuzumab; R², rituximab + lenalidomide.

1. NCT05409066. 2. NCT04663347. 3. NCT06191744. 4. NCT05283720. 5. NCT06284122. 6. NCT05207670. 7. NCT04246086. 8. NCT04712097. 9. NCT03671018. 10. NCT06091254. 11. NCT06097364. 12. NCT06149286.

Therapy	Trial identifier	Trial phase	Publication	Follow-up, median, months	Number of patients with R/R FL	Number of prior therapies, median (range)	Efficacy outcomes reported (95% CI)
Polatuzumab vedotin + obinutuzumab + venetoclax	NCT02611323	1b	Lasater et al. 2023 [74]	-	33	3 (1–7)	ORR: 75.8% CRR: 57.6%
Polatuzumab vedotin + obinutuzumab + lenalidomide	NCT02600897	1b/2	Diefenbach et al. 2021 [75]	26.7	46	3 (IQR 2–4)	ORR: 76% (64–86) CRR: 63% (50–75) mPFS: NE
Loncastuximab tesirine	NCT04998669	2	Alderuccio et al. 2023 [62]	4.8	26	1 (1–6)	ORR: 95.2% CRR: 66.7%
Relmacabtagene autoleucel	RELIANCE (NCT04089215)	2	Song et al. 2022 [64]	11.7	28	-	6-month ORR: 92.6% (75.7–99.1) 6-month CRR: 77.8% (57.7–91.4) mPFS: NR
Lisocabtagene maraleucel	TRANSCEND FL (NCT04245839)	2	Morschhauser et al. 2024 [49]	18.1	130	2 (1–10)	ORR: 93% (87.2–96.5) CRR: 91% (84.5–94.9) mPFS: NR (21.4-NR)
Pirtobrutinib	BRUIN (NCT03740529)	1/2	Shah et al. 2023 [65]	18.4	48	3 (1–12)	ORR: 50.5% (35.2–64.8) CRR: 14.6%



Zinzani Exp and Hematology, 2024

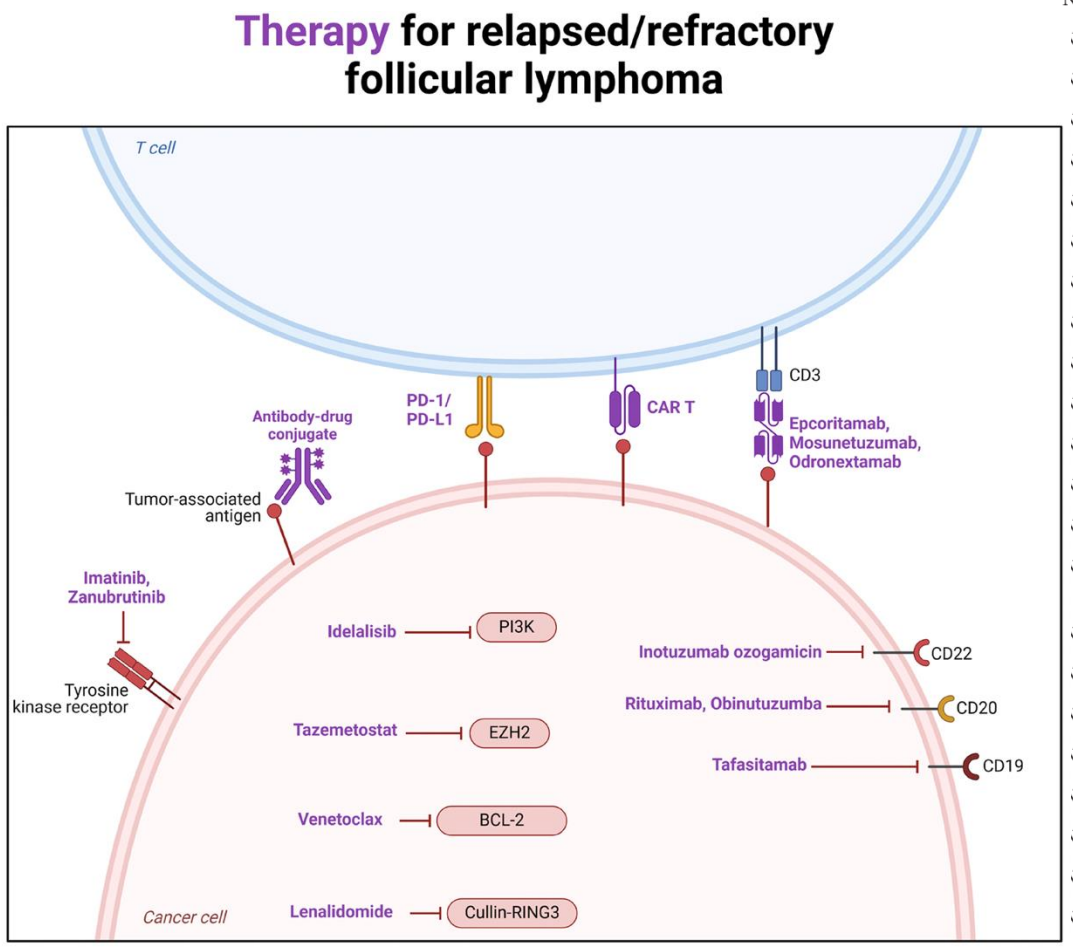


FIGURE 1 | Mechanism of action of new drugs for R/R FL.

TABLE 2 | Ongoing trials involving new molecules or new combinations of drugs for R/R FL.

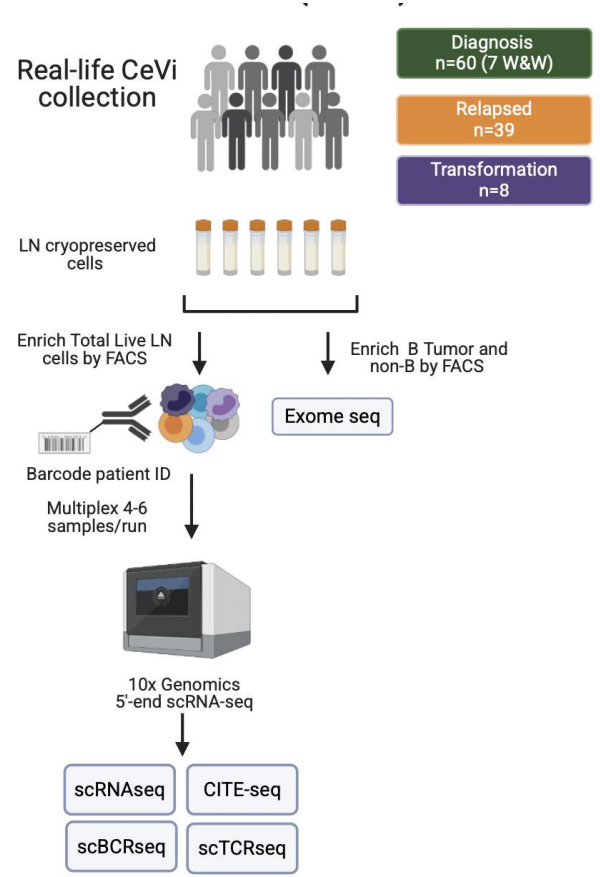
NCT code	Phase	Experimental therapy	Endpoint
NCT04224493	III	Tazemetostat in combination with lenalidomide plus rituximab	PFS, safety
NCT02956382	I/II	Ibrutinib plus venetoclax	Recommended dose, ORR
NCT04587687	II	Brentuximab vedotin plus bendamustine	CR
NCT06492837	II	Mosunetuzumab plus zanubrutinib	CR
NCT06368167	II	SHR2554	ORR
NCT03600441	II	Abexinostat	ORR
NCT04998669	II	Loncastuximab tesirine plus rituximab	CR
NCT03269669	II	Obinutuzumab plus lenalidomide or umbrelasib or CHOP	CR
NCT02390869	III	Rituximab plus lenalidomide versus rituximab alone	PFS
NCT06575686	II	Epcoritamab plus tazemetostat	Safety, CR
NCT06453044	II	Mosunetuzumab plus polatuzumab vedotin	Safety, CR
NCT04712097	III	Mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide	PFS
NCT06563596	II	Epcoritamab plus zanubrutinib and rituximab	CR
NCT06149286	III	Odronextamab plus lenalidomide versus rituximab plus lenalidomide	Safety, PFS
NCT06097364	III	Odronextamab plus CT (O-CHOP) versus R-CHOP	Safety, CR
NCT03401853	II	Pembrolizumab plus rituximab or obinutuzumab	ORR
NCT04680052	III	Tafasitamab plus lenalidomide and rituximab versus placebo plus lenalidomide and tituximab	PFS
NCT02568553	I	Lenalidomide plus blinatumomab	Safety
NCT05683171	I/II	Valemetostat plus rituximab and lenalidomide	Safety
NCT03015896	I/II	Nivolumab plus lenalidomide	Safety, maximum dose
NCT05618366	I	Tazemetostat and venetoclax	Maximum dose
NCT02992522	I	Obinutuzumab, venetoclax, and lenalidomide	Maximum dose
NCT06526793	II	AZD0486	ORR
NCT03150329	I	Pembrolizumab plus vorinostat	Safety
NCT04578600	I	CC-486, lenalidomide, and obinutuzumab	Safety
NCT04305444	II	DTRM-555	CR, PR
NCT05453396	II	Loncastuximab tesirine	ORR
NCT04775745	I	LP-168	Maximus dose
NCT05008055	II	Capivasertib	ORR
NCT03547115	I	Voruciclib alone or plus venetoclax	Maximus dose, safety
NCT05950165	I	CHO-H01 alone or plus lenalidomide	Safety, ORR
NCT00717925	I	Inotuzumab ozogamicin	Safety, MTD

AMM/AP en France

Médicament	Type (classe)	Indication dans le folliculaire / ligne de traitement
Rituximab (et ses biosimilaires : Mabthera®, Rixathon®, etc.)	Ac monoclonal anti-CD20	Première ligne en association à chimiothérapie (R-CHOP, R-CVP, etc.), maintien (entretien), en rechute,
Obinutuzumab (GAZYVARO®)	Ac monoclonal anti-CD20 (type II)	AMM pour LF en rechute précoce : utilisé avec bendamustine en induction suivi d'entretien.
Bendamustine	Agent alkylant chimiothérapique	Utilisé en induction avec rituximab, ou en monothérapie dans certaines rechutes ou quand la chimio-standard est moins adaptée.
Lenalidomide (REVLIMID®)	Immunomodulateur	En association avec rituximab, pour lymphome folliculaire de grade 1, 2 ou 3a, préalablement traité, non réfractaire au rituximab.
Idelalisib (ZYDELIG®)	Inhibiteur PI3K-δ	En monothérapie pour les patients adultes atteints de LF réfractaire après au moins deux lignes de traitement antérieures.
Mosunetuzumab (Lunsumio®)	Ac bispécifique CD20 × CD3	Autorisé par l'UE pour lymphome folliculaire récidivant ou réfractaire après au moins deux traitements systémiques antérieurs.
CAR-T : Tisagenlecleucel (KYMRIAH®)	Thérapie cellulaire (CAR-T)	Pour les patients adultes avec LF après au moins deux lignes de traitement, dans certaines situations (rechute/réfractaire, etc.) (
CAR-T : Axicabtagene ciloleucel (YESCARTA®)	Thérapie cellulaire (CAR-T)	AMM dans LF en rechute ou réfractaire après **au moins trois** lignes de traitement systémique.

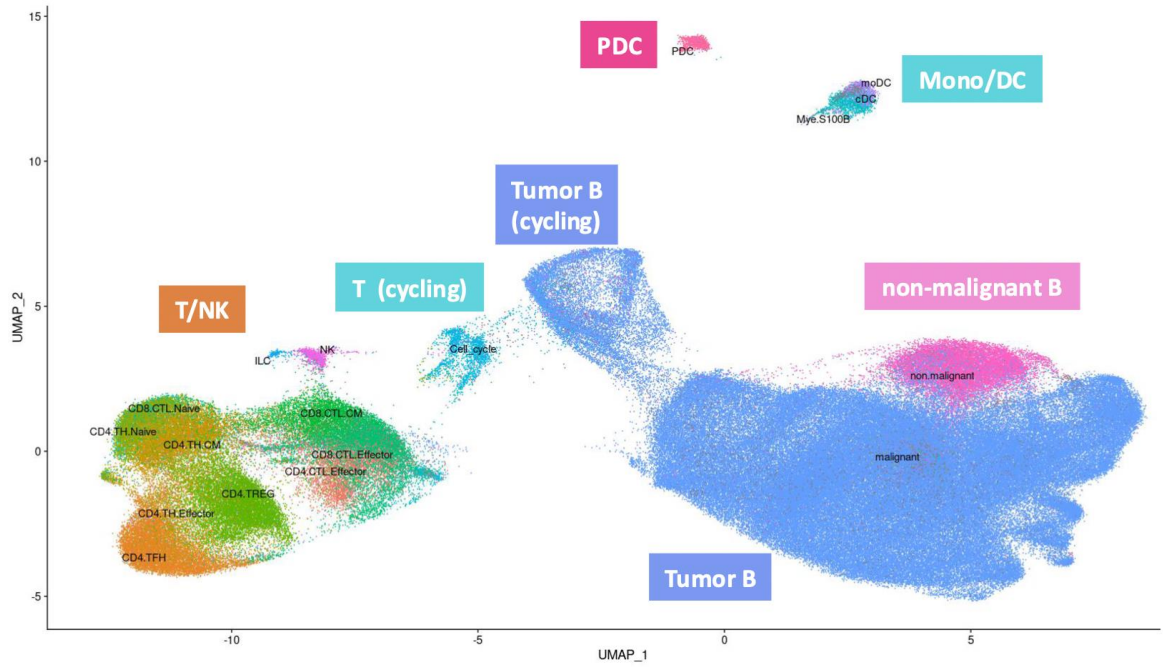
A Follicular Lymphoma single cell atlas of 102 patients covering the full spectrum of disease progression

107 LN biopsies: 60 diagnosis, 39 relapsed, 8 transformation (t-FL)



Integrated FL lymph node atlas: **238,200 single cells after QC**

Cells colored by cell types



Roulland et al, ICML2025

Each FL tumor has a unique gene expression profile reflecting the unique genetics of each patient

Single cell atlas of merged B cells
(n=102 patients)
Cells colored by patient ID

Cells colored by sample of origin

Malignant assignment: BCR & cluster-based

Residual normal B | Diagnosis W&W | Diagnosis | Relapse | Transformation

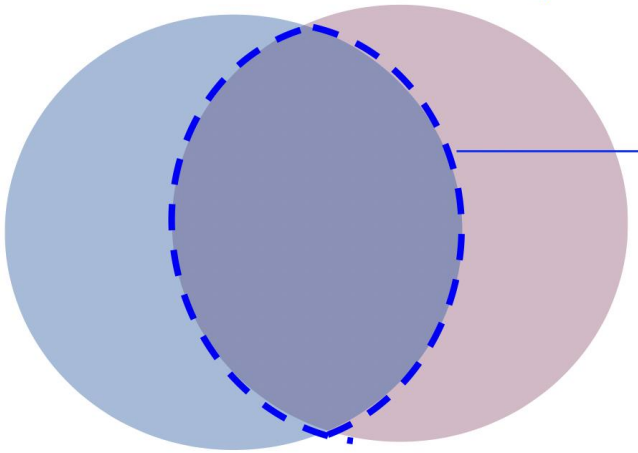
Roulland et al, ICML2025

From single cells to recurrent patterns of intra-tumor heterogeneity across FL tumors

Single cell gene expression dataset of malignant B cells

Metaclustering
(Rank-based overlap)

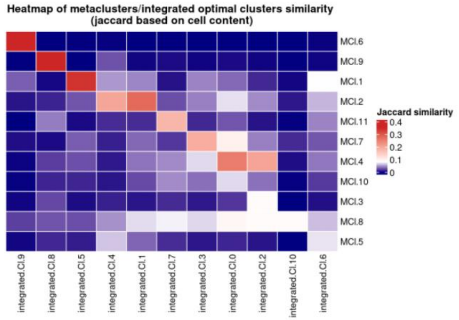
Seurat3 Integration

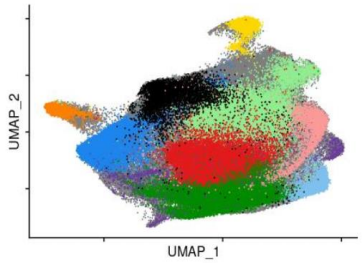


Filtered out :
- *Insufficient # of tumor cells (<100)*
- *Archetype made of single sample*
- *Merge archetype +/- stress markers*

ARCHETYPES : similar cell content and marker genes across approaches

10 archetypes (Arch. 1 to 10)





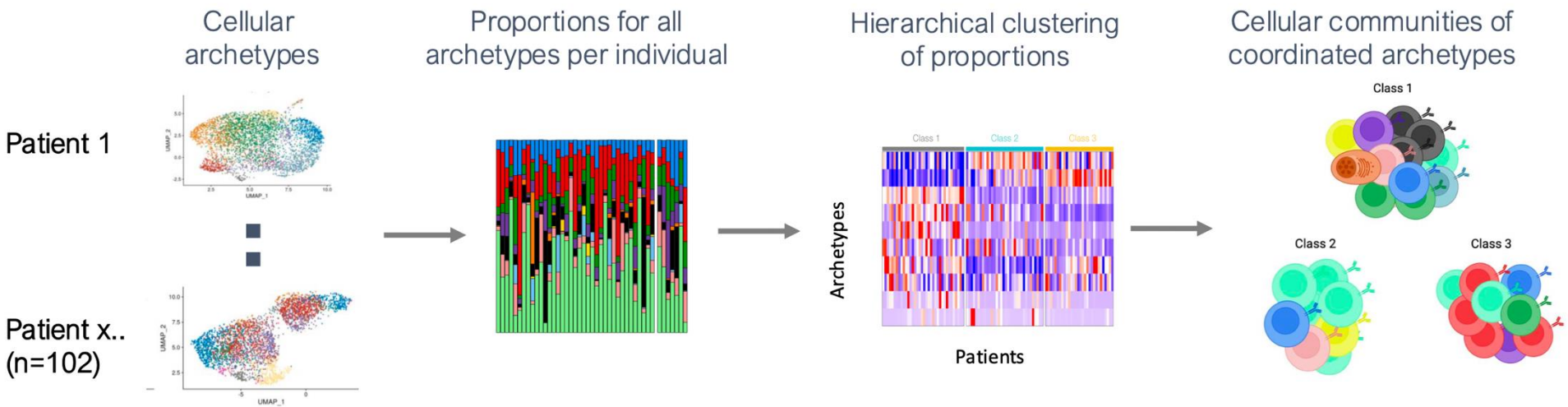
Stuart et al. Cell 2019, Lopez et al. Nat Methods 2018, Baaklini et al. Abstract 848, ASH 2023

Roulland et al, ICML2025

From individual archetype proportions to multicellular ecosystems

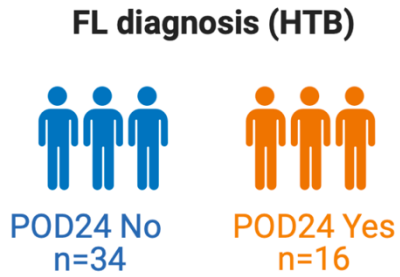
Analysis framework

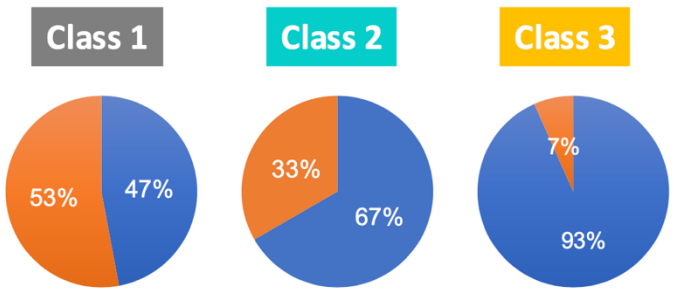
Multicellular Ecosystems: a combination of archetypes that are coordinated together in the tumor



Roulland et al, ICML2025

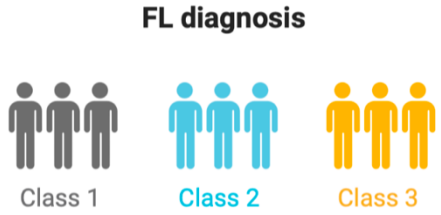
The multicellular ecosystem 1 is enriched in High-Risk, early relapsed patients

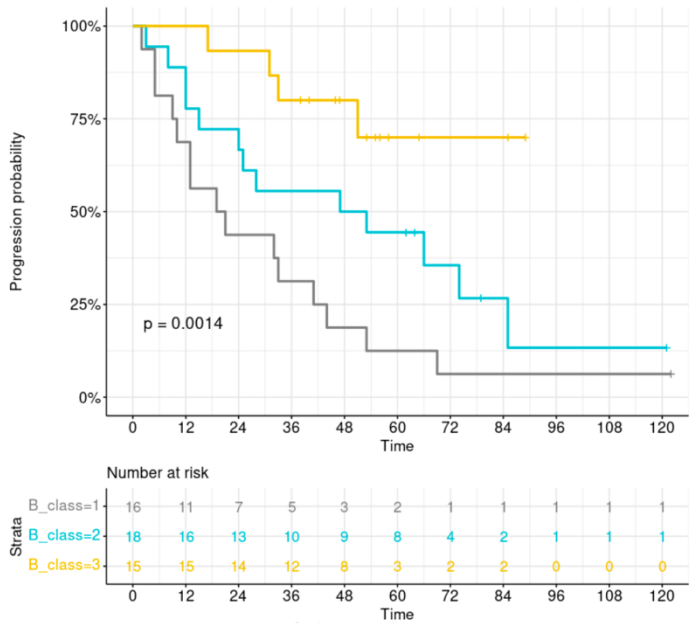




Chi-squared test p-value: 0.0196

- **POD24 FL patients are significantly enriched in Class 1 and depleted from Class 3**



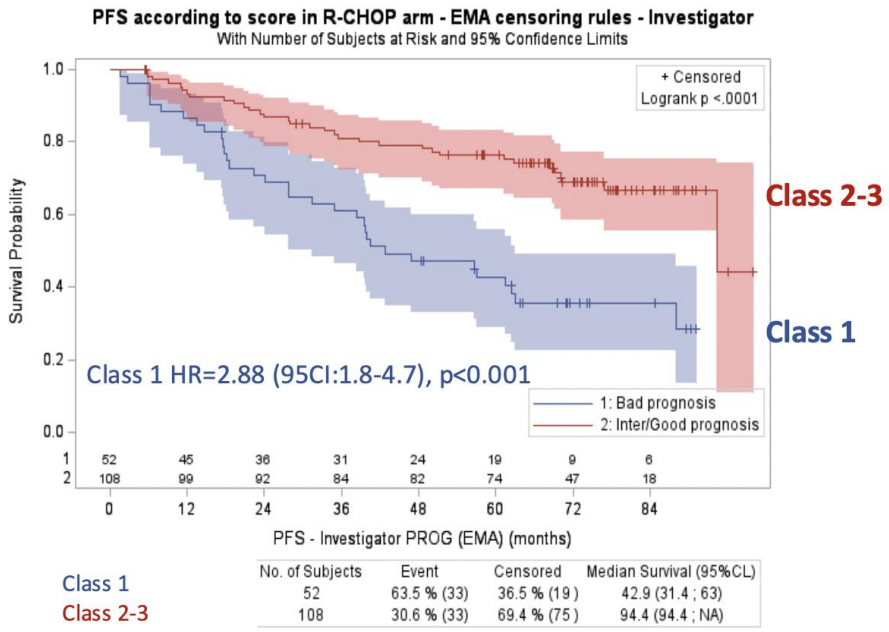


Roulland et al, ICML2025

FL Patients classified in MCE Class 1 have a selected benefit from R2 therapy

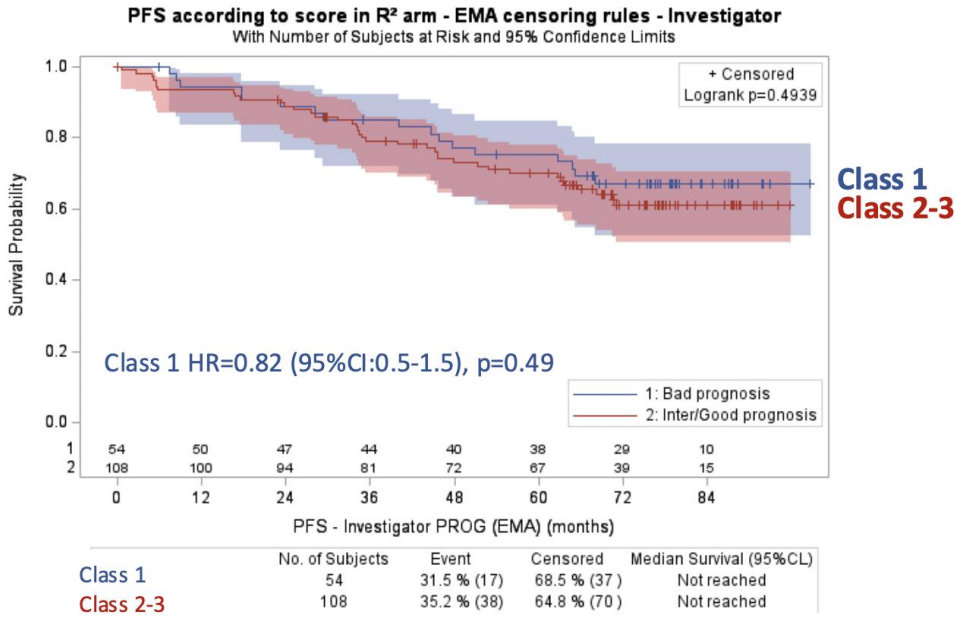
PFS stratified by MCE class and treatment arm

R-chemo arm



Interaction : p=0.0010

R2 arm



- **R2-containing regimen abrogated the predicted poor outcome of MCE1 'high' score patients**

Morschhauser et al. NEJM 2018; Laurent et al. Blood 2024

Roulland et al, ICML2025

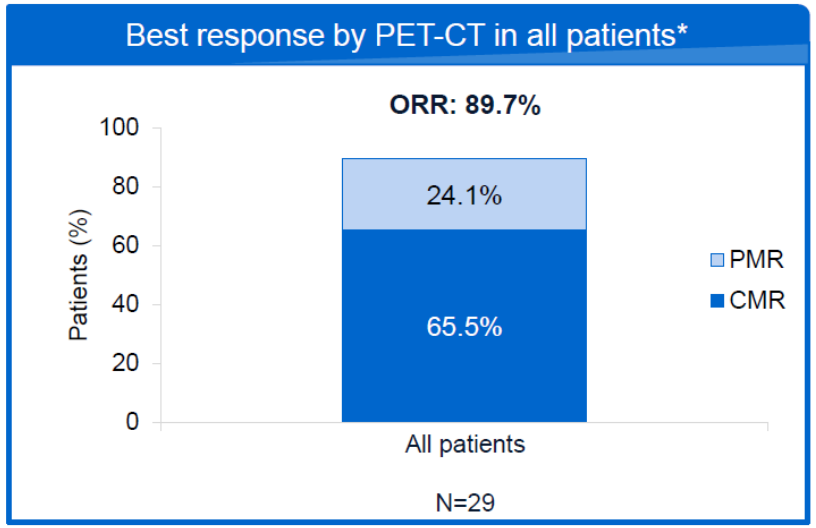
Conclusions

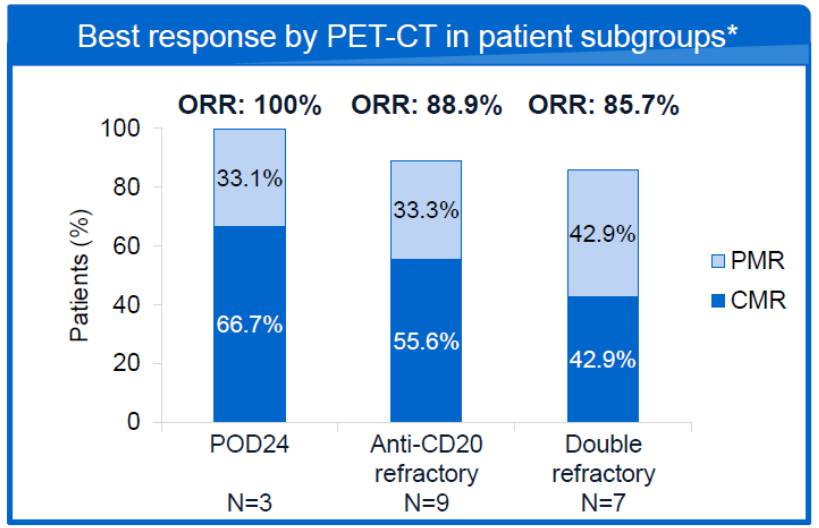
- FL est une pathologie très hétérogène
  - FL = Composant B + TME
- Bien distinguer les transformations vs FL (à chaque poussée)
- **Lenalidomide + rituximab** est sans la 1ere option à privilégier en 2L
- **CAR T cells**
  - **Pour les POD24 (3L)**
  - **Pour les patients en rechutes multiples**
- Bi-Spécifiques
  - Bénéfice/risque

Mosu-Len

	N=29
Age in years, median (range)	59 (30–79)
Male	13 (44.8%)
Ann Arbor stage at study entry	
I–II	2 (6.8%)
III–IV	27 (93.1%)
FLIPI risk factors at study entry	
0–1	7 (24.1%)
2	8 (27.6%)
3–5	14 (48.3%)
Number of prior lines of therapy, median (range)	1 (1–6)
1 prior line	16 (55.2%)
≥2 prior lines	13 (44.8%)
Refractory to any prior aCD20 therapy	9 (31.0%)
Refractory to any prior aCD20 therapy AND an alkylating agent (double refractory)	7 (24.1%)
POD24	3 (10.3%)

	N=29
AE Related to mosunetuzumab / lenalidomide	29 (100%) 27 (93.1%) / 23 (79.3%)
Grade 3–4 AE Related to mosunetuzumab / lenalidomide	13 (44.8%) 1 (3.4%) / 1 (3.4%)
Serious AE Related to mosunetuzumab / lenalidomide	9 (31.0%) 6 (20.7%) / 1 (3.4%)
Grade 5 (fatal) AE	0
AE leading to mosunetuzumab / lenalidomide discontinuation	0 / 1 (3.4%)
AE leading to mosunetuzumab dose delay	6 (20.7%)
AE leading to lenalidomide dose reduction	2 (6.9%)
AE leading to lenalidomide temporary dose interruption	6 (20.7%)
AE leading to lenalidomide dose reduction AND temporary dose interruption	4 (13.7%)





Morschhauser et al, ASH 2021