The young side of LYMPHOMA

gli under 40 a confronto

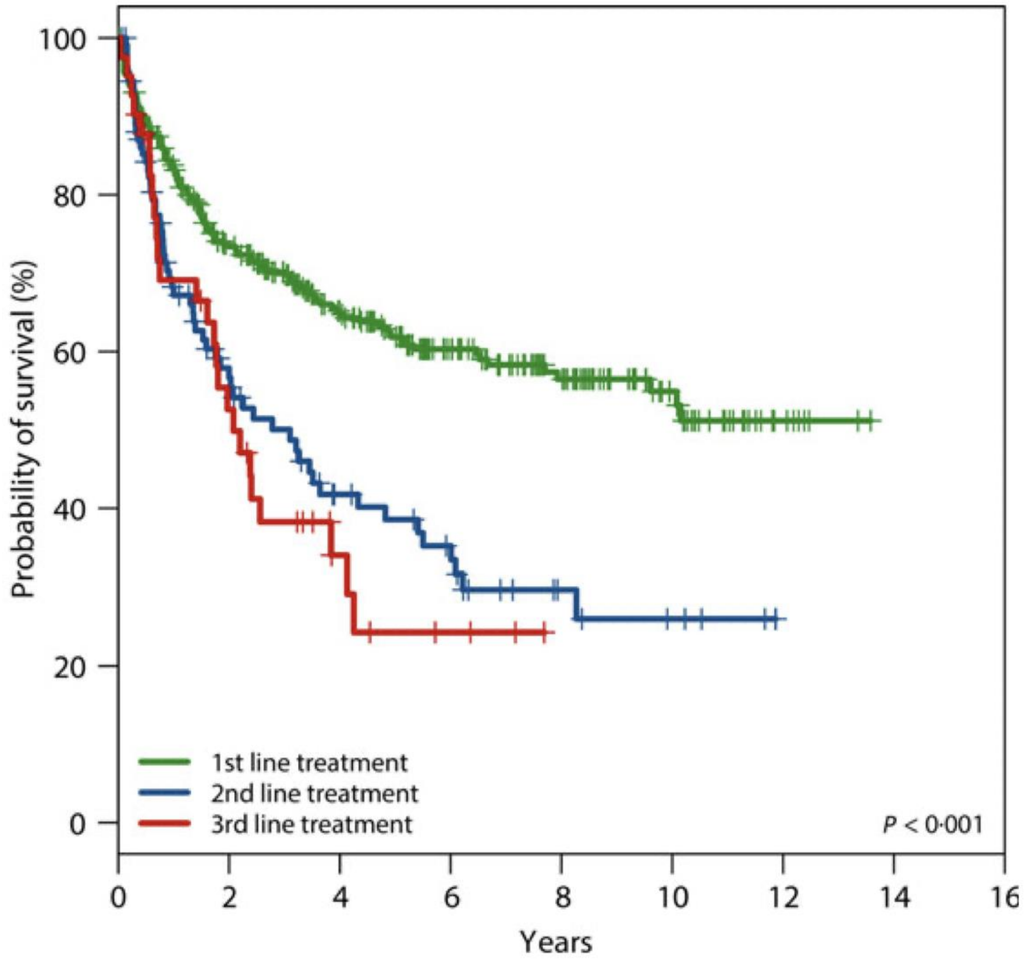
Pescara, Auditorium Petruzzi
11-12 ottobre 2024

Linfoma Follicolare R/R: pro CAR-T

Fabrizio Marino
IRCCS San Raffaele Scientific Institute

Disclosures

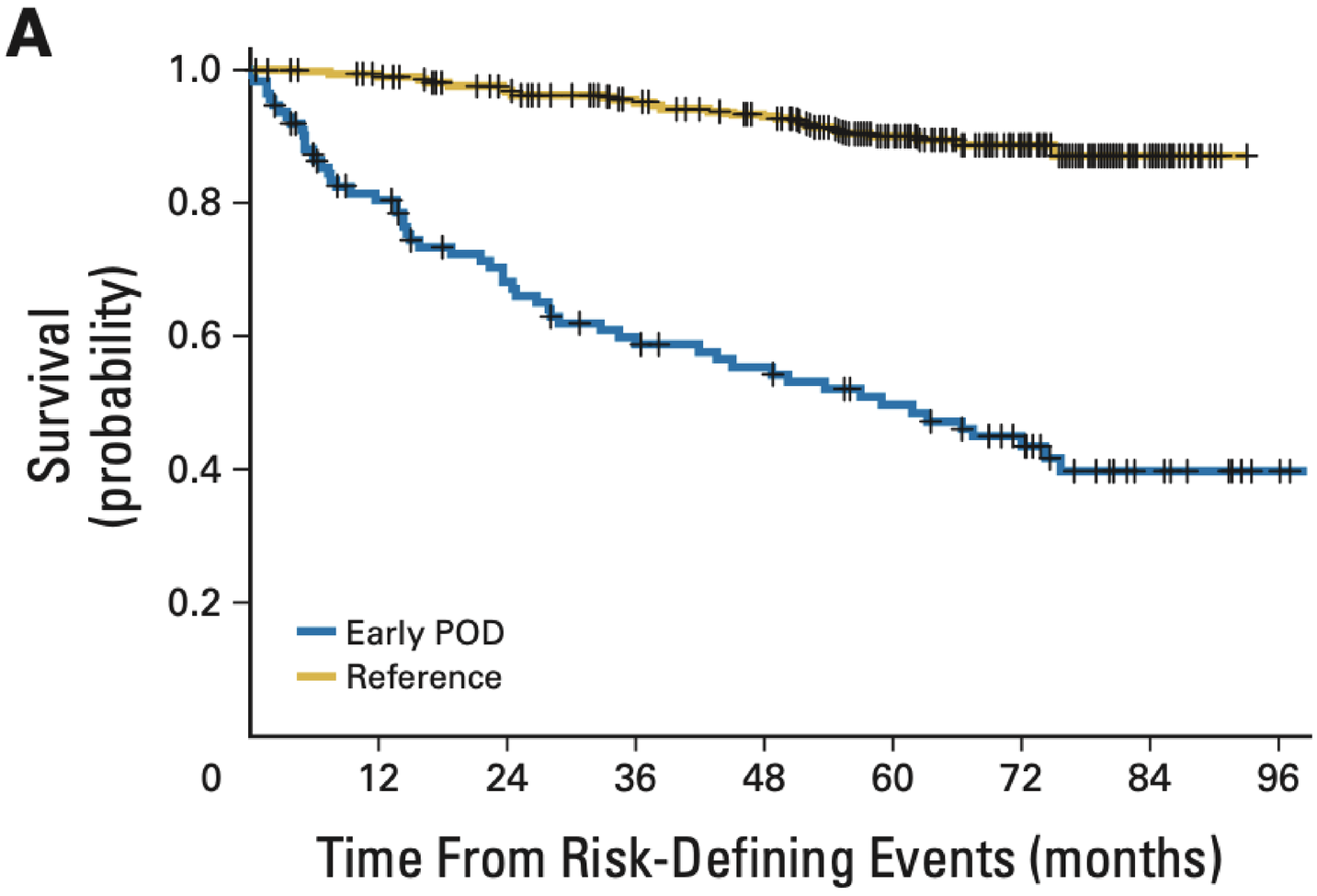
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda			X			X	



No. at risk:

1st line treatment	348	210	148	100	62	31	7	0	0
2nd line treatment	111	47	27	20	8	5	0	0	0
3rd line treatment	41	19	7	3	0	0	0	0	0

Rivas-Delgado A, Response duration and survival shorten after each relapse in patients with follicular lymphoma treated in the rituximab era. Br J Haematol. 2019



Casulo C. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol. 2015

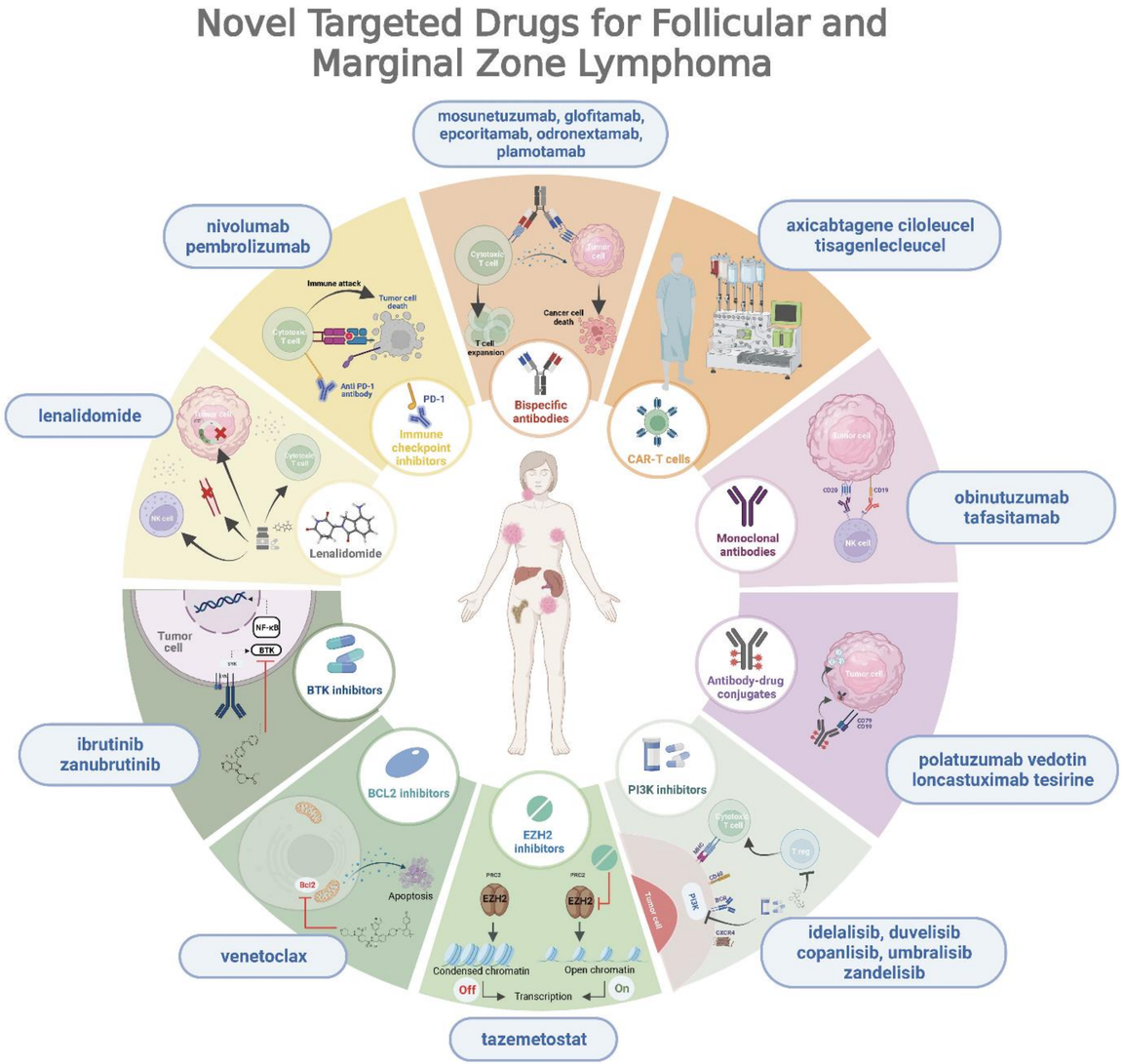


FIGURE 1
Overview of novel targeted drugs for follicular and marginal zone lymphoma, depicting their mechanisms of action.

Rivero A, Mozas P. Novel targeted drugs for follicular and marginal zone lymphoma: a comprehensive review. Front Oncol. 2023.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Classic Follicular Lymphoma

THIRD-LINE AND SUBSEQUENT THERAPY

Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given.

Preferred regimens (in alphabetical order)

- T-cell engager therapy
  - Bispecific antibody therapy[l]
    - ◊ Epcoritamab-bysp
    - ◊ Mosunetuzumab-axgb
  - Chimeric antigen receptor (CAR) T-cell therapy[m]
    - ◊ Axicabtagene ciloleucel (CD19-directed)
    - ◊ Lisocabtagene maraleucel (CD19-directed)
    - ◊ Tisagenlecleucel (CD19-directed)

Other recommended regimens

- *EZH2* inhibitor
  - Tazemetostat[l] (irrespective of *EZH2* mutation status)
- BTK inhibitor (BTKi)
  - Zanubrutinib[l] + obinutuzumab

THIRD-LINE CONSOLIDATION THERAPY

Useful in Certain Circumstances

- Allogeneic hematopoietic cell transplantation (HCT) in selected cases[n]

CLINICAL TRIALS AND OBSERVATIONS

Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update

Martin Dreyling,[1] Nathan Hale Fowler,[2,3] Michael Dickinson,[4] Joaquin Martinez-Lopez,[5] Arne Kolstad,[6] Jason Butler,[7] Monalisa Ghosh,[8] Leslie Popplewell,[9] Julio C. Chavez,[10] Emmanuel Bachy,[11] Koji Kato,[12] Hideo Harigae,[13] Marie José Kersten,[14] Charalambos Andreadis,[15] Peter A. Riedell,[16] P. Joy Ho,[17] José Antonio Pérez-Simón,[18] Andy I. Chen,[19] Loretta J. Nastoupil,[20] Bastian von Tresckow,[21,22] Andrés José María Ferreri,[23] Takanori Teshima,[24] Piers E. M. Patten,[25,26] Joseph P. McGuirk,[27] Andreas L. Petzer,[28] Fritz Offner,[29] Andreas Viardot,[30] Pier Luigi Zinzani,[31,32] Ram Malladi,[33] Ines Paule,[34] Aiesha Zia,[34] Rakesh Awasthi,[35] Xia Han,[36] Davide Germano,[34] Darragh O'Donovan,[37] Roberto Ramos,[36] Harald J. Maier,[34] Aisha Masood,[36] Catherine Thieblemont,[38] and Stephen J. Schuster[39]

blood® 25 APRIL 2024 | VOLUME 143, NUMBER 17

Table 1 | Baseline demographic and disease characteristics of all treated patients

Parameter	Infused patients, *n* = 97
Median age (IQR), years	57.0 (49–64)
≥65 Years, *n* (%)	24 (24.7)
Male, *n* (%)	64 (66.0)
Female, *n* (%)	33 (34)
ECOG PS ≥1 before infusion, *n* (%)	41 (43.3)
Stage at study entry III–IV, *n* (%)	83 (85.6)
Bone marrow involvement at study entry, *n* (%)	37 (38.1)
Bulky disease at baseline, *n* (%)	62 (63.9)
FLIPI high (≥3) at study entry, *n* (%)	58 (59.8)
Median no. of previous therapies (range)	4 (2–13)
>4 lines of therapy, *n* (%)	27 (27.8)
POD24 from first anti-CD20 mAb-containing therapy, *n* (%)	61 (62.9)
Previous antineoplastic therapy, *n* (%)	
Anti-CD20 mAb	97 (100)
Alkylating agents	97 (100)
Anti-CD20 mAb + alkylating agent (same or different regimen)	97 (100)
PI3K inhibitors	20 (20.6)
Lenalidomide	21 (21.6)
Lenalidomide + rituximab	16 (16.5)
Previous therapy to which the disease was refractory,[a] *n* (%)	
Anti-CD20 mAb	84 (86.6)
Alkylating agents	69 (71.1)
Anti-CD20 mAb + alkylating agent combination (same regimen)	61 (62.9)
Anthracyclines	43 (44.3)
Lenalidomide	18 (18.6)
Lenalidomide + anti-CD20 mAb (same regimen)	18 (18.6)
PI3K inhibitors	14 (14.4)
Refractory disease to last line of therapy, *n* (%)	76 (78.4)
Best response SD/PD	54 (55.7)
Relapse within 6 months	22 (22.7)
Previous autologous HSCT, *n* (%)	35 (36.1)
Relapsed ≤12 months after HSCT, n (%)	15 (15.5)
Refractory[a] to at least two regimens, *n* (%)	69 (71.1)
Double refractory,[b] *n* (%)	66 (68.0)

[a]Refractory is defined as failure to respond to previous treatment (SD/PD as best response) or PD within 6 months of previous therapy completion. [b]Double refractory is defined as failure to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen. mAb, monoclonal antibody; PS, performance score.

Table 2 | Best overall response in the EAS and per-protocol population[a]

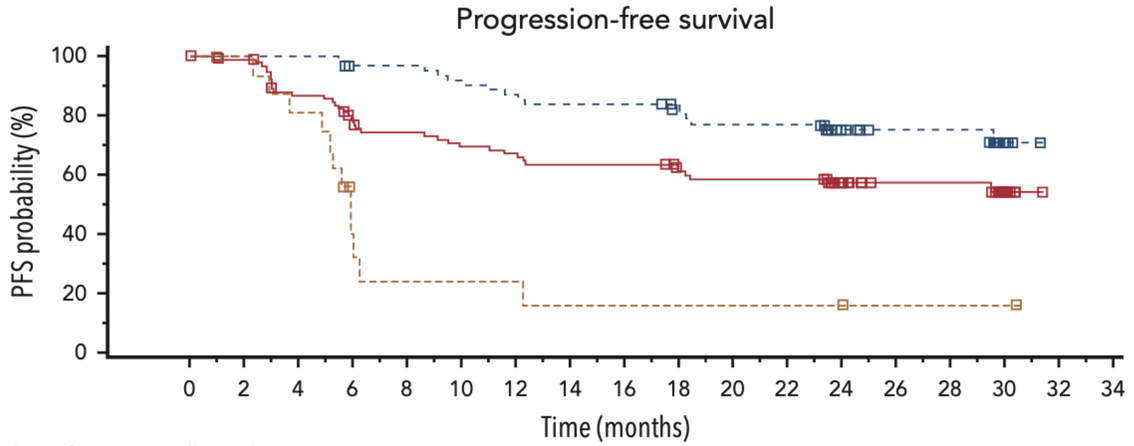
Parameter	Per-protocol set, *n* = 85		EAS, *n* = 94	
	Local assessment	IRC assessment	Local assessment	IRC assessment
Best overall response, *n* (%)				
CR	64 (75.3); 95% CI, 64.7–84.0	62 (72.9); 95% CI, 62.2–82.0	68 (72.3); 95% CI, 62.2–81.1	65 (69.1); 95% CI, 58.5–78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), *n* (%)	78 (91.8); 95% CI, 83.8–96.6	74 (87.1); 95% CI, 78.0–93.4	85 (90.4); 95% CI, 82.6–95.5	81 (86.2); 95% CI, 77.5–92.4

[a]The per-protocol set is a subset of patients in the primary analysis efficacy set with no major protocol deviations. UNK, unknown.

PFS Probability	% (95% CI)
12 months, all patients	67.2 (56.3-75.9)
24 months, all patients	57.4 (46.2-67.0)
12 months, patients in CR	87.2 (76.0-93.4)
24 months, patients in CR	75.3 (62.4-84.3)

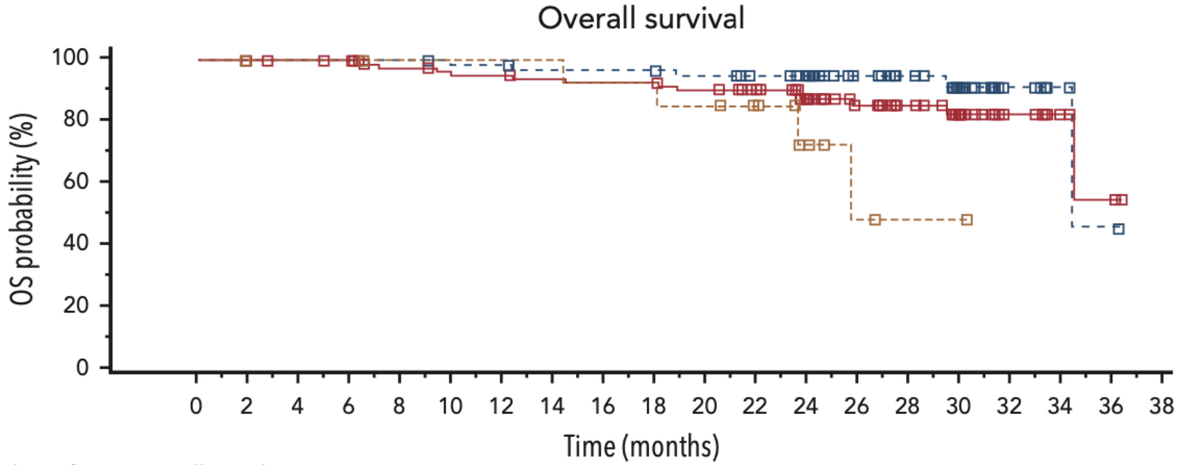
OS Probability	% (95% CI)
12 months, all patients	95.3 (88.1-98.2)
24 months, all patients	87.7 (78.3-93.2)
12 months, patients in CR	98.4 (88.9-99.8)
24 months, patients in CR	95.0 (85.3-98.4)

TTNT Probability	% (95% CI)
12 months, all patients	79.6 (69.6-86.7)
24 months, all patients	69.7 (58.7-78.3)
12 months, patients in CR	95.1 (85.6-98.4)
24 months, patients in CR	83.3 (71.2-90.7)



Number of patients still at risk

All patients (N = 94)	94	91	78	67	63	59	57	54	54	49	47	47	32	19	19	6	0	0
CR (N = 64)	64	64	64	61	60	56	54	52	52	47	45	45	31	18	18	5	0	0
PR (N = 17)	17	16	13	5	3	3	3	2	2	2	2	2	1	1	1	1	0	0



Number of patients still at risk

All patients (N = 94)	94	93	92	91	84	81	81	79	78	78	75	69	55	38	32	19	9	4	2	0
CR (N = 64)	64	64	64	64	62	60	60	58	58	58	56	52	45	32	27	16	7	3	1	0
PR (N = 17)	17	16	16	16	13	13	13	13	12	12	11	9	4	2	1	1	0	0	0	0

CLINICAL TRIALS AND OBSERVATIONS

Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5)

Sattva S. Neelapu,[1,*] Julio C. Chavez,[2,*] Alison R. Sehgal,[3] Narendranath Epperla,[4] Matthew Ulrickson,[5] Emmanuel Bachy,[6] Pashna N. Munshi,[7] Carla Casulo,[8] David G. Maloney,[9] Sven de Vos,[10] Ran Reshef,[11] Lori A. Leslie,[12] Olalekan O. Oluwole,[13] Ibrahim Yakoub-Agha,[14] Rashmi Khanal,[15] Joseph Rosenblatt,[16] Ronald Korn,[17] Weixin Peng,[18] Christine Lui,[18] Jacob Wulff,[18] Rhine Shen,[18] Soumya Poddar,[18] A. Scott Jung,[18] Harry Miao,[18] Sara Beygi,[18] and Caron A. Jacobson[19]

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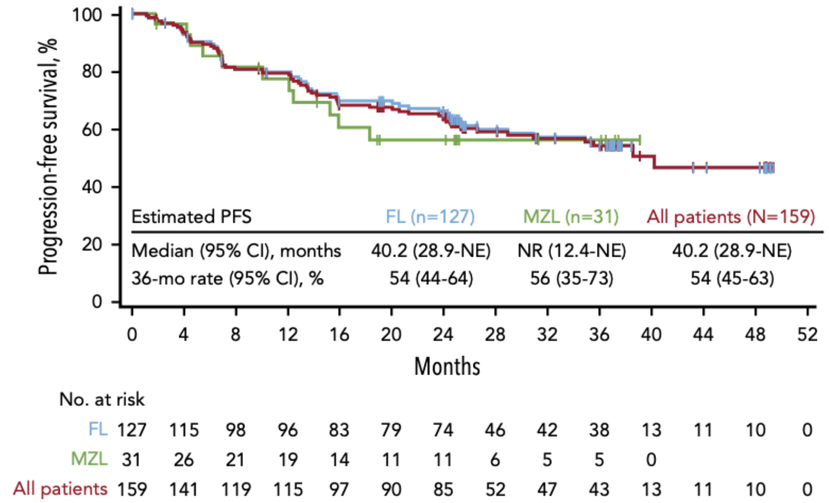
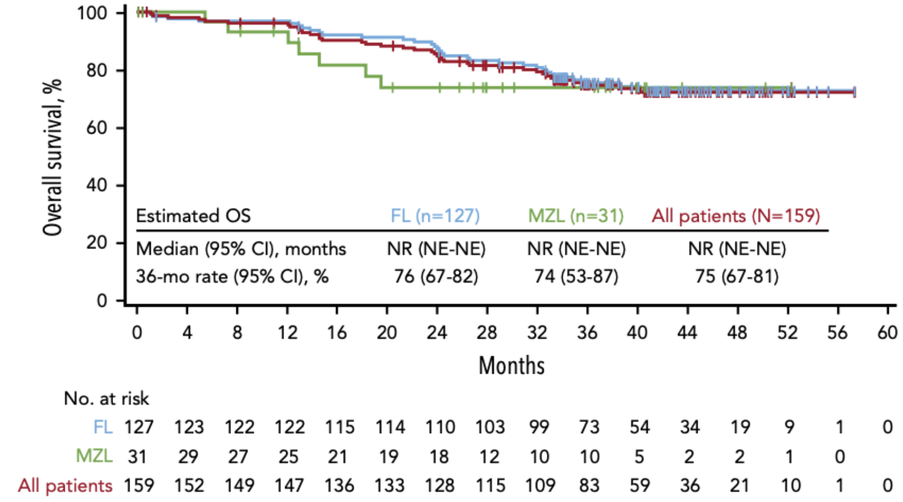
Table 1. Baseline characteristics of all enrolled patients

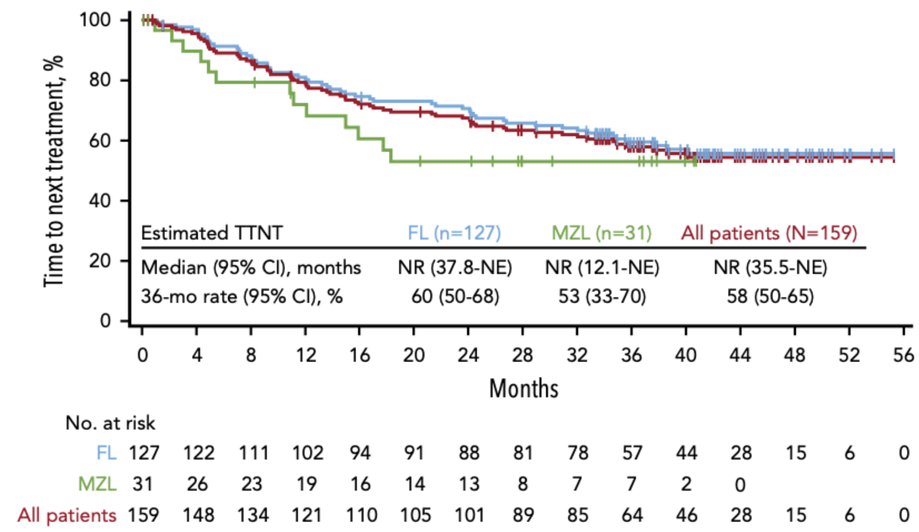
Characteristic	FL (n = 127)	MZL (n = 31)	All patients (N = 159)*
Age, median (range), y	60 (34-79)	64 (43-77)	60 (34-79)
≥65 y, n (%)	46 (37)	14 (45)	54 (34)
Male sex, n (%)	75 (59)	15 (48)	90 (57)
FL histological category, n (%)			
Grade 1	34 (27)	—	—
Grade 2	63 (50)	—	—
Grade 3a	30 (24)	—	—
MZL histological category, n (%)			
Nodal	—	10 (32)	—
Extranodal	—	21 (68)	—
ECOG PS of 1, n (%)	48 (38)	16 (52)	65 (41)
Stage III-IV disease, n (%)	109 (86)	29 (94)	139 (87)
High-risk FLIPI (≥3), n (%)	56 (44)	—	—
High tumor bulk (GELF criteria), n (%)†	65 (51)	16 (52)	82 (52)
SPD, median (range), mm^2	2604.15 (289.2-34 675.0)	1746.45 (306.5-7 471.8)	2449.50 (289.2-34 675.0)
TMTV, median (range), mL	438.50 (11.21-5 576.58)	368.83 (5.15-3 239.43)	420.33 (5.15-5 576.58)
Number of prior therapies, median (range)‡	3 (1-10)	3 (2-8)	3 (1-10)
3 prior lines of therapy, n (%)	33 (26)	10 (32)	44 (28)
4 prior lines of therapy, n (%)	25 (20)	1 (3)	26 (16)
≥5 prior lines of therapy, n (%)	22 (17)	9 (29)	31 (19)
Prior PI3K inhibitor, n (%)	36 (28)	10 (32)	46 (29)
Prior autologous SCT, n (%)	30 (24)	4 (13)	34 (21)
Prior anti-CD20 mAb single agent, n (%)	40 (31)	11 (35)	51 (32)
Prior lenalidomide, n (%)	38 (30)	9 (29)	48 (30)
Prior bendamustine, n (%)	88 (69)	24 (77)	113 (71)
≤6 mo of leukapheresis	8 (6)	3 (10)	11 (7)
≥6 mo and <12 mo of leukapheresis	10 (8)	1 (3)	12 (8)
>12 mo of leukapheresis	70 (55)	20 (65)	90 (57)
R/R subgroup, n (%)			
Refractory to last prior therapy	87 (69)	25 (81)	113 (71)
Double refractory to prior anti-CD20 mAb and alkylating agent	57 (45)	13 (42)	70 (44)
POD24 from initiating first anti-CD20 mAb–containing therapy§	70 (56)	18 (60)	89 (57)
Lymphoma present in bone marrow, n (%)‖	35 (28)	14 (45)	49 (31)
Received bridging therapy, n (%)	4 (3)	3 (10)	7 (4)

Table 2. Investigator-assessed best response among all enrolled patients in the 3-year analysis

	FL (n = 127)	MZL (n = 31)	All patients (N = 159)*
ORR, n (%)	119 (94)	24 (77)	143 (90)
CR	100 (79)	20 (65)	120 (75)
PR	19 (15)	4 (13)	23 (14)
SD, n (%)	2 (2)	3 (10)	5 (3)
PD, n (%)	2 (2)	1 (3)	3 (2)
Not done, n (%)	4 (3)	3 (10)	8 (5)
DOR, median (95% CI), mo	38.6 (29.0-NE)	NR (13.4-NE)	38.6 (33.1-NE)
Estimate at 36 mo (95% CI), %	57 (47-66)	64 (40-80)	58 (48-66)
Duration of CR, median (95% CI), mo	NR (35.4-NE)	NR (14.2-NE)	NR (35.4-NE)
Estimate at 36 mo (95% CI), %	62 (48-72)	NR (NE-NE)	61 (49-72)
Duration of PR, median (95% CI), mo	4.9 (2.2-8.2)	3.5 (1.9-NE)	4.9 (2.1-6.2)
Estimate at 36 mo (95% CI), %	NR (NE-NE)	0 (NE-NE)	NR (NE-NE)

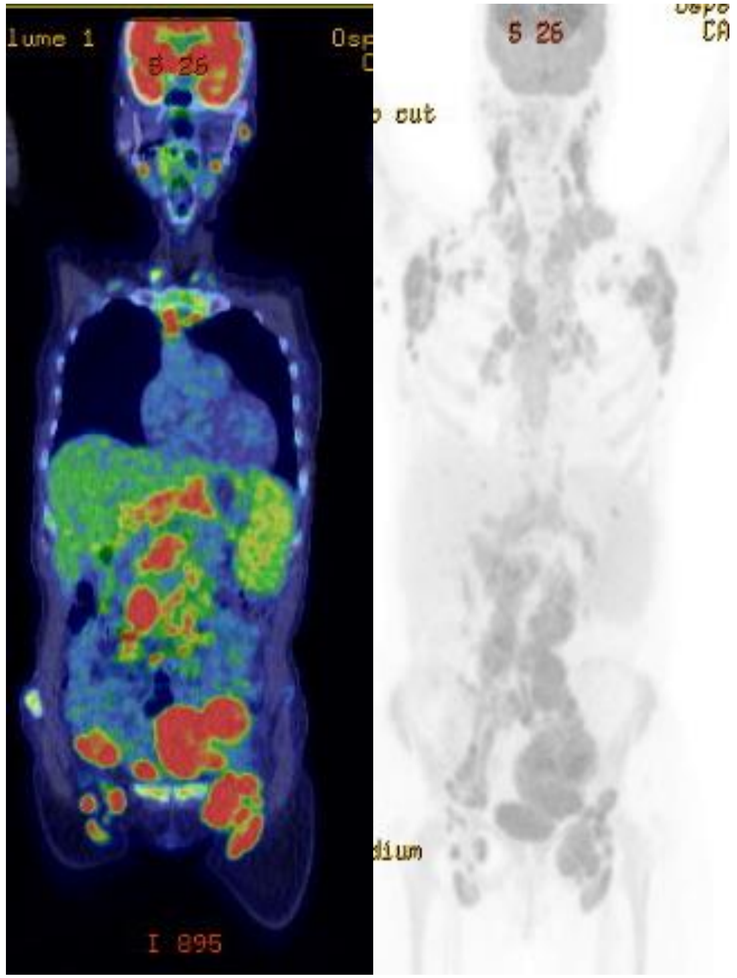

Progression-free survival, %
100
80
60
40
20
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Months
Estimated PFS | FL (n=127) | MZL (n=31) | All patients (N=159)
Median (95% CI), months | 40.2 (28.9-NE) | NR (12.4-NE) | 40.2 (28.9-NE)
36-mo rate (95% CI), % | 54 (44-64) | 56 (35-73) | 54 (45-63)
No. at risk
FL 127 115 98 96 83 79 74 46 42 38 13 11 10 0
MZL 31 26 21 19 14 11 11 6 5 5 0
All patients 159 141 119 115 97 90 85 52 47 43 13 11 10 0


Overall survival, %
100
80
60
40
20
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
Months
Estimated OS | FL (n=127) | MZL (n=31) | All patients (N=159)
Median (95% CI), months | NR (NE-NE) | NR (NE-NE) | NR (NE-NE)
36-mo rate (95% CI), % | 76 (67-82) | 74 (53-87) | 75 (67-81)
No. at risk
FL 127 123 122 122 115 114 110 103 99 73 54 34 19 9 1 0
MZL 31 29 27 25 21 19 18 12 10 10 5 2 2 1 0
All patients 159 152 149 147 136 133 128 115 109 83 59 36 21 10 1 0


Time to next treatment, %
100
80
60
40
20
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56
Months
Estimated TTNT | FL (n=127) | MZL (n=31) | All patients (N=159)
Median (95% CI), months | NR (37.8-NE) | NR (12.1-NE) | NR (35.5-NE)
36-mo rate (95% CI), % | 60 (50-68) | 53 (33-70) | 58 (50-65)
No. at risk
FL 127 122 111 102 94 91 88 81 78 57 44 28 15 6 0
MZL 31 26 23 19 16 14 13 8 7 7 2 0
All patients 159 148 134 121 110 105 101 89 85 64 46 28 15 6 0

Caso clinico #1

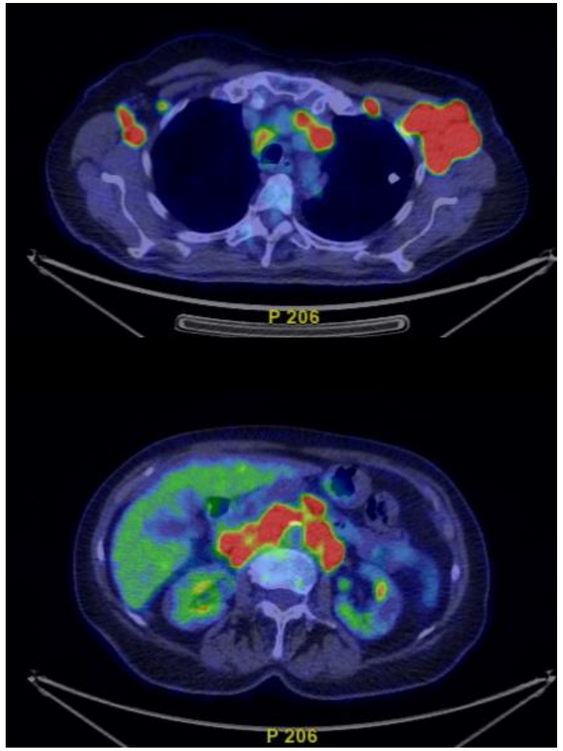
- F, 70 anni (1946)
- Ipertensione arteriosa, rimozione fibromi uterini, appendicectomia
- 2016: LN inguinali -> EI: Linfoma Follicolare, grado 1, ki67 <10%
- Stadiazione: stadio IIIA
- W&W
- EE (2017): linfocitosi (L 42.000, presenza di linfociti atipici), LDH 478, CM IgM kappa e IgG lambda. IF: linfocitosi monoclonale
- TC: in sede iliaca comune-esterna sn (70x52 mm) e determinanti marcata compressione sulla vena iliaca sinistra
- Conclusione: Linfoma Follicolare, stadio IVA (LN sovra e sottodiaframmatici, SVP, midollo)



Caso clinico #1

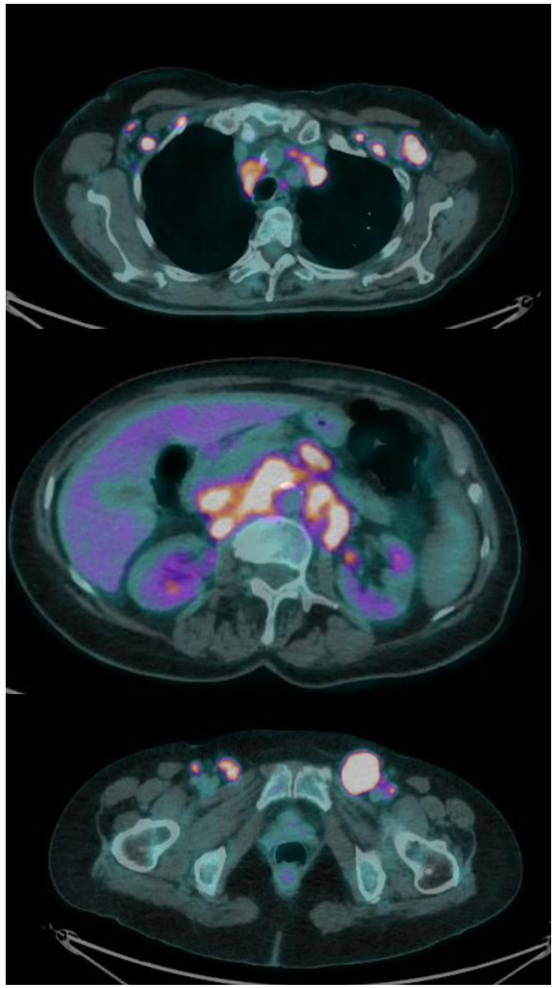
- 10/2017: avvio terapia con R-CHOP x 6 cicli
- Rivalutazione EoT: Risposta completa (DS 3) -> mantenimento R x 12
- 09/2020 **recidiva** ascella sn (25x14 mm) -> w&w
- 03/2022 Sintomi B (sudorazioni) -> ristadiazione
- 6 stazioni >3 cm, splenomegalia, BOM+
- Biopsia LN ascella sn: FL

- 06/2022 avvio terapia con R-Bendamustina x 6 cicli
- Rivalutazione EoT: Risposta completa (DS 2)
- LN inguine sn 20x17 mm -> PD



Caso clinico #1

- 02/2024 sintomi B (sudorazioni), L 9.900 (linfociti atipici), LDH 362
- Ristadiazione: LN sovra e sottodiaframmatici e midollo (BOM)
- Biopsia inguine: FL grado 2, ki67 50%

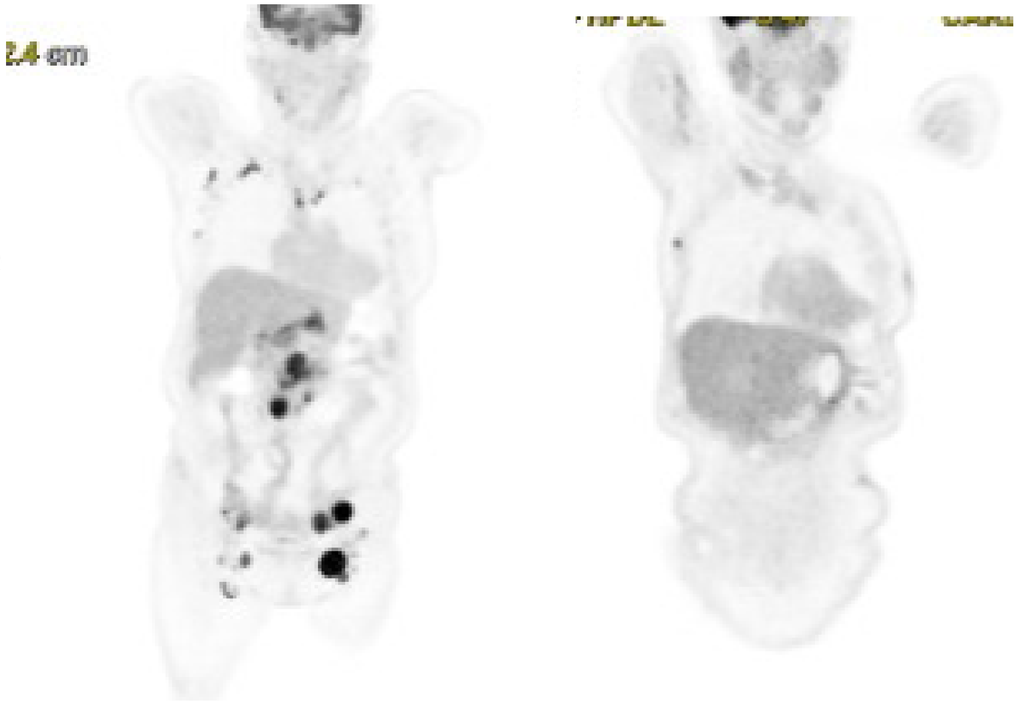


- Terza linea:

- Mosunetuzumab
- CAR-T
- R-Lenalidomide
- Idelalisib

Caso clinico #1

- Mosu/CAR-T rifiutate per rischio AE (CRS e ICANS) e accessi H
- Scelta: R-Lenalidomide



ELARA (Tisa-cel)

Events, n (%)	Infused patients N=97
CRS	47 (48.5)
Grade 1 or 2	47 (48.5)
Grade ≥3	0
In patients with CRS (n=47)	
Tocilizumab use during CRS	16 (34.0)
1 dose	8 (17.0)
2 doses	5 (10.6)
3 doses	3 (6.4)
Corticosteroids	3 (6.4)
Median time to onset, days (IQR)	4.0 (2–7)
Admitted to ICU, n (%)	4 (8.5)
Median total duration of ICU stay during CRS, days (range)	4.0 (2.5–5)
Patients with resolved events, n (%)	47 (100)

	Treated patients N=97	
Events, n (%)	All Grades	Grade ≥3
Number of patients with at least one event	36 (37.1)	3 (3.1)
Headache	23 (23.7)	1 (1.0)
Dizziness	6 (6.2)	0
Encephalopathy	2 (2.1)	0
Immune effector cell-associated neurotoxicity syndrome	4 (4.1)	1 (1.0)
Paraesthesia	2 (2.1)	0
Tremor	2 (2.1)	0
Dyskinesia	1 (1.0)	0
Dysgeusia	1 (1.0)	0
Migraine	1 (1.0)	0
Peripheral sensory neuropathy	1 (1.0)	0
Syncope	1 (1.0)	1 (1.0)

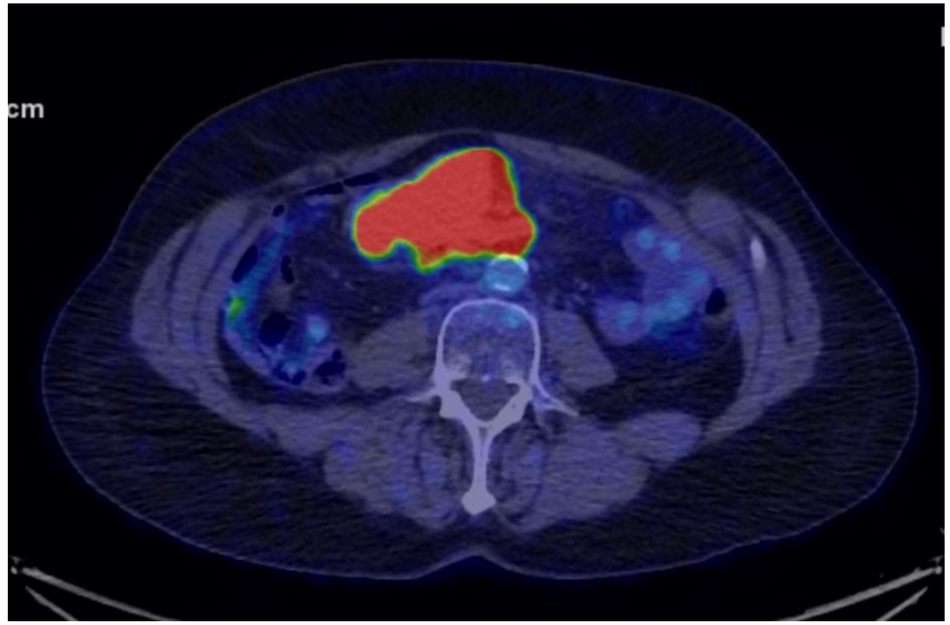
ZUMA-5 (Axi-cel)

Toxicity	CRS • Any grade: 82%, grade > 3: 7% • Time to onset: 4 days (1–15) NT • Any grade: 60%, grade >3: 19% • Median time to onset: 7 (1–177)

	FL (n = 124)		MZL (n = 28)		All patients (N = 152)	
n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	20 (16)	10 (8)	10 (36)	7 (25)	30 (20)	17 (11)
Serious AEs	11 (9)	10 (8)	4 (14)	3 (11)	15 (10)	13 (9)
Cytopenias	3 (2)	2 (2)	5 (18)	5 (18)	8 (5)	7 (5)
CRS	0	0	3 (11)	0	3 (2)	0
Neurologic events	0	0	1 (4)	1 (4)	1 (1)	1 (1)
Infections	14 (11)	6 (5)	7 (25)	2 (7)	21 (14)	8 (5)
Hypogammaglobulinemia	1 (1)	0	1 (4)	0	2 (1)	0
Tumor lysis syndrome	0	0	0	0	0	0

Caso clinico #2

- M, 64 anni (1951)
- 09/2015: Linfoma Follicolare, grado 2, stadio IIA
- 12/2015: R-Bendamustina x 6 cicli (PR) + R mantenimento x 6
- 08/2017: Progressione (PD) con compressione e infiltrazione vascolare -> R-CHOP x 3 -> SD
- Terapia di terza linea: R-DHAP -> ASCT (08/2018) -> CR
- 06/2023: tessuto addominale patologico 78 x 48 mm



- Terapia di quarta linea:
- BiTE
- CAR-T
- R-Lena

Caso clinico #2

- CAR-T rifiutate per necessità di ricovero

- Scelta: GCT3013-01 (Epcoritamab):
- CRS G1
- Terapia per 7 cicli -> CR

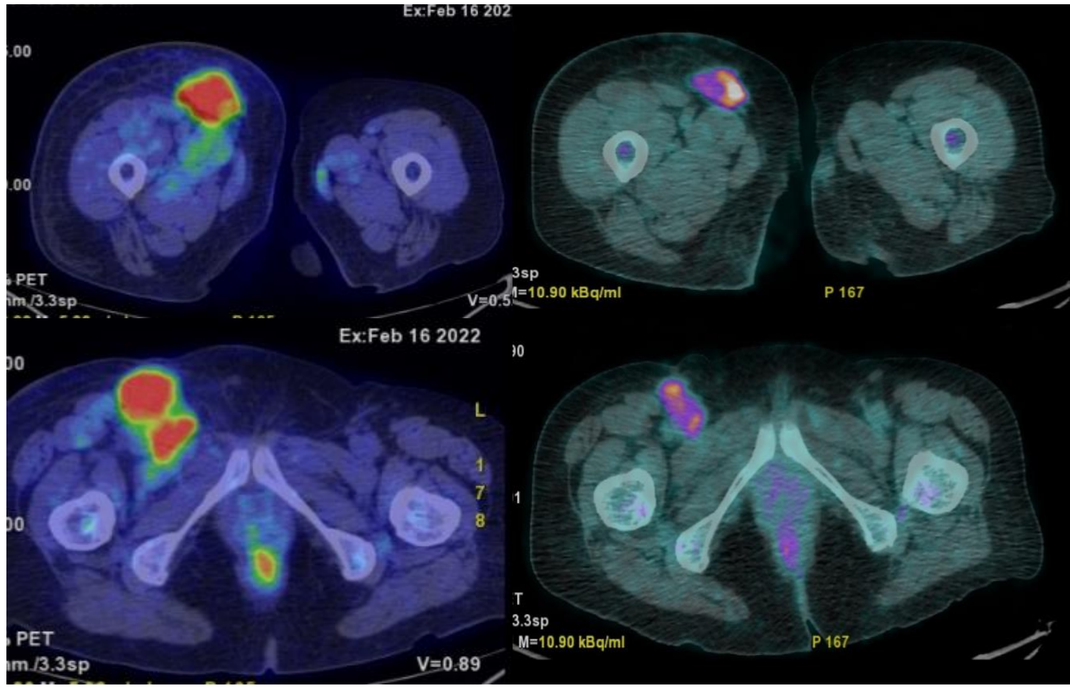
Tisagenlecleucel was administered in the outpatient setting in 18% of patients. Most patients (93/97, 95.9%) received the

Caso clinico #3

- F, 51 anni (1961)
- Diabete mellito in terapia insulinica, ipertensione arteriosa, ipercolesterolemia
- 2015 Diagnosi di Linfoma Follicolare variante diffusa, stadio IV -> R-CHOP x 6 cicli + mantenimento con Rituximab
- 06/2022 Recidiva di FL -> R-CVP x 6 cicli -> PD inguine (5 cm)

- Terza linea: Epcoritamab rifiutato

- 04/2023 Idelalisib
- 09/2023 Progressione inguinale con compressione bacinetto renale dx



Caso clinico #3

- CAR-T: Axi-cel
- Linfodeplezione: Flu-Cy (-5, -3)
- Infusione 11/2023

- Complicanze: CRS G2 in giornata +3 -> Toci x 3 dosi

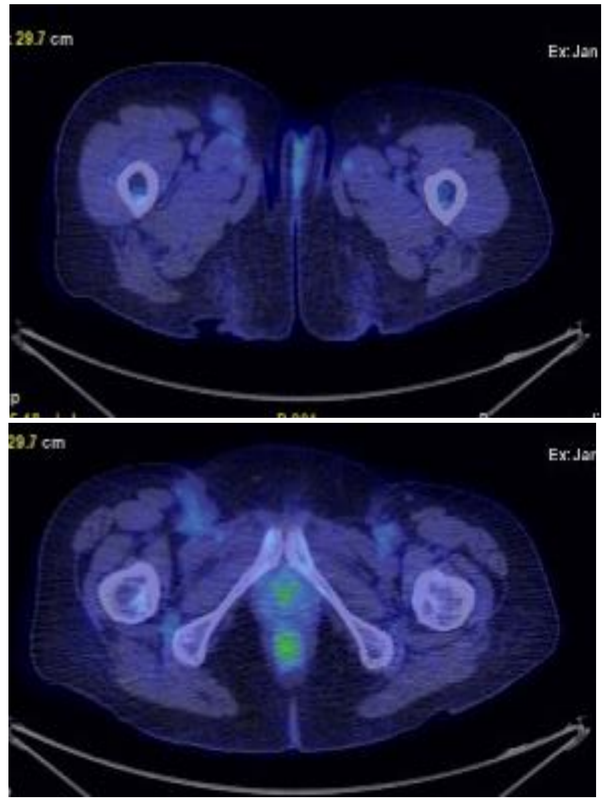
INDICAZIONE 2.1.B

In ragione del buon rapporto tra benefici e rischi riportato sia da studi prospettici che da ampi studi di registro, si raccomanda l'impiego dei corticosteroidi (desametazone 10 mg ogni 6-12 ore) nella gestione della CRS che non riporta una pronta risposta alle prime due dosi di tocilizumab.

Caso clinico #3

- ICANS G1: giornata +5 -> dex 10 mg x4
- ICANS G3: giornata +6 -> metilprednisolone 1000 mg/di -> risoluzione completa giornata +9

- Dimissione giornata +16



INDICAZIONE 2.2.B

In ragione dell'efficacia degli steroidi nel limitare la mortalità dell'ICANS e in ragione dell'assenza di alternative terapeutiche valide, un breve trattamento steroideo risulta altamente raccomandato nei pazienti con ICANS grado 2-4.

Il desametazone (10/20 mg ogni 6 ore) è il trattamento di scelta per l'ICANS grado 2-3 mentre il metilprednisolone (1000 mg/die) è preferibile nelle ICANS grado 3-4.

CONCLUSIONI

- **Necessità Terapeutica**: malattia recidivante non guaribile con prognosi progressivamente peggiorativa, alti rischi

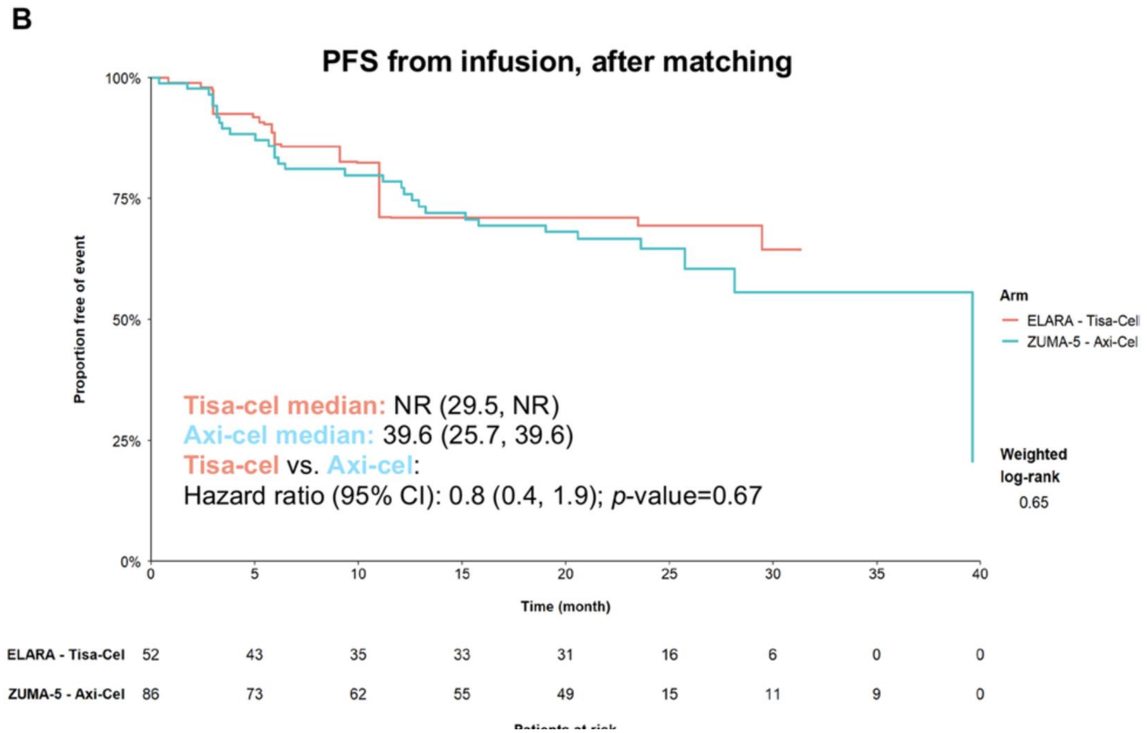
- **Indicazioni**: Tisa (3^), Axi (4^)

- **Efficacia**: Tisa (ORR 86%, CR 69%; 2yPFS 57%, OS 87%), Axi (ORR 94%, OS 79%; 3yPFS 54%, OS 76%)

- **Tossicità**: Tisa (CRS G3-4 0%, ICANS G3-4 3%), Axi (CRS G3-4 7%, ICANS G3-4 19%)
- **Pratica clinica**: giovani? POD24?

Comparative efficacy and safety of tisagenlecleucel and axicabtagene ciloleucel among adults with r/r follicular lymphoma

Michael Dickinson[a], Joaquin Martinez-Lopez[b], Etienne Jousseaume[c], Hongbo Yang[d], Xinglei Chai[d], Cheryl Xiang[d], Travis Wang[d], Jie Zhang[e], Roberto Ramos[e], Stephen J. Schuster[f] and Nathan Fowler[g]



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