GIORNATE EMATOLOGICHE VICENTINE

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MCL: ruolo dell'alloSCT in era CAR T

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen						x	
Takeda						x	
Incyte						x	
Novartis						x	
Abbvie						x	

Background-1

Il linfoma mantellare è ancora ad oggi una malattia inguaribile, caratterizzata da ripetute recidive

La prognosi è particolarmente sfavorevole per i pz con caratteristiche biologiche ad alto rischio (TP53 mut, blastoid morphology, Ki 67> 30%) e per i pz recidivati/refrattari entro 24 mesi (POD24)

I pz rec/refr dopo immunoCT e trattati con ibrutinib hanno mediane di risposta di 18-14 mesi; i pz che perdono la risposta a BTKi, non eleggibili terapie cellulari, hanno OS di circa 6 mesi

Background-2

Il trapianto allogenico offre il vantaggio di un graft sicuramente non contaminato da cellule linfoidi patologiche

Sfrutta un effetto graft versus lymphoma, dimostrato indirettamente da un < rischio di recidiva nei pz con GVHD e dall'efficacia della DLI

Table 1. Summary of the allo-HCT in MCL studies

Author, year	*N*	Disease status	Conditioning	NRM	GVHD (acute/chronic)	Relapse	Disease-free survival	OS
Prospective								
Khouri et al., 2003	18	R/R	RIC/NMA	2/18	0%/NR	1/18	NR	82% (3 yrs)
Maris et al., 2004	33	R/R	NMA	24%	57%/64%	9%	60% (2 yrs)	65% (2 yrs)
Kruger et al., 2014	39	Frontline= 24 R/R =15	MAC/RIC	24%	57%	15%	67%	73%
Rule et al., 2019	25	Frontline	RIC/NMA	13%	38%/58%	21%	56%	76%
Retrospective								
Robinson et al. EBMT. 2018 [35]	324	Frontline 93 Salvage 231	RIC	24%	52%/41%	40% (5 yrs)	31% (5 yrs)	40% (5 yrs)
Hamadani et al., 2013 CIBMTR [44]	202	202 Mixed	MAC=74 RIC=128	47% 43%	MAC=36/35% RIC=37/43%	33% 32%	MAC=20% RIC=25% (3 yrs)	MAC=25% RIC =30% (3 yrs)
Fenske et al., 2014 [45]	138	Frontline 50 Salvage 88	RIC	17% 25%	NR	15% 38%	F=55% S=29%	25% 31% (5 yrs)
Kharfan-Dabaja et al., 2016*[46]	701	Mixed	MAC=138 RIC=507	MAC= 37% RIC=24%	MAC=36/35% RIC=31/42%	MAC=18% RIC=29%	MAC=34%% RIC 47%	MAC=40% RIC=53%

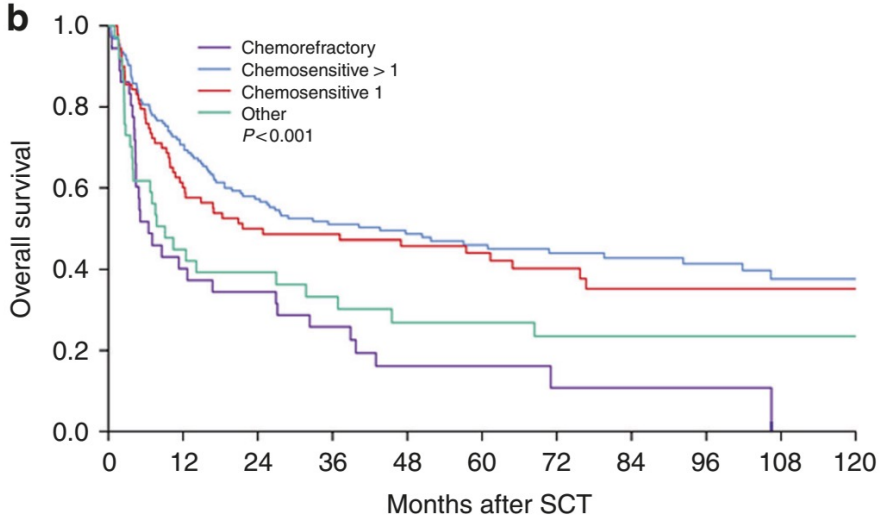
*Systemic review

Bone Marrow Transplantation (2018) 53:617–624
https://doi.org/10.1038/s41409-017-0067-3

ARTICLE

Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation in patients with mantle cell lymphoma: a retrospective study from the EBMT Lymphoma Working Party

Stephen P. Robinson[1] · Ariane Boumendil[2] · Herve Finel[2] · Karl S. Peggs[3] · Patrice Chevallier[4] · Jorge Sierra[5] · Jürgen Finke[6] · Xavier Poiré[7] · Natacha Maillard[8] · Noël Milpied[9] · Ibrahim Yakoub-Agha[10] · Mickey Koh[11] · Nicolaus Kröger[12] · Arnon Nagler[13] · Yener Koc[14] · Sascha Dietrich[15] · Silvia Montoto[16] · Peter Dreger[15]

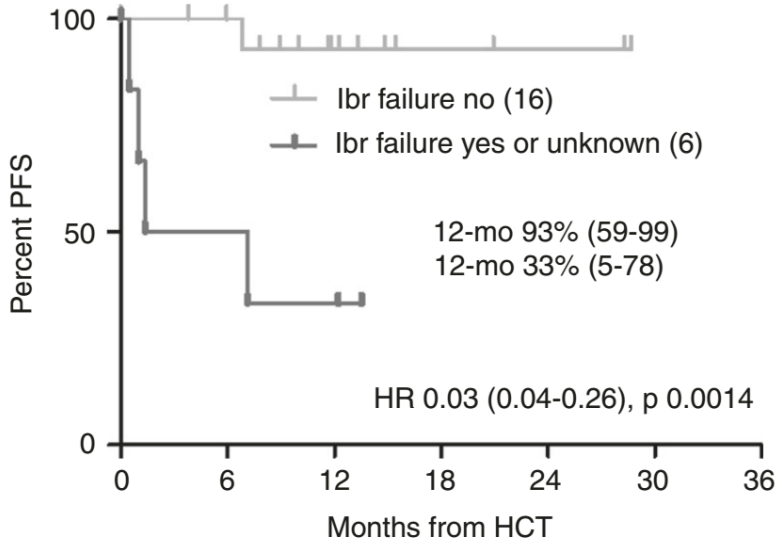


324 pz sottoposti ad allo RIC dal 2000 al 2008
1y-NRM 24%
Long term disease control in 30-40% of pts

Bone Marrow Transplantation (2019) 54:44–52
https://doi.org/10.1038/s41409-018-0207-4

ARTICLE

Ibrutinib for bridging to allogeneic hematopoietic cell transplantation in patients with chronic lymphocytic leukemia or mantle cell lymphoma: a study by the EBMT Chronic Malignancies and Lymphoma Working Parties



Mentre i pz affetti da CLL mostrano un elevato tasso di recidive, i pz affetti da MCL, in particolare se arrivano a trapianto con malattia ben controllata e sensibile ad ibrutinib, hanno buona prognosi (1y PFS 76%)

Allogeneic stem cell transplantation in patients with mantle cell lymphoma: results from the MANTLE-FIRST study on behalf of Fondazione Italiana Linfomi

Annalisa Arcari[a], Lucia Morello[b], Daniele Vallisa[a], Luigi Marcheselli[c], Cristina Tecchio[d], Francesca Maria Quaglia[d], Maria Chiara Tisi[e], Vittorio Ruggero Zilioli[f], Alice Di Rocco[g], Tommasina Perrone[h], Guido Gini[i], Irene Dogliotti[j], Nicola Bianchetti[k], Valentina Bozzoli[l], Chiara De Philippis[b], Maria Isabel Alvarez De Celis[m], Annalisa Chiappella[n,o], Alberto Fabbri[p], Matteo Pelosini[q], Michele Merli[r], Anna Lia Molinari[s], Roberta Sciarra[t], Stefano Volpetti[u], Stefan Hohaus[v], Luca Nassi[w] and Carlo Visco[d]

261 pz recidivati/refrattari dopo terapia I linea con regimi basati su HD-Ara C ± ASCT

59 pz sottoposti ad alloSCT di cui 55 valutabili

2008-2019 (era pre CAR T)

Arcari et al. Leuk Lymphoma 2021

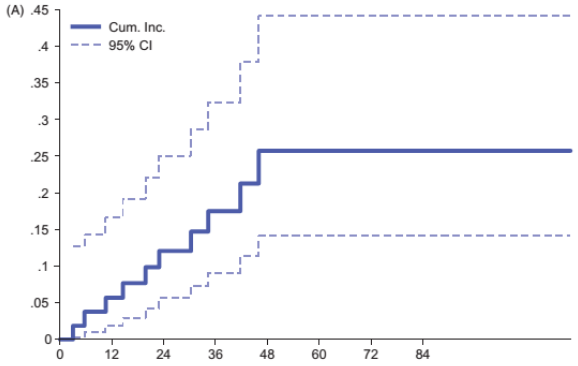
Table 1. Patient characteristics.

Variable	Status	*N* (%)
Age at diagnosis	Median (range)	52 (35–69)
Age at 1st relapse	Median (range)	54 (37–69)
	>60 years	14 (25)
Gender	Male	42 (76)
Morphology	Blastoid	10 (18)
Ki 67 ($n = 30$)	≥30%	20 (67)
Ann Arbor stage ($n = 53$)	III	4 (8)
	IV	49 (92)
★ MIPI ($n = 49$)	Low	24 (49)
	Intermediate	15 (31)
	High	10 (20)
Upfront therapy	R HyperCVAD	17 (31)
	R CHOP/R DHAP	11 (20)
	Nordic/R HDS	27 (49)
Auto-SCT	Yes, front line	43 (78)
Time to 1st relapse, months	Median (range)	29 (4-94)
	Early POD (24 m)	25 (45)
	Refractory	4 (7)
2nd line therapy	R-Bendamustine	5 (9)
	R-BAC	22 (40)
	Ibrutinib	12 (22)
	Others[a]	16 (29)
Response to 2nd line therapy	ORR	39 (71)
	CR	32 (58)
Relapse/progression after 2nd line therapy	yes	29 (53)
3rd line therapy ($n = 21$)	R-Bendamustine	4 (19)
	R-BAC	8 (38)
	Ibrutinib	6 (29)
	Others[b]	3 (14)

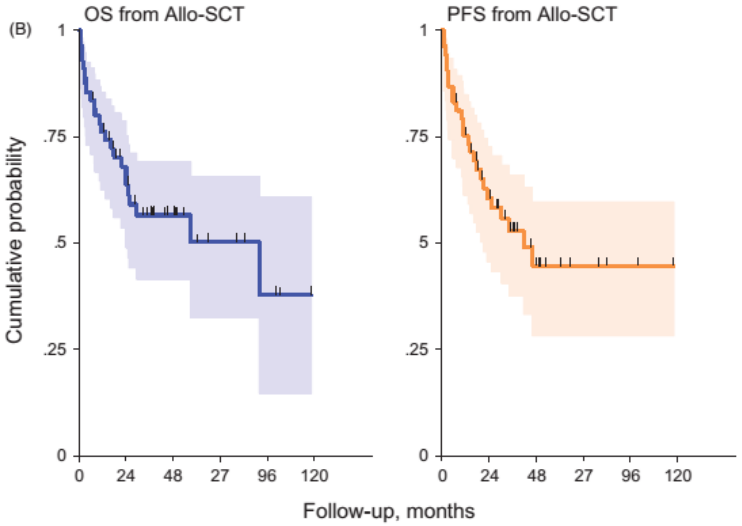
★ TP53 status not available

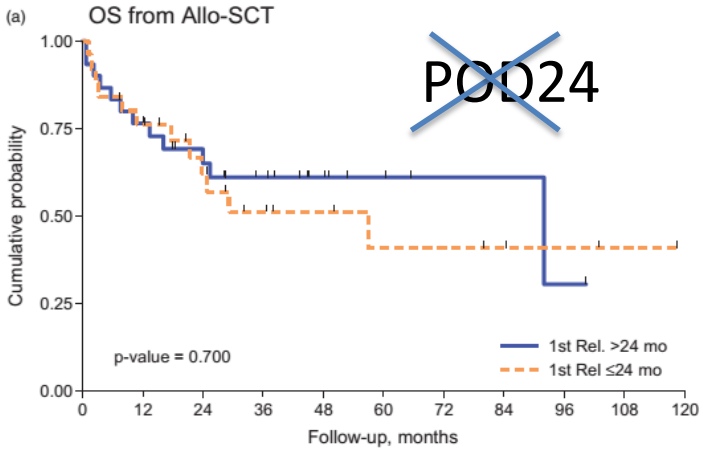
Table 2. Transplant characteristics.

Variable	Status	*N* (%)
Age at allo-SCT	Median (range)	56 (38–70)
	>60 years	16 (29)
HCT-CI (Sorror)	Low (0)	21 (43)
	Intermediate (1–2)	15 (31)
	High (≥ 3)	13 (26)
Disease status at allo-SCT	CR	35 (64)
	PR	16 (29)
	SD/PD	4 (7)
N. prior lines before allo-SCT	2	35 (64)
	3	12 (22)
	>3	8 (14)
Bridging therapy to allo-SCT	Bendamustine-based	31 (56)
	Ibrutinib	15 (27)
	Others[a]	9 (16)
Timing of allo-SCT	At 1st relapse	35 (64)
	At 2nd relapse (and beyond)	20 (36)
	Time from diagnosis, months	40 (11–137)
	Time from 1st relapse, months	11 (5–96)
Donor type	Sibling	24 (44)
	MUD	30 (56)
Matching	HLA identical	26 (48)
	Mismatched	16 (30)
	Haploidentical	12 (22)
Donor gender	Female	19 (35)
CMV status patient/donor	CMV pos/neg	7 (13)
	CMV pos/pos	33 (60)
Source	PBSC	49 (89)
	Bone Marrow	6 (11)
Conditioning	RIC	44 (80)
	Myeloablative	11 (20)
Engraftment	Time to neutrophil engraftment, days (median, range)	16 (7–49)
	Time to platelet engraftment, Days (median, range)	17 (7–181)
Infections	Grades I and II	15 (38)
	Grades III–V	24 (62)
Cumulative incidence of acute GVHD	Yes	25 (46)
	Grades III and IV	6/24 (25)
Cumulative incidence of chronic GVHD	Yes	21 (40)
	Extensive	9/20 (45)



Cumulative incidence of relapse/progression at 3 y 26%



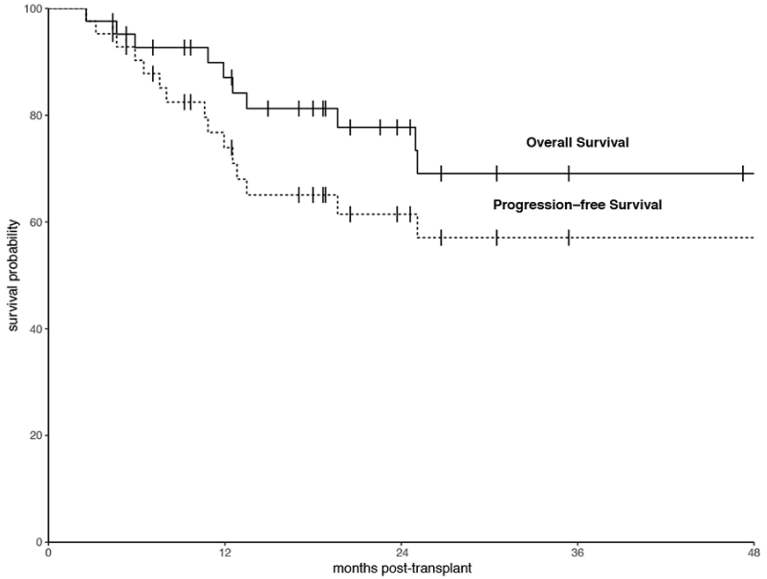


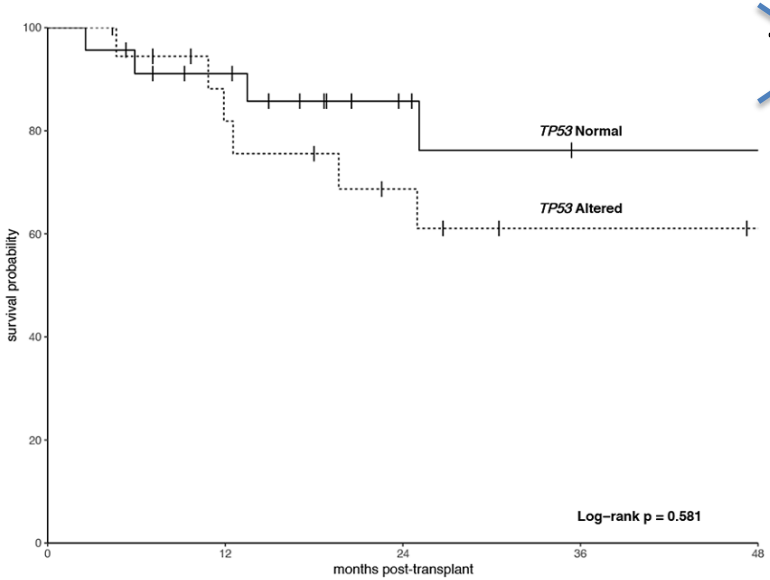
NRM at 1 y 6.9%, at 3 y 23% (higher in case of aGVHD, for pts > 60 y and > 2 prior lines of therapy)

3y PFS 53%, OS 56%

Allogeneic Haematopoietic Cell Transplantation Impacts on Outcomes of Mantle Cell Lymphoma with *TP53* Alterations

DR. Richard J. Lin, MD, PhD[1], Caleb Ho, MD[2], Patrick D. Hilden, MS[3], Juliet N. Barker, MD[1,5], Sergio A. Giralt, MD[1,5], Paul A. Hamlin, MD[4,5], Ann A. Jakubowski, MD, PhD[1,5], Hugo R. Castro-Malaspina, MD[1,5], Kevin S. Robinson, BS[1], Esperanza B. Papadopoulos, MD[1,5], Miguel-Angel Perales, MD[1,5], and Craig S. Sauter, MD[1,5]





~~TP53~~

L’interpretazione dei risultati è difficoltosa, trattandosi nella maggior parte dei casi di studi retrospettivi/da registro su casistiche eterogenee, in pochi casi nell’era dei nuovi agenti biologici

L’allotrapianto è l’unica procedura ad aver evidenziato ad oggi, in alcuni studi, il raggiungimento di un plateau nelle curve, con alcuni lungo sopravviventi. Sembra annullare l’impatto prognostico negativo della POD24 e TP53

La NRM è probabilmente migliorabile con nuove strategie di profilassi della GVHD ma rimane il problema principale

QUALE INDICAZIONE?

In era pre-CAR T, l'alloSCT era suggerito dalle principali LG nei pz giovani/fit con MCL recidivato/refrattario dopo terapia ad alte dosi, soprattutto in caso di malattia ad alto rischio (POD24, TP53).

Pochi studi sull'uso up front nei pz very high risk

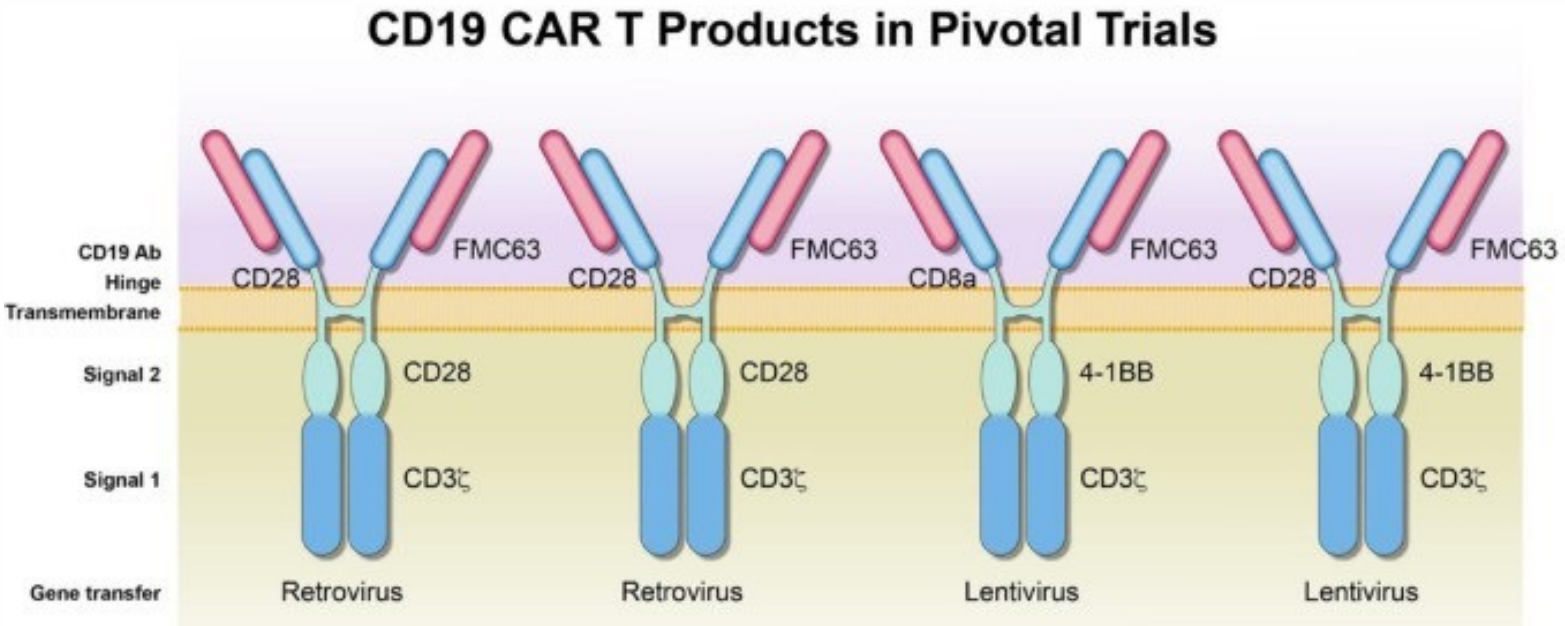
Lin et al Br J Haematol 2019, Rule et al Br J Haematol 2019

QUALE BRIDGE?

L'alloSCT si poneva come consolidamento della risposta ottenuta usando ibrutinib come salvataggio. Pochi dati al momento con altri BTKi

Schemi di immunoCT come R BAC o VR CAP possono essere una valida alternativa come bridge

Dreger et al BMT 2019; McCulloch et al Haematologica 2020



KTE C19	KTE X19	CTL 019	JCAR017
axi-cel	Brexu-cel	Tisa-cel	Liso-cel

ZUMA-2 trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

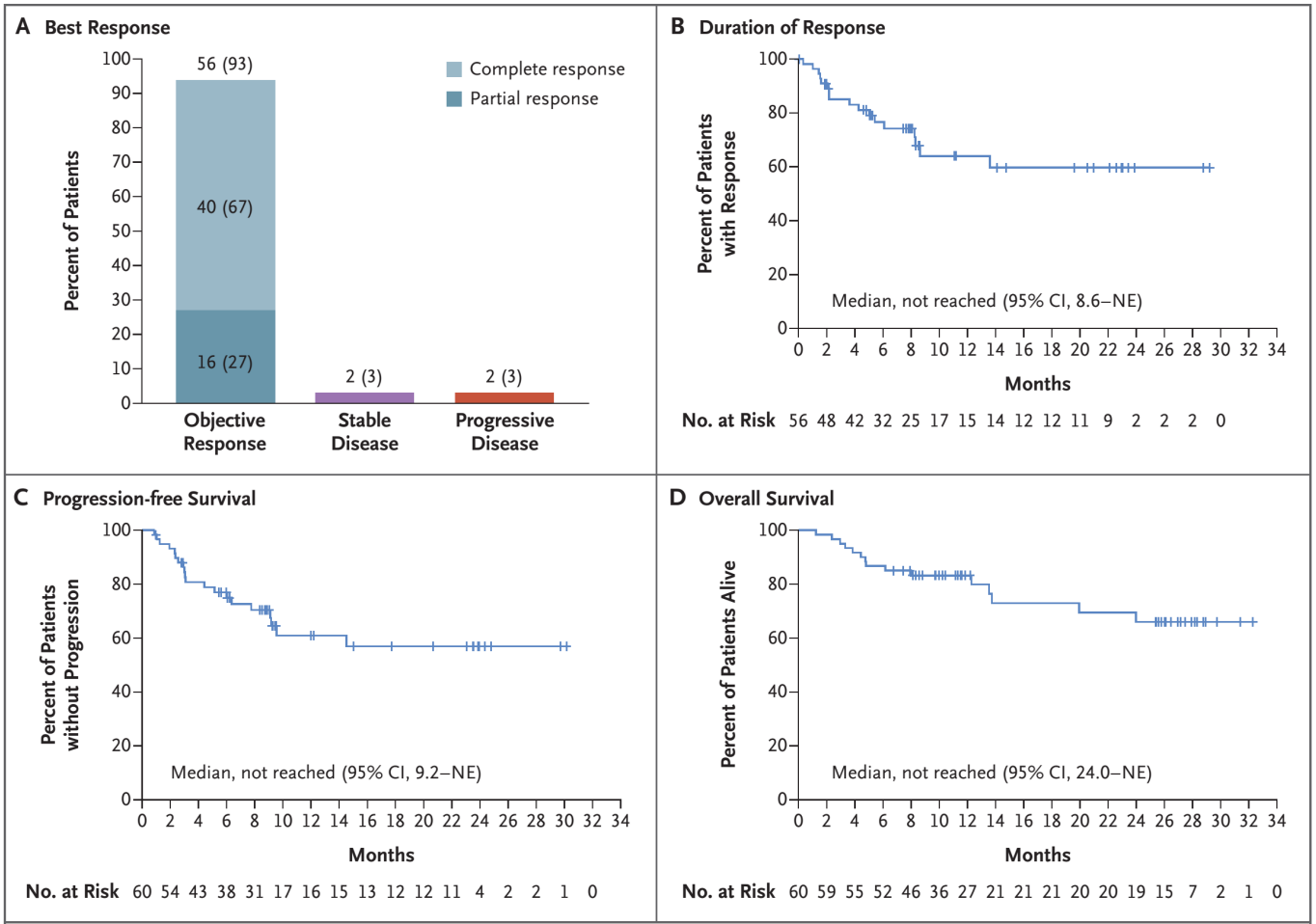
M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

Phase II study, 68 total pts
Rel/refr after at least 1 prior line of therapy including anthracyclines or bendamustine, anti CD20 and BTKi.

Median time to reinfusion 16 days
Bridging tx in 37% of pts (ibru, acala, steroids)

Table 1. Baseline Characteristics of All 68 Treated Patients.*

Characteristic	Patients
Median age (range) — yr	65 (38–79)
Intermediate or high risk according to Simplified MIPI — no. (%)†‡	38 (56)
Blastoid or pleomorphic morphologic characteristics of MCL — no. (%)	21 (31)
Ki-67 proliferation index ≥30% — no./total no. (%)‡	40/49 (82)
TP53 mutation — no. (%)	6/36 (17)
Positive CD19 status — no./total no. (%)	47/51 (92)
Median no. of previous therapies (range)§	3 (1–5)
≥3 Previous lines of therapy — no. (%)	55 (81)
Previous autologous stem-cell transplantation — no. (%)	29 (43)
Previous BTK inhibitor therapy — no. (%)§	68 (100)
Ibrutinib	58 (85)
Acalabrutinib	16 (24)
Both	6 (9)
Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)



ORR 93%
CRR 67%
1y-PFS 61%
1y-OS 83%

Wang et al NEJM 2020

Table 3. Cytokine Release Syndrome and Neurologic Events among All 68 Treated Patients.*

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Symptom of cytokine release syndrome						
Any	62 (91)	20 (29)	32 (47)	8 (12)	2 (3)	0
Pyrexia	62 (91)	15 (22)	40 (59)	7 (10)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	14 (21)	1 (1)	0
Hypoxemia	23 (34)	1 (1)	10 (15)	8 (12)	4 (6)	0
Chills	21 (31)	12 (18)	9 (13)	0	0	0
Tachycardia	16 (24)	11 (16)	5 (7)	0	0	0
Headache	15 (22)	7 (10)	8 (12)	0	0	0
Alanine aminotransferase increased	10 (15)	5 (7)	1 (1)	3 (4)	1 (1)	0
Aspartate aminotransferase increased	9 (13)	4 (6)	0	5 (7)	0	0
Fatigue	9 (13)	6 (9)	2 (3)	1 (1)	0	0
Nausea	9 (13)	5 (7)	4 (6)	0	0	0
Neurologic event	43 (63)	13 (19)	9 (13)	15 (22)	6 (9)	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Confusional state	14 (21)	3 (4)	3 (4)	8 (12)	0	0
Aphasia	10 (15)	3 (4)	4 (6)	3 (4)	0	0

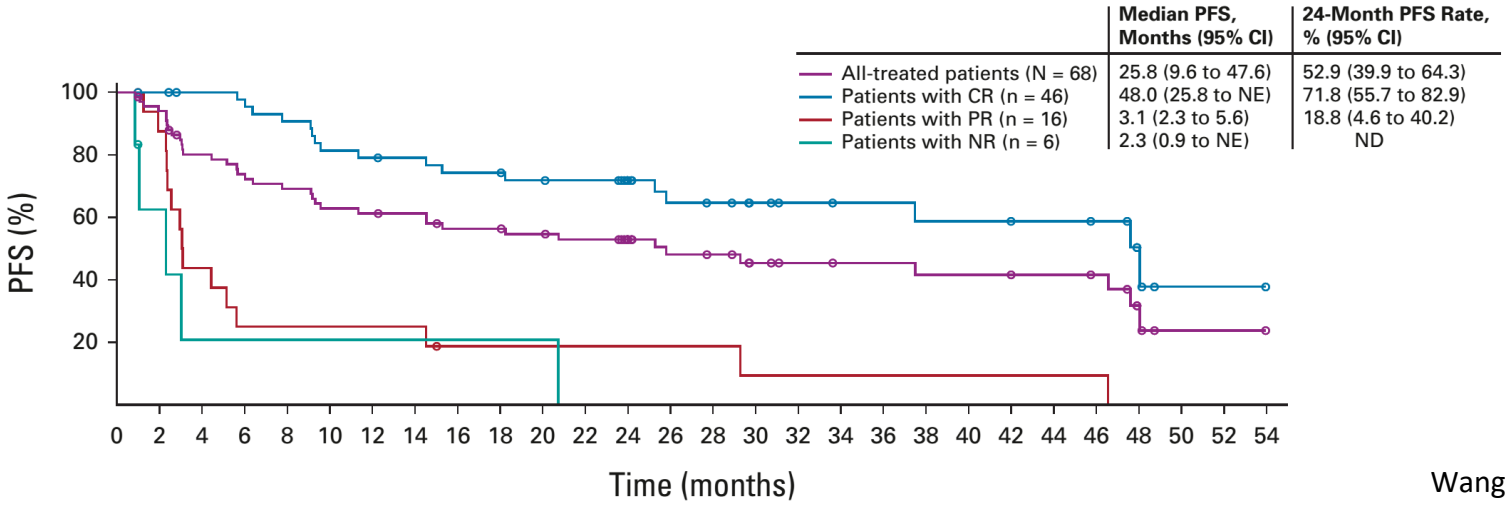
CRS gr ≥3 15%
ICANS gr≥3 31%
Infections gr≥3 32%

Wang et al NEJM 2020

original reports

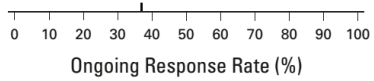
Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study

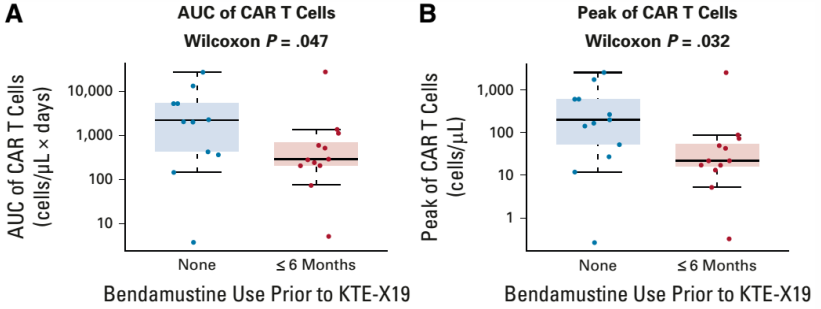
Michael Wang, MD[1]; Javier Munoz, MD, MS, MBA[2]; Andre Goy, MD, MS[3]; Frederick L. Locke, MD[4]; Caron A. Jacobson, MD, MMSc[5]; Brian T. Hill, MD, PhD[6]; John M. Timmerman, MD[7]; Houston Holmes, MD, MBA[8]; Samantha Jaglowski, MD[9]; Ian W. Flinn, MD, PhD[10]; Peter A. McSweeney, MB, ChB[11]; David B. Miklos, MD, PhD[12]; John M. Pagel, MD, PhD, DSc[13]; Marie José Kersten, MD, PhD[14]; Krimo Bouabdallah, MD[15]; Rashmi Khanal, MD[16]; Max S. Topp, MD[17]; Roch Houot, MD, PhD[18]; Amer Beitinjaneh, MD[19]; Weimin Peng, PhD[20]; Xiang Fang, PhD[20]; Rhine R. Shen, PhD[20]; Rubina Siddiqi, PhD[20]; Ioana Kloos, MD[20]; and Patrick M. Reagan, MD[21]



Wang M et al JCO 2022

	No. of Patients	No. of Patients With Ongoing Response	Patients With Ongoing Response, % (95% CI)
Overall	68	25	37 (25 to 49)
Morphologic characteristics			
Classical MCL	40	14	35 (21 to 52)
Diffuse	20	5	25 (9 to 49)
Nodular	10	6	60 (26 to 88)
Pleomorphic	4	2	50 (7 to 93)
Others	6	1	17 (0 to 64)
Blastoid	17	4	24 (7 to 50)
Others	1	1	100 (3 to 100)
Unknown	10	6	60 (26 to 88)
Ki-67 PI (%)			
< 30	9	4	44 (14 to 79)
≥ 30	43	17	40 (25 to 56)
< 50	15	5	33 (12 to 62)
≥ 50	37	16	43 (27 to 61)
Prior ibrutinib			
Yes	58	24	41 (29 to 55)
No	10	1	10 (0 to 45)
Prior acalabrutinib			
Yes	16	7	44 (20 to 70)
No	52	18	35 (22 to 49)
TP53 mutation			
Mutation detected	6	2	33 (4 to 78)
Mutation undetected	30	14	47 (28 to 66)
Missing	32	9	28 (14 to 47)
MRD at month 6 (10^{-5} sensitivity)			
Positive	4	0	0 (0 to 60)
Negative	15	9	60 (32 to 84)
Indeterminate	0	0	NA (NA to NA)
Missing	49	16	33 (20 to 48)
POD24			
Yes	33	9	27 (13 to 46)
No	35	16	46 (29 to 63)
BTKi subgroup			
Ibrutinib only	52	18	35 (22 to 49)
Acalabrutinib only	10	1	10 (0 to 45)
Both	6	6	100 (54 to 100)





Le mediane di PFS e OS sono simili in tutti i sottogruppi esaminati post hoc ma sembra esserci un trend inferiore nei pz POD24, nei pz con TP53 mut e morfologia blastoide

L'esposizione a Bendamustina, soprattutto se nei 6 mesi precedenti, riduce l'efficacia di espansione delle CAR T cells

LISOCABTAGENE MARALEUCEL (LISO-CEL) IN R/R MCL: PRIMARY ANALYSIS RESULTS FROM THE MCL COHORT OF THE SINGLE-ARM, MULTICENTER, SEAMLESS DESIGN TRANSCEND NHL 001 STUDY

Eligible pts had R/R MCL after ≥2 lines of prior therapy, including a BTKi, alkylating agent, and CD20-targeted agent.
Bridging therapy was allowed

Median age 68 y
Prior lines of therapy: median 3 (1-11)
53% BTKi refractory

ORR was 83.1% with CR rate of 72.3%
Responses were durable:
median DOR, 15.7 m
median PFS, 15.3 m
Low rates of CRS gr ≥3 (1%)
and ICANS gr ≥3 (9%)

Wang et al ICML 2023

CAR T vs ALLO

indicazione AIFA in pz sottoposti ad almeno 2 precedenti LT e in progressione in corso di BTKi: in caso di malattia rapidamente progressiva difficile bridge efficace

Le risposte a CAR T sono molto buone ma le curve non mostrano plateau.

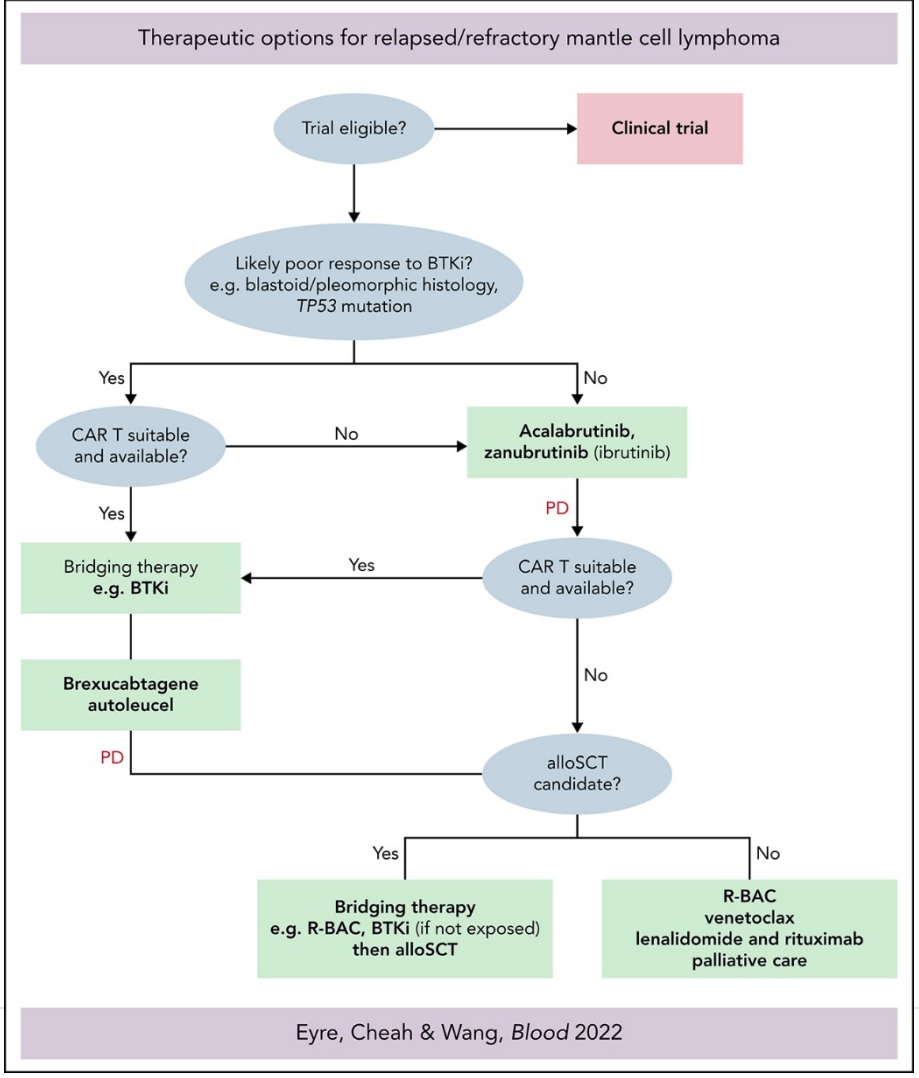
Complessità di gestione legata a ingegnerizzazione centralizzata, tempi di infusione
Costi elevati

dati di studi con lungo follow up

Evidenza di effetto GVL che consente controllo di malattia a lungo termine con verosimile plateau nelle curve

Tossicità elevata

Necessità di donatore



Therapeutic options for relapsed/ refractory mantle cell lymphoma

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Guideline

American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and European Society for Blood and Marrow Transplantation Clinical Practice Recommendations for Transplantation and Cellular Therapies in Mantle Cell Lymphoma

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Table 4
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T Cell Treatments for R/R MCL

Consensus Statement	Grading of Recommendation*
1. If a TP53 mutation (or biallelic deletion) is present, the panel does not recommend autologous transplantation in relapsed MCL patients achieving a complete or partial remission after second or subsequent lines of therapy.	B
2. The panel recommends both CAR T cell therapy or allogeneic transplant consolidation as acceptable options, in relapsed MCL patients with TP53 mutation (or biallelic deletion) in a complete or partial remission after second or subsequent lines of therapy.	C
3. If a TP53 mutation (or biallelic deletion) is present, the panel recommends treatment with CAR T cells in relapsed MCL patients, with disease unresponsive to last antilymphoma therapy.	B
4. In relapsed MCL patients, the panel recommends offering CAR T cell therapy before proceeding with allogeneic transplantation.	C
5. Regarding timing of CAR T cell application in relapsed MCL patients (without TP53 mutation or biallelic deletion), the panel recommends offering CAR T cell therapy to patients relapsing after (or who are intolerant to) at least one BTK inhibitor.	B
6. The panel does not recommend allogeneic transplantation in relapsed MCL patients with disease refractory to most recent antilymphoma treatment.	B
7 The panel recommends allogeneic transplantation for eligible relapsed MCL patients who have achieved only a partial remission with a BTK inhibitor in second or subsequent treatment line, particularly in regions without access to CAR T cell therapy or in subjects where such therapy is not feasible.	B
8. The panel recommends allogeneic transplantation in eligible MCL patients relapsing/progressing after CAR T cell therapy, if they achieve a complete or partial remission or if they have stable disease with subsequent antilymphoma therapies.	C
9. Among eligible MCL patients lacking a TP53 mutation (or biallelic deletion) not undergoing autologous transplant consolidation following first-line therapies, the panel recommends considering autologous transplantation consolidation therapy in patients who have achieved a complete remission after second-line chemoimmunotherapies.	B
10. The panel recommends considering allogeneic transplant consolidation in eligible MCL patients who still have detectable disease at 3 or more months following CAR T cell therapy.	C

With the approval of CAR T cell therapy for R/R MCL, the role of allo-HCT merits reevaluation. The Consensus Panel recognizes the increased toxicities and life-threatening complications of allo-HCT and thus recommends considering CAR T cell treatments before allo-HCT. In practical terms and taking into account recommendation 5 (Table 4) for R/R disease, this means that the treatment sequence would be to treat with BTK inhibitors until failure or intolerance, then move to CAR T cell therapy, and reserve allo-HCT for CAR T cell therapy failure.


thank you
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謝謝
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teşekkür ederim
Баярлалаа
спасибо
faafetai lava
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Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma

37 pts, median age 72 y
Median prior lines of therapy 3 (1-5)
Refractory to last therapy 73%
Prior BTKi 65%

After a median follow up of 8 months, overall response rate (ORR) and complete response (CR) rates were 83.8% (31/37) and 73.0% (27/37)
Median duration of response was 12.6 m
CRS events were manageable and mostly low grade

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