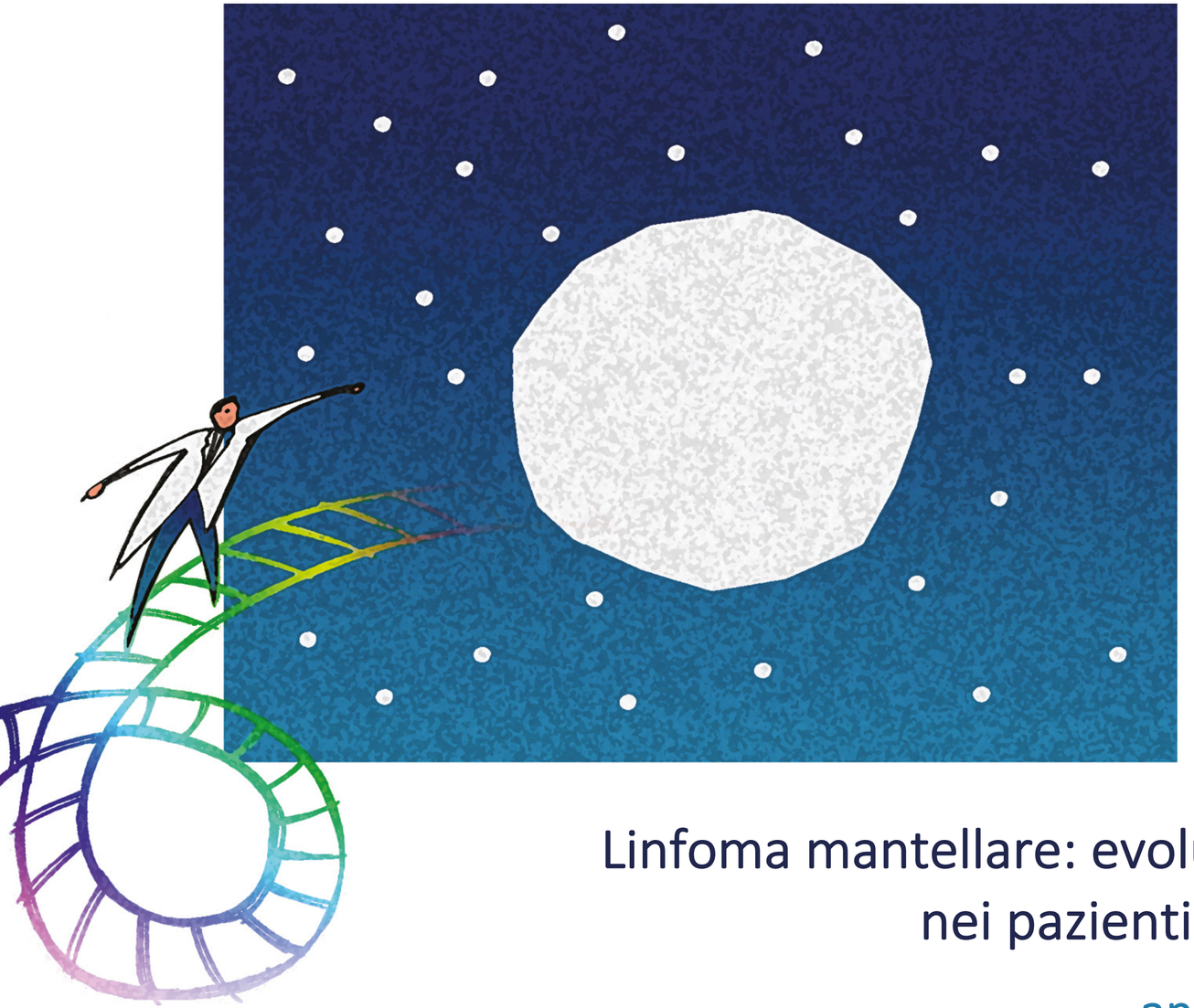


The young side of
LYMPHOMA

gli under 40 a confronto

Milano, 14-15 aprile 2023

Linfoma mantellare: evoluzione del programma terapeutico nei pazienti recidivati e refrattari

..and finally, Car T

Francesca Maria Quaglia
UOC Ematologia e CTMO, AOUI Verona

Disclosures of Francesca Maria Quaglia

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Astra Zeneca					x	x	
Janssen					x	x	x
Sandoz			x				
Amgen							x
Roche							x

Indice

- Caso Clinico
- Linee guida e algoritmi terapeutici
- Focus on…
- Nuove combinazioni
- Terapie innovative
- Prospettive future
- Conclusioni

- ♀ d.n. 1956, 57 aa

- **Ott 2013 diagnosi MCL su lesione base lingua**
  - ✓ Variante classica, SOX11+,Ki67 20-25%
  - ✓ Stadio IIIA, BOM negativa
  - ✓ Emocromo nei limiti, MIPI 6.5 (int)
  - ✓ PET SUV max 8 (Ly paratracheali dx)

- Dic 2013: protocollo MCL0208 (R-CHOPx3, CTX-HD, R-HDAra-Cx2)
- Dic 2014: ASCT (condizionamento Carmustina, Etoposide, Ara-C e Melphalan)
- CR, mantenimento con Lenalidomide fino a Mar 2017

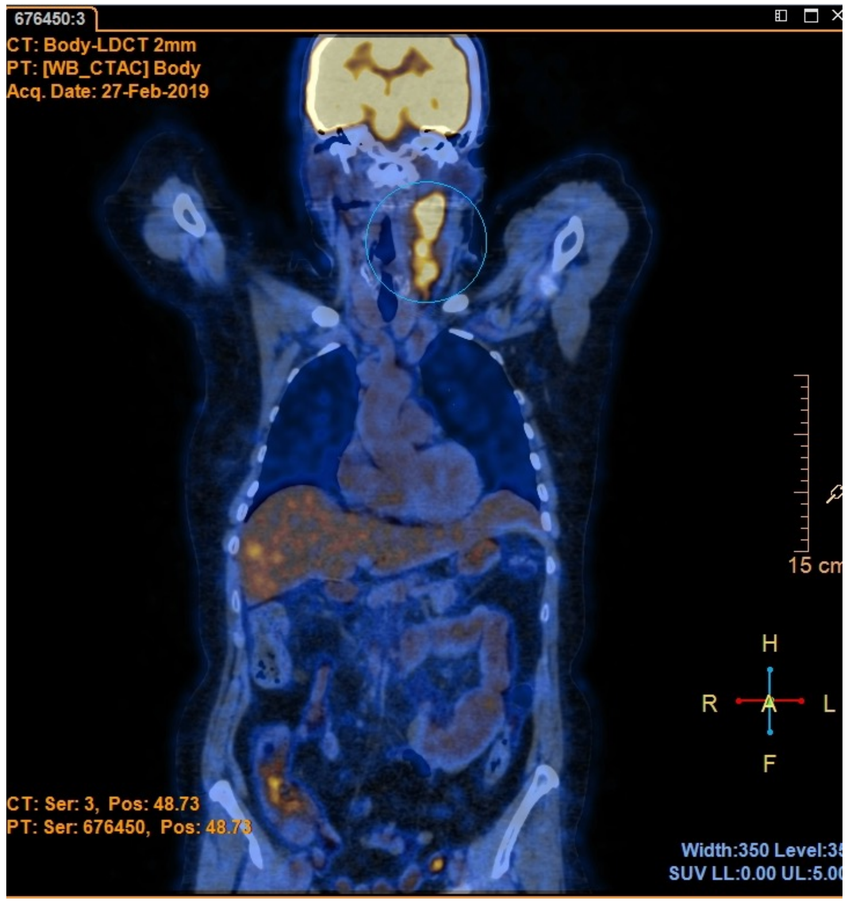
Sdr ansioso-depressiva (depressione maggiore+psicosi)

aloperidolo, sertralina, biperidene e benziodiazepine

Pregressa appendicectomia, tonsillectomia, colecistectomia

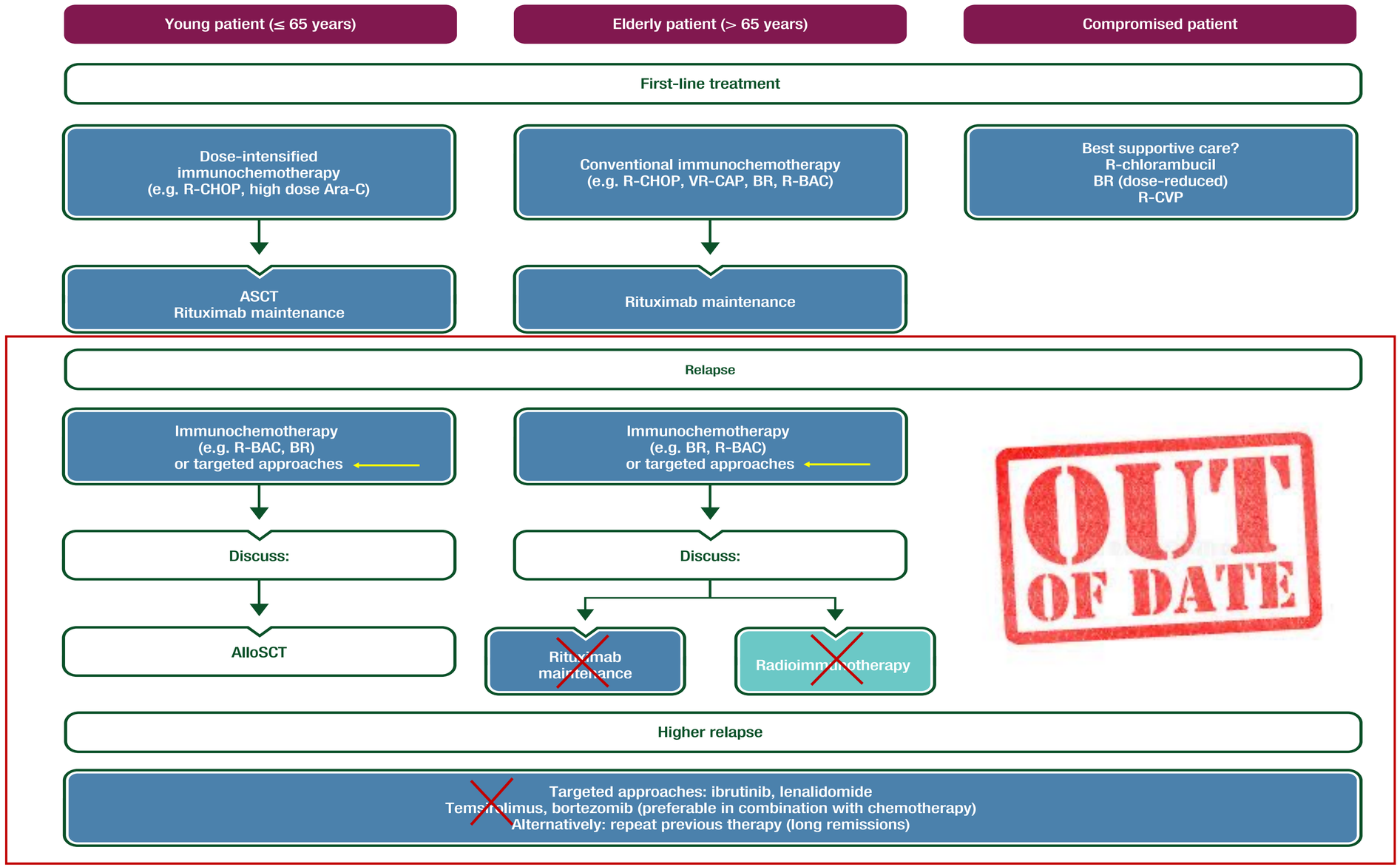
- +5 anni dalla diagnosi, ~4 anni da ASCT, +19 mesi dal termine mantenimento

- **Ott 2018**: eco-collo Ly LC sx → PET colata adenopatica LC sx SUVmax 8.8, paratracheale dx SUV 4
- Mar 2019: Biopsia Ly LC sx: **I recidiva di MCL (late-POD)**
  - ✓ Variante classica, SOX11+, Ki67 30%
  - ✓ Stadio IIIA, BOM negativa
  - ✓ Emocromo nei limiti, LDH nella norma



Linee guida ESMO, 2017

R/R MCL



Dreyling et al, 2017. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

- **Ripetere la biopsia:** aspetti prognostici importanti
- **Early** vs **Late-POD**, ancora poche evidenze sulla migliore terapia in II linea/algoritmo terapeutico
- **Ibrutinib:** ORR elevate, remissioni di lunga durata, ma recidive precoci molto aggressive
- Pazienti giovani: allo-SCT potenzialmente curativo, remissioni di lunga durata anche dopo recidive precoci/malattia refrattaria

2017

- Partecipazione a clinical trial
- Markers molecolari → approccio personalizzato

Dreyling et al, 2017. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

HemaSphere
Powered by EHA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Editorial
OPEN ACCESS

EHA Endorsement of ESMO Clinical Practice Guidelines for Newly Diagnosed and Relapsed Mantle Cell Lymphoma

Kim Linton[1], Martin Dreyling[2], on behalf of the EHA Guidelines Committee

Correspondence: Martin Dreyling (e-mail: Martin.Dreyling@med.uni-muenchen.de).

2020

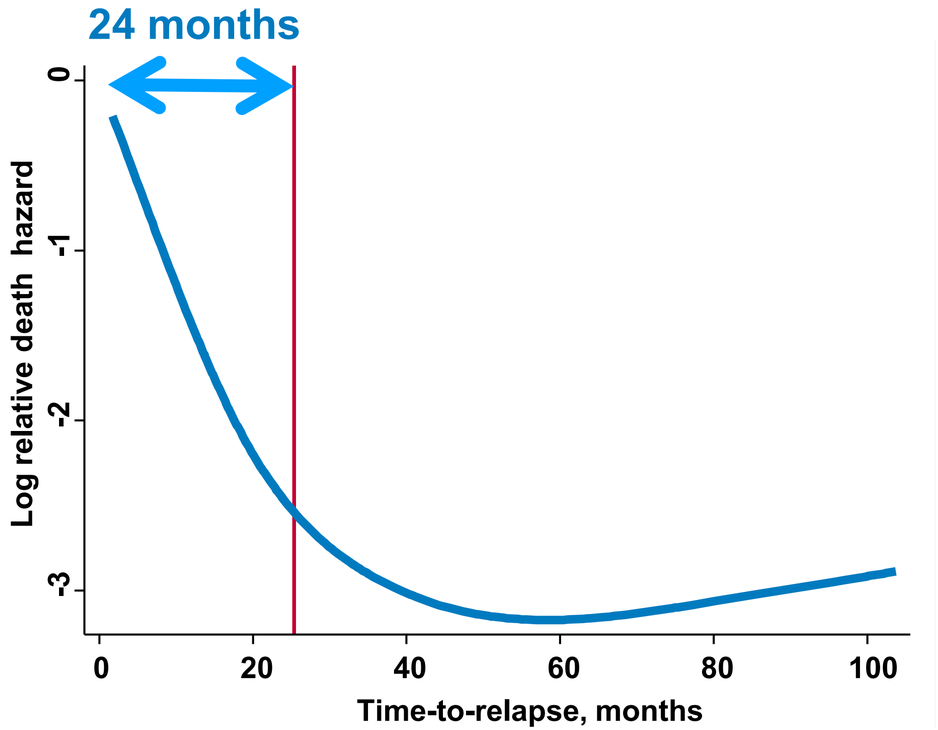
- **MCL entità relativamente rara, pazienti anziani**
- R-AraC: componenti chiave dell'induzione/salvataggio
- Bendamustina: efficace, *backbone* per nuovi schemi di combinazione

- Ongoing trials: è possibile sostituire la chemioterapia con nuovi farmaci?
- **Sfide: *risk adapted/personalized management***
  - ✓ Morfologia blastoide, Ki67 pretrattamento, MRD post-trattamento, mutazioni TP53
  - ✓ Biologia della malattia indolente (SOX11-): non completamente chiara, cauto W&W, biomarkers per selezionare i pazienti a basso rischio

HemaSphere (**2020**) 4:5(e464). http://dx.doi.org/10.1097/ HS9.0000000000000464.

Definition of early POD

Trend in the risk of death*



*linear regression model using restricted cubic splines: the relationship between time to POD and survival was not linear but could be usefully summarized by a linear graph

Visco et al, BJH 2018

Leukemia (2021) 35:787–795
https://doi.org/10.1038/s41375-020-01013-3

ARTICLE

Lymphoma

Outcomes in first relapsed-refractory younger patients with mantle cell lymphoma: results from the MANTLE-FIRST study

Carlo Visco[1] · Alice Di Rocco[2] · Andrea Evangelista[3] · Francesca Maria Quaglia[1] · Maria Chiara Tisi[4] · Lucia Morello[5] · Vittorio Ruggero Zilioli[6] · Chiara Rusconi[6,7] · Stefan Hohaus[8] · Roberta Sciarra[9] · Alessandro Re[10] · Cristina Tecchio[1] · Annalisa Chiappella[7,11] · Ana Marin-Niebla[12] · Rory McCulloch[13] · Guido Gini[14] · Tommasina Perrone[15] · Luca Nassi[16] · Elsa Pennese[17] · Piero Maria Stefani[18] · Maria Christina Cox[19] · Valentina Bozzoli[20] · Alberto Fabbri[21] · Valentina Polli[22] · Simone Ferrero[23] · Maria Isabel Alvarez De Celis[24] · Antonello Sica[25] · Luca Petrucci[2] · Luca Arcaini[9] · Simon Rule[13] · Mauro Krampera[1] · Umberto Vitolo[26] · Monica Balzarotti[5]

MANTLE-FIRST

MANTLE-FIRST is the first patient-level analysis of outcomes of r-r MCL after cytarabine containing induction

Overall, R-BAC associated with higher CR rate and similar PFS to ibrutinib

Ibrutinib best performer in early-POD (and apparently in CNS progression)

Benda-based similar to Ibrutinib in late POD

2021

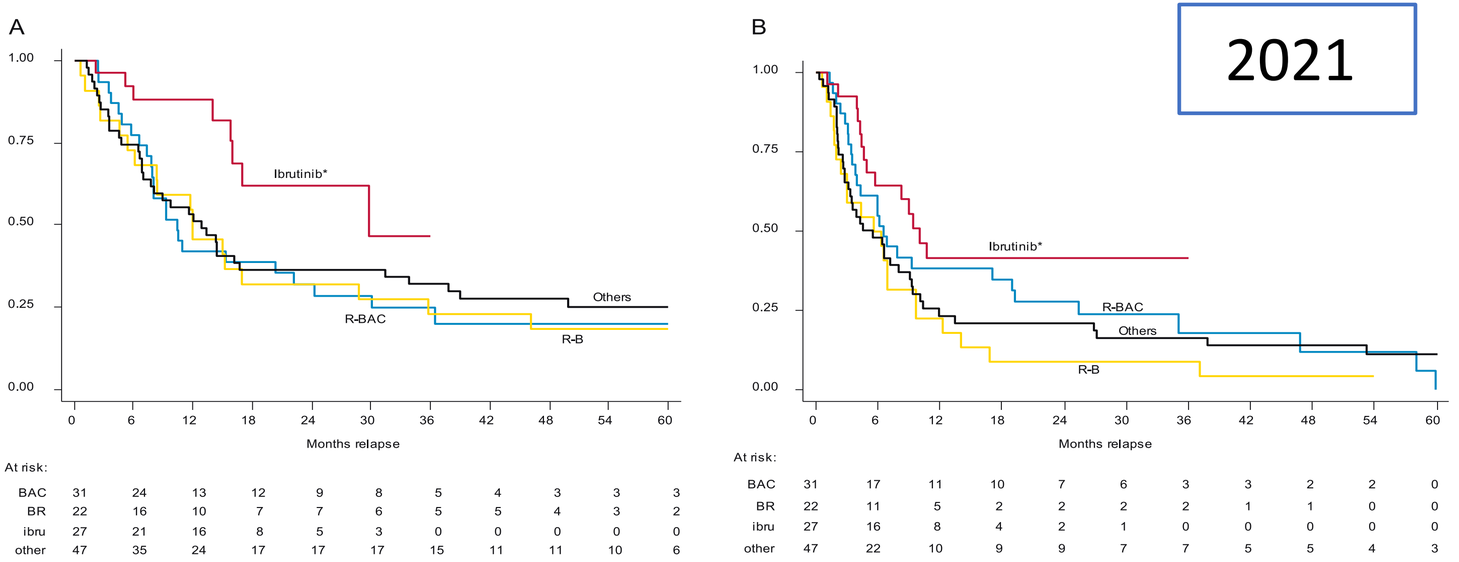
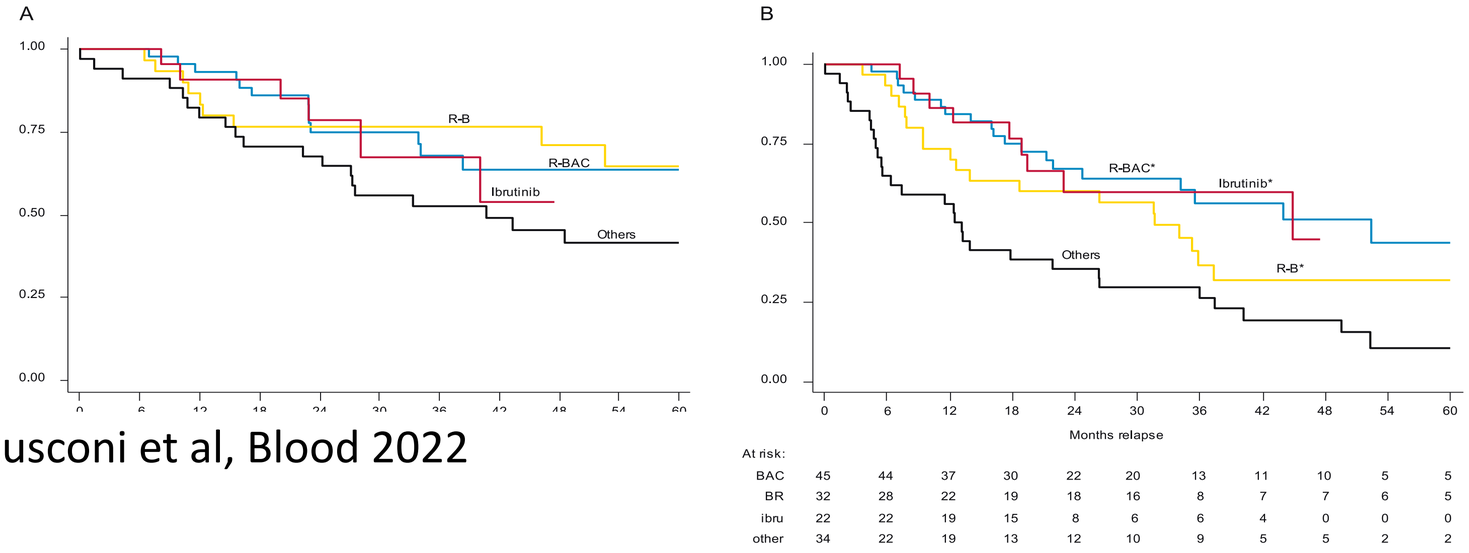


Fig. 2 Survival curves for patients with early-POD. a Overall survival (OS-2) and **b** progression-free survival (PFS-2) according to second line therapy. **a** Ibrutinib versus R-B and R-BAC ($P = 0.02$); ibrutinib versus others ($P = 0.03$). **b** Ibrutinib versus R-B ($P = 0.01$); ibrutinib versus others ($P = 0.02$); ibrutinib versus R-BAC ($P = 0.23$).



Rusconi et al, Blood 2022

Visco et al, Lugano 2023

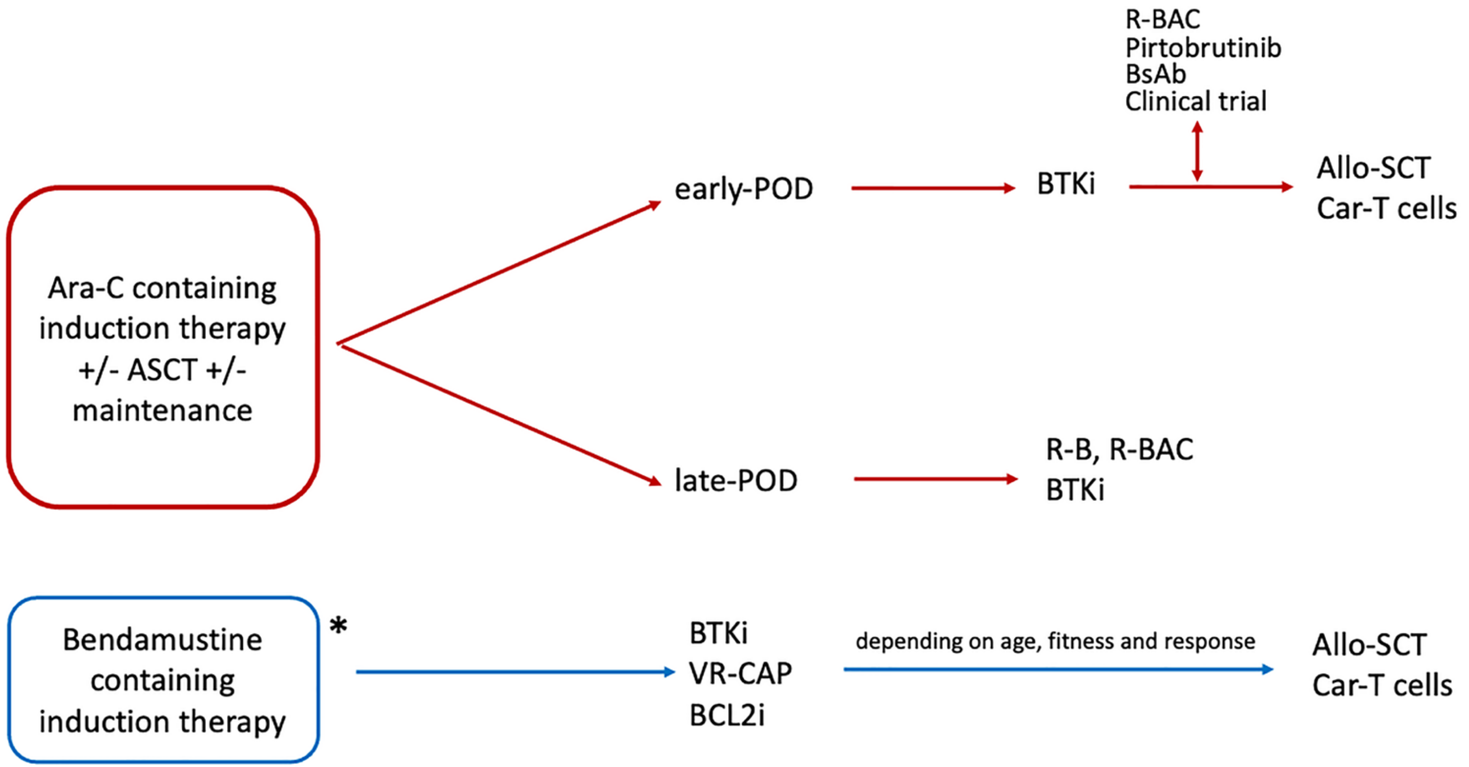
statistically significant. **b** Ibrutinib versus others ($P = 0.008$); R-BAC versus others ($P < 0.0001$); R-B versus others ($P = 0.02$).

www.oncotarget.com Oncotarget, 2021, Vol. 12, (No. 17), pp: 1724-1726

Editorial

Mantle cell lymphoma patients in first relapse: we pretty much know what to do

Our proposal for a treatment algorithm with a **perspective view** on MCL management



Triangle, ASH 2022

*Anthracycline containing induction (R-CHOP/VR-CAP) plus maintenance behave like late-POD younger patients

1) Quale terapia proporreste in II linea? (63 aa, 2019)

a. R-BAC
b. Acalabrutinib o Zanubrutinib
c. Pirtobrutinib
d. Ibrutinib
e. VR-CAP

- Dal 2/5/2019: ibrutinib

2) Le comorbidità della paziente:

a. Richiedono modifiche della dose di ibrutinib
b. Richiedono modifiche della dose dei farmaci psichiatrici
c. Non richiedono alcuna modifica della dose di ibrutinib e dei farmaci psichiatrici
d. Controindicherebbero la terapia con BTKi

- Dal 2/5/2019: **ibrutinib 280 mg**, riduzione sertralina
  ✓ Recrudescenza della depressione, aumento della sertralina

- **Nov 2019 (+6 mesi)**: PET netta riduzione dell'intensità di segnale e volumetrica delle note linfoadenopatie (**CR**)

- **28/12/2020 (+1 anno e 8 mesi):** iniziale **ricomparsa di discreto ipermetabolismo** (SUVmax 4.8) linfonodi LC sx come da **ripresa di malattia,** moderato ipermetabolismo di linfonodo 1.5 cm in iliaca esterna dx (SUVmax 4.6)

3) Cosa proporreste in questa fase? (64 anni, 2020)

a. Passaggio a BTKi di nuova generazione

b. Proseguire ibrutinib con vigile follow up, in attesa di franca progressione

c. Trapianto allogenico

d. Stop ibrutinib e inizio di RBAC

- Implementato dosaggio ibrutinib (420 mg/die)
- Quadro stabile fino all'ottobre 2022 (+3 anni e 8 mesi da inizio di ibrutinib)

- **+3 anni e 8 mesi da inizio di ibrutinib**
- Ott 2022: disfagia→ TAC collo formazione solida vascolarizzata 18x15x24mm alla tonsilla palatina sx
- Biopsia: **II recidiva di MCL, 66 aa**
  - ✓ Variante classica, SOX11+, Ki67 10-15%
  - ✓ Stadio IIIA, BOM non eseguita
  - ✓ Emocromo nei limiti, LDH nella norma

- *Eco addome: adenopatie retroperitoneali (fino a **43x23 mm**)*
- *PET: adenopatie ipermetaboliche colata LC, in sede **ascellare** (**SUVmax 21**), sottopettorali, periclaveari e mediastiniche. Adenopatie retroperitoneali, in particolare ilo epatico e stazioni lombo-aortiche, iliache, inguinocrurali; diffuso ipermetabolismo splenico; **SUV 15.2** tessuto linfatico **radice linguale***

Quadro clinico-radiologico compatibile con progressione di MCL
La paziente viene candidata a Car T

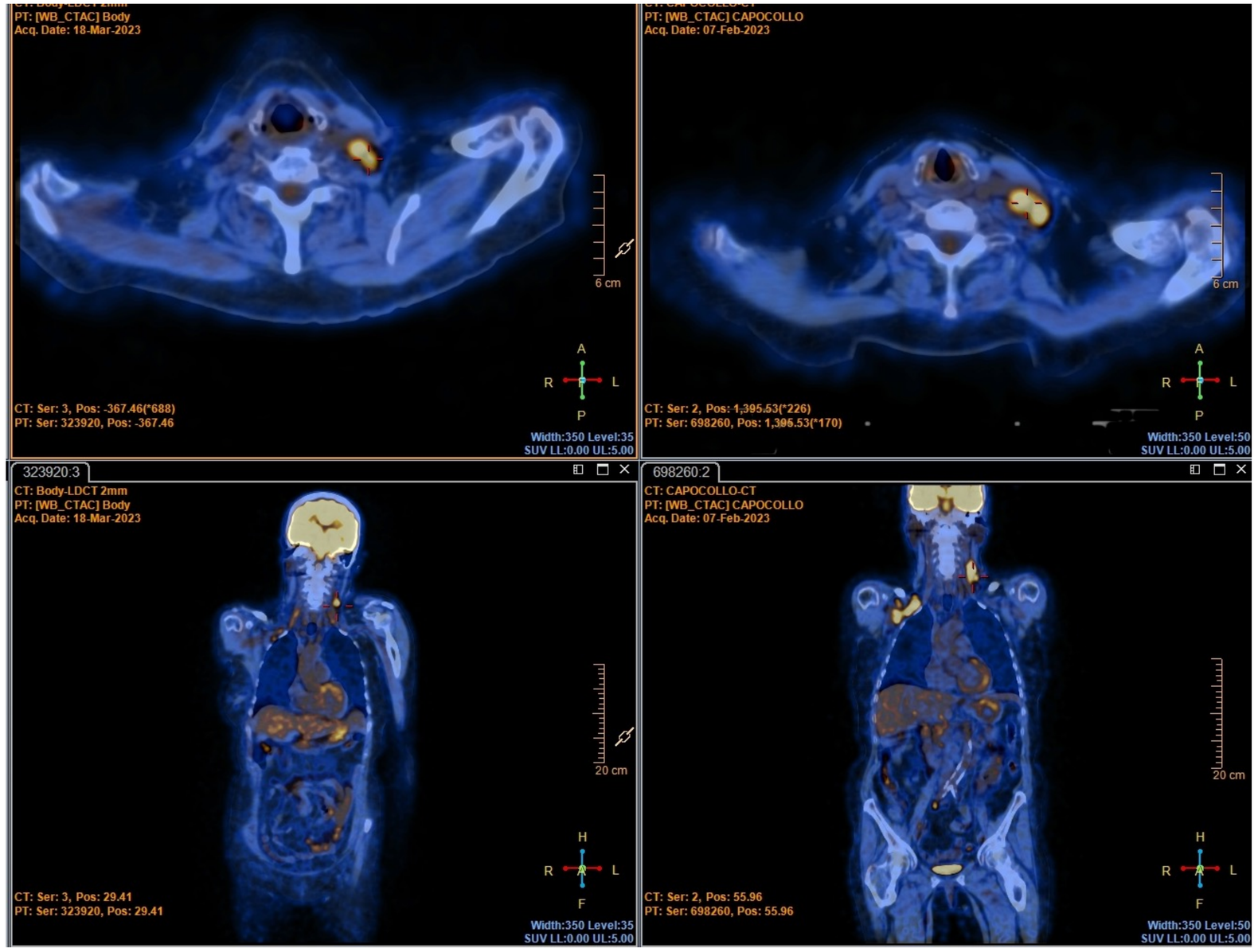
- Dal 15/12/2022: *debulking* VR-CAP; ibrutinib dal 7/1 al 19/1/23

✓ 25/1/2023 Linfocitoaferesi

- 28/1/2023 PET: PR (regressione completa adenopatie addominali e parziale adenopatie sovra-diaframmatiche, iper-metabolismo invariato base lingua SUVmax 15.5)

- 1/2/23 terapia *bridge* VR-CAPx1+ RT a basse dosi tonsillare sin (23.4 Gy dal 17/2 al 10/3/23) + ibrutinib (dal 26/1 all'8/2, dal 16/2 al 20/3/23); odinofagia post-attinica, sospese le ultime 4 sedute

18/3/2023 PET pre-CAR T: PR, SUVmax 8.7 regione oro-tonsillare/linguale



- Day -5, -4, -3 (22,23,24/3) ciclo linfodepletivo Flu 40 mg/mq e Cy 800 mg/mq
- Valutazione neurologica: nella norma
- **Day 0 (27/3): Infusione di** brexucabtagene autoleucel **(0.4 - 2 x 10^8)**
- Parametri vitali e ICE score pre-infusione nella norma, non eventi avversi

- Day +3-4: T 38.5°C, CRS 1, ICE 10: ceftazidime+vancomicina
- Day +5: TC 39.1°C, PAO 110/60 mmHg, SpO2 94% aa, FC 80 R. Per pressione arteriosa in calo e persistenza stato febbrile → *Tocilizumab 520 mg ev (8 mg/kg)*
- Day +6 apiretica, ICE score 10, CRS 0
- Aplasia (dal 6 al 9/4: filgrastim)

Espansione CAR-T su s.p.
+1: 0/ul, LDH: 216 U/L
+4: 0/uL, LDH: 189 U/L
+7: 13/uL, LDH: 210 U/L
+9: 14/uL, LDH: 194 U/L
+11: 11/uL, LDH: 179 U/L

- Dimessa il 12/4/23 a +16 giorni dall'infusione…

In attesa di eseguire PET a +30 dalla terapia con Car T

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Mantle Cell Lymphoma

NCCN Guidelines Index
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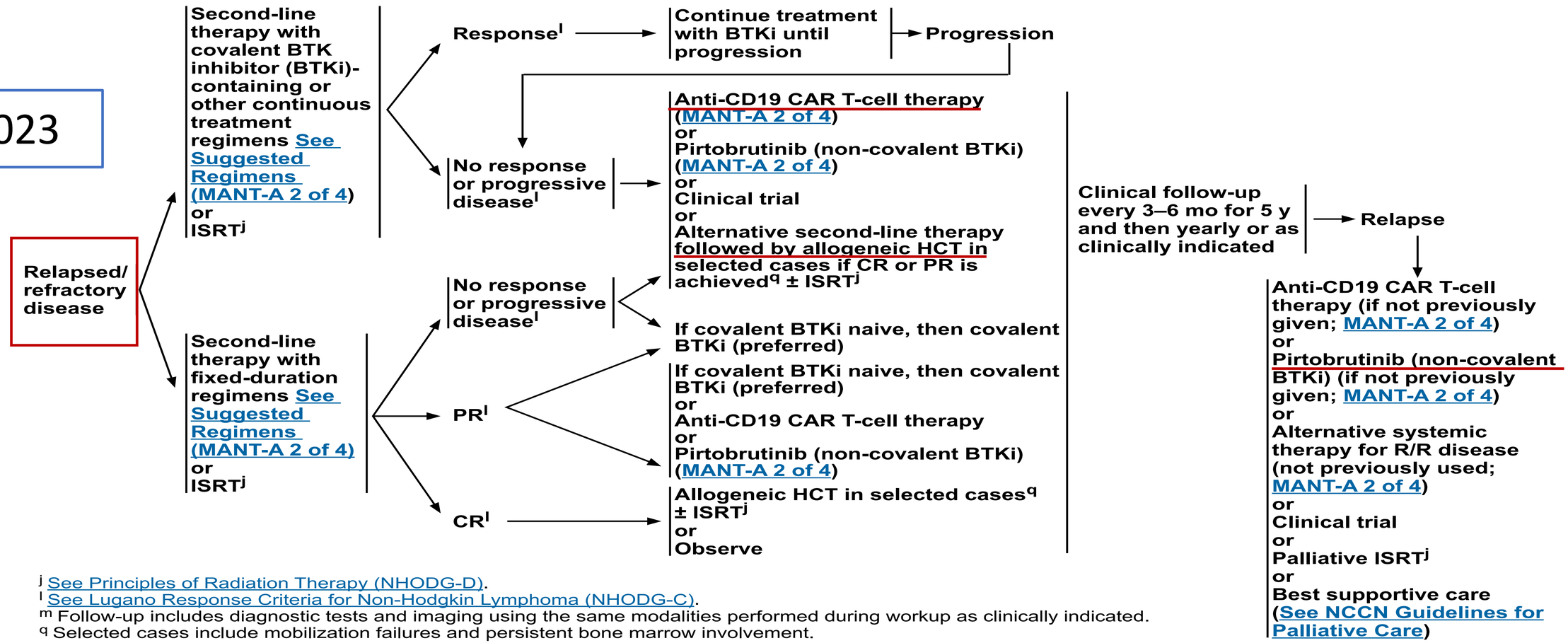
Discussion

2023



[j] See Principles of Radiation Therapy (NHODG-D).
[l] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C).
[m] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.
[q] Selected cases include mobilization failures and persistent bone marrow involvement.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SUGGESTED TREATMENT REGIMENS[a]
An FDA-approved biosimilar is an appropriate substitute for rituximab.[b]

SECOND-LINE AND SUBSEQUENT THERAPY

Preferred regimens (in alphabetical order)
- Covalent BTK inhibitors (continuous)[f,g]
  - Acalabrutinib[h]
  - Zanubrutinib
- Lenalidomide + rituximab

Other recommended regimen
- Covalent BTK inhibitor (continuous)[f]
  - Ibrutinib[i] ± rituximab

Useful in Certain Circumstances (in alphabetical order)
- Bendamustine[d] + rituximab (if not previously given)
- Bendamustine[d] + rituximab + cytarabine (RBAC500) (if not previously given)
- Bortezomib ± rituximab
- GemOx (gemcitabine, oxaliplatin) + rituximab
- Ibrutinib[f] + venetoclax
- RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) (if not previously given)
- Venetoclax[f] (continuous) ± rituximab

THIRD-LINE AND SUBSEQUENT THERAPY

- Brexucabtagene autoleucel[j] (only given after chemoimmunotherapy and BTK inhibitor)
- Pirtobrutinib[k] (non-covalent BTK inhibitor)
- Allogeneic HCT in selected cases[l]

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens MANT-A 3 of 4 and MANT-A 4 of 4.
[b] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion.
[d] In patients intended to receive HDT/ASCR, bendamustine should be used with caution as there are conflicting data regarding ability to collect peripheral progenitor cell collection. In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless after leukapheresis prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.
[f] See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).
[g] Acalabrutinib and zanubrutinib have not been shown to be effective for ibrutinib-refractory MCL with *BTK* C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib or zanubrutinib without recurrence of symptoms.
[h] Studies of acalabrutinib excluded concomitant use of warfarin or equivalent vitamin K antagonists.
[i] Head-to-head clinical trials in other B-cell malignancies have demonstrated a more favorable toxicity profile for acalabrutinib and zanubrutinib compared to ibrutinib without compromising efficacy.
[j] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).
[k] Pirtobrutinib inhibits both wild type and C481S mutant BTK and has been shown to be effective in patients with intolerance or disease that is refractory to prior covalent BTKis without recurrence of prior symptoms. Pirtobrutinib may be used for disease progression or intolerance to covalent BTKi therapy.
[l] Selected cases include mobilization failures and persistent bone marrow involvement.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Focus on: CAR-T

- CD19 CAR T-cell brexucabtagene autoleucel (KTE-X19), risultati del trial ZUMA-2 (NCT02601313) → In Italia da marzo 2022
- E’ indicato per il trattamento di pazienti adulti con MCL R/R dopo due o più linee di terapia sistemica che includano un BTKi

- I noti fattori prognostici/markers biologici: si applicano ai pazienti con MCL R/R trattati sia con CIT che con BTKi, ma sembrano essere meno predittivi di risposta alle CAR T, e questo ha implicazione sulla sequenza dei trattamenti

Silkenstedt et al, 2021; Bond et al, 2021

Recidiva post CAR T?

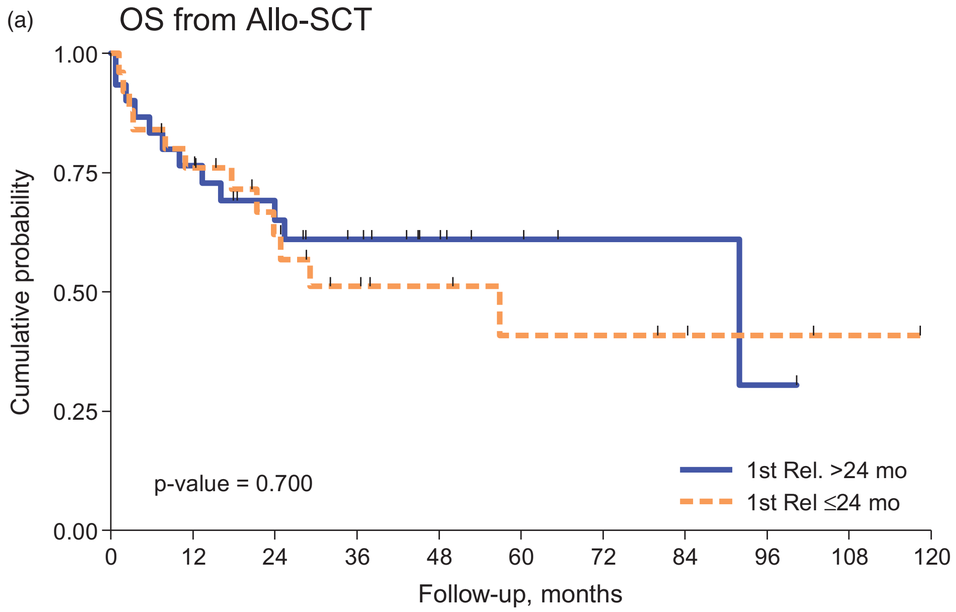
Jain et al, Br H Haematol, 2021

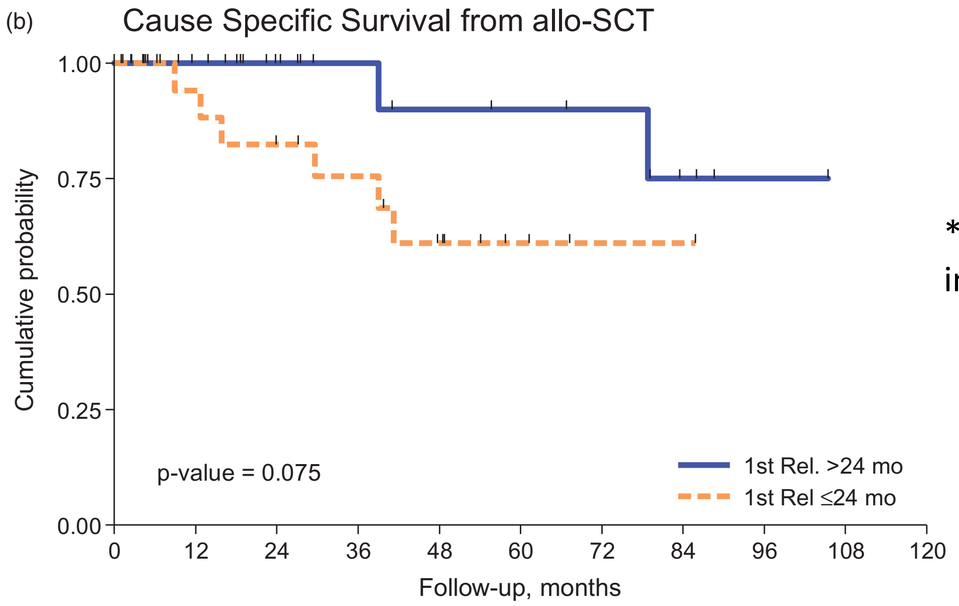
Focus on: allo-SCT

- 55 pts allo-SCT per R/R MCL post R+HD-AraC (MANTLE-FIRST), median FU 3.7 anni
- NRM, PFS, OS 23%, 53%,56%, rispettivamente
- NRM maggiore se aGVHD, > 2 linee, età > 60 anni
- **Outcome simili in early e late-POD**
- BTKi ponte all'allo-SCT non aumentano la tossicità con buon controllo della malattia

Arcari et al, 2021

Esperienza real-life conferma che l'allo-SCT è una opzione di cura per i pazienti con MCL soprattutto se giovani e con recidiva precoce





*TP53 was not available in this series

- Pazienti candidabili a trapianto, MCL recidivato, alto rischio, con mutazioni di TP53
- RIC alloSCT: long-term DFS ~30% dei pazienti, anche pazienti >60 anni
- Tossicità severe acute e croniche (cGVHD) comuni, 20– 25% TRM
- Non in I linea, riservato a **pazienti selezionati (high-risk recurrent disease), considerando attentamente il rapporto rischio beneficio**

Bond et al, 2021; Lin et al, 2018

Allo-SCT era l'unica opzione per una remissione di lunga durata e possibile cura per MCL recidivato dopo ASCT

Curr. Treat. Options in Oncol. (2022) 23:1614–1625
DOI 10.1007/s11864-022-01020-9

A. Beitinjaneh, A. Kaufman, Y. Wang, P.Jain, S.A. Srour, M. Wang, 2022

Lymphoma (JL Muñoz, Section Editor)

Is There Still a Role for Transplant for Patients with Mantle Cell Lymphoma (MCL) in the Era of CAR-T Cell Therapy?

- ***Paradigm shift*** dall'approvazione FDA in luglio 2020 (Eu Dic 2020, IT Mar 2022) di brexucabtagene autoleucel per il R/R MCL, con iniziali evidenze che le CAR-T possano superare i noti fattori di rischio biologici
- CAR-T: attualmente opzione preferita nel R/R MCL post BTKi
- Pazienti high-risk (Ki67 elevato, mutazioni TP53, CK, morfologia blastoide, early relapse) CAR-T prima dei BTKi (clinical trial)?

Il ruolo dell'allo-SCT non è chiaro nell'era delle CAR-T, ma rimane una valida opzione per i pazienti candidabili che non possono accedere alle CAR-T o che falliscono la terapia con CAR-T

Studi prospettici basati sui fattori di rischio sono necessari per definire la sequenza ottimale di allo-SCT, terapie cellulari e altre nuove terapie

Nuove combinazioni

Table 1. Summary of Published Combination Studies in Relapsed Mantle Cell Lymphoma.

Combination	Number of Patients	ORR% (CR%)	Median PFS	Toxicities
Rituximab and ibrutinib [16,73]	50	88 (44)	43 months	Gr 3/4 diarrhea 4%, Gr 3 atrial fibrillation 12%, Gr 3 Hypertension 2%
Obinutuzumab and ibrutinib [74]	9	78 (78)	2 year—89%	Gr 3 febrile neutropenia 11%
Obinutuzumab, ibrutinib, and venetoclax [74]	24	84 (67)	1 year—75%	Gr 3 diarrhea 12%, Gr 3 hypertension 4%
Venetoclax and ibrutinib [75]	24	71 (71)	1 year—75%	Gr 3 diarrhea 12%, Gr 3 atrial fibrillation 8%, Gr 3 respiratory infection 8%
Rituximab, lenalidomide, and ibrutinib [76]	50	76 (56)	16 months	Gr 3 Rash 14%, Gr $\geq$3 infection 24%, Gr 3/4 Diarrhea 12%
Ibrutinib and palbociclib [77]	27	67 (37)	2 year—59%	Gr 3/4 hypertension 15%, Gr 3/4 lung infection 11%, Gr 3/4 rash 7%.

Legend: ORR- overall response rate, CR- complete response rate, PFS- progression free survival, Gr- grade.

Table 2. Summary of Ongoing Combination Studies Enrolling Patients with Relapsed Mantle Cell Lymphoma.

Combination	Phase	Target Enrollment	Clinicaltrials.gov ID
Ibrutinib and venetoclax	Phase 3	362 patients	NCT03112174
Acalabrutinib and venetoclax	Phase 2	50 patients	NCT03946878
Venetoclax, lenalidomide, and rituximab	Phase 1/2	77 patients	NCT03505944
Carfilzomib, lenalidomide, and dexamethasone	Phase 2	59 patients	NCT03891355
Palbociclib and ibrutinib	Phase 2	61 patients	NCT03478514
Copanlisib and ibrutinib	Phase 1/2	45 patients	NCT03877055
Iaxazomib and ibrutinib	Phase 1/2	43 patients	NCT03323151
Iaxazomib and rituximab	Phase 2	24 patients	NCT04047797
Ibrutinib and tisagenlecleucel	Phase 2	20 patients	NCT04234061
Acalabrutinib and CD19 CAR-T cells	Phase 2	36 patients	NCT04484012
Loncastuximab and ibrutinib	Phase 2	161 patients *	NCT03684694
Polatuzumab vedotin, venetoclax, and rituximab	Phase 2	63 patients *	NCT04659044
Abexinostat and ibrutinib	Phase 1/2	40 patients *	NCT03939182
Lenalidomide, umbralisib, and ublituximab	Phase 1	42 patients *	NCT04635683
Venetoclax, obinutuzumab, magrolimab	Phase 1	76 patients *	NCT04599634
Lenalidomide and blinatumumab	Phase 1	44 patients *	NCT02568553
Pevonedistat and ibrutinib	Phase 1	30 patients *	NCT03479268

Legend: ID- identifier, * Includes other Non-Hodgkin's lymphoma subtypes in addition to mantle cell lymphoma and/or alternative single agent or combination cohorts.

Bond et al, 2021

haematologica
Journal of The Ferrata Storti Foundation

Pirtobrutinib and venetoclax combination overcomes resistance to targeted and CAR T-cell therapy in aggressive mantle cell lymphoma

by Yang Liu, Fangfang Yan, Vivian Changying Jiang, Yijing Li, Yuxuan Che, Joseph McIntosh, Alexa Jordan, Ian Hou, Lei Nie, Jingling Jin, Wei Wang, Heng-Huan Lee, Yixin Yao, and Michael Wang

Received: September 1, 2022.
Accepted: November 28, 2022.

Given the clinical success of combinatorial ibrutinib and venetoclax in MCL, we investigated and here report the antitumor effects of **pirtobrutinib in combination with venetoclax** in various MCL models *in vitro* and *in vivo* to provide proof of concept for further exploration in the clinic.

	Study Design
Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	30 participants
Allocation:	N/A
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	**Phase II Study** of Pirtobrutinib With Venetoclax In Relapsed-Refractory MCL (Mantle Cell Lymphoma) Patients
Actual Study Start Date :	January 25, 2023
Estimated Primary Completion Date :	April 28, 2027
Estimated Study Completion Date :	April 28, 2027

NCT05529069

Terapie innovative

ASH 2022 abstracts

New therapies in development

74	Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma
75	Time-Limited Ibrutinib and Tisagenlecleucel Is Highly Effective in the Treatment of Patients with Relapsed or Refractory Mantle Cell Lymphoma, Including Those with TP53 Mutated and Btki-Refractory Disease: First Report of the Tarmac Study
78	Safety and Efficacy of the PI3Kδ Inhibitor Zandelisib in Combination with the BTK Inhibitor Zanubrutinib in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) or Mantle Cell Lymphoma (MCL)
232	Phase 1/2 Study of Zilovertamab and Ibrutinib in Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL), or Marginal Zone Lymphoma (MZL)

Practice-changing abstracts

1	Efficacy and Safety of Ibrutinib Combined with Standard First-Line Treatment or As Substitute for Autologous Stem Cell Transplantation in Younger Patients with Mantle Cell Lymphoma: Results from the Randomized Triangle Trial By the European MCL Network

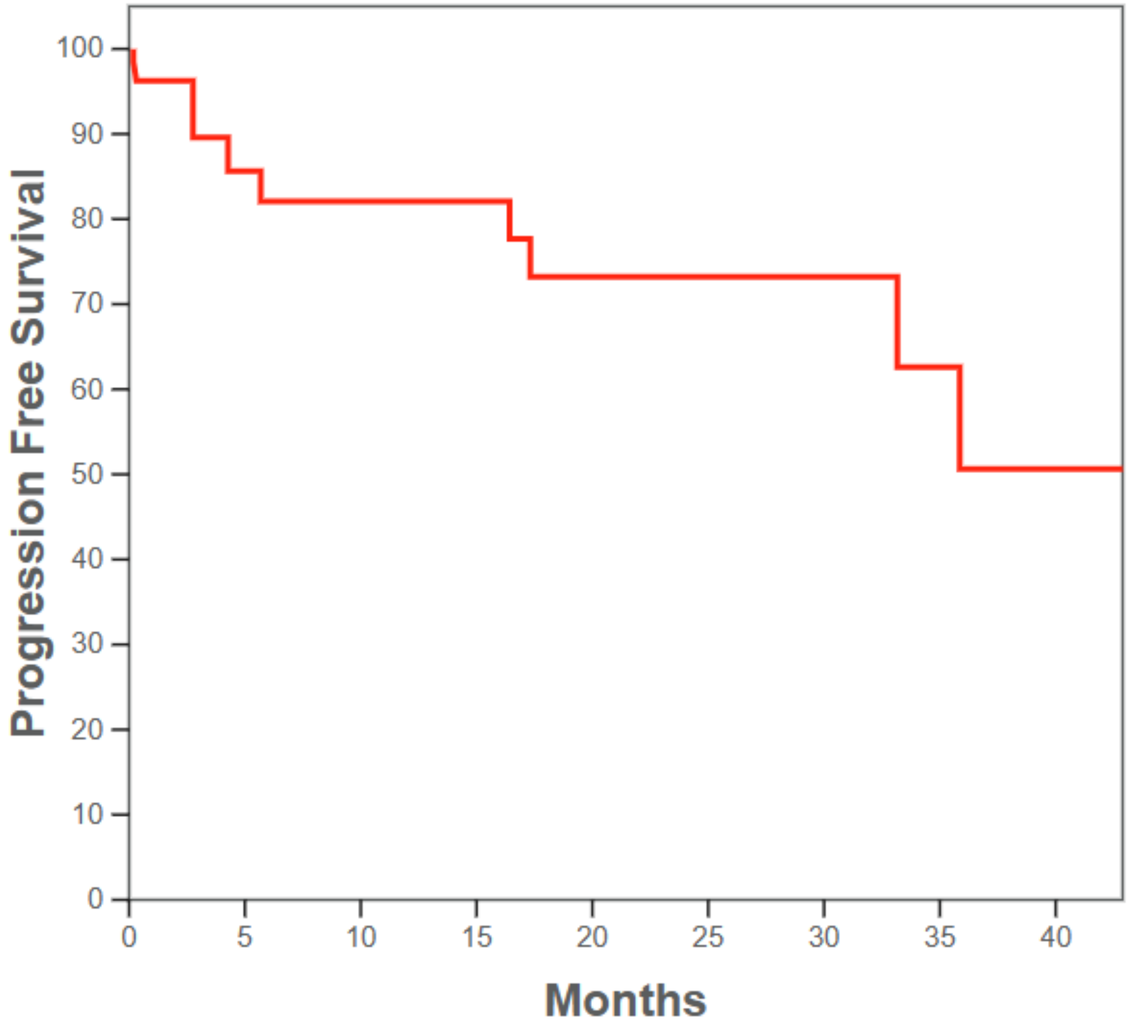
Advances in disease biology

750	Kinase Dead BTK Mutations Confer Resistance to Covalent and Noncovalent BTK Inhibitors but Are Susceptible to Clinical Stage BTK Degraders

Nuovi farmaci

- Anti ROR1: ADC or mAb (Trial ZILO-301)
- Glofitamab
- Ibrutinib+Tisagenlecleucel
- Lisocabtagene maraleucel
- Parsaclisib, zandelisib
- BTK degraders

Phase 1/2 Study of Zilovertamab and Ibrutinib in Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL), or Marginal Zone Lymphoma (MZL). Lee HJ et al.



Curves	N	Median (95% CI)
Zilovertamab + Ibrutinib	28	35.9 (17.3-0)

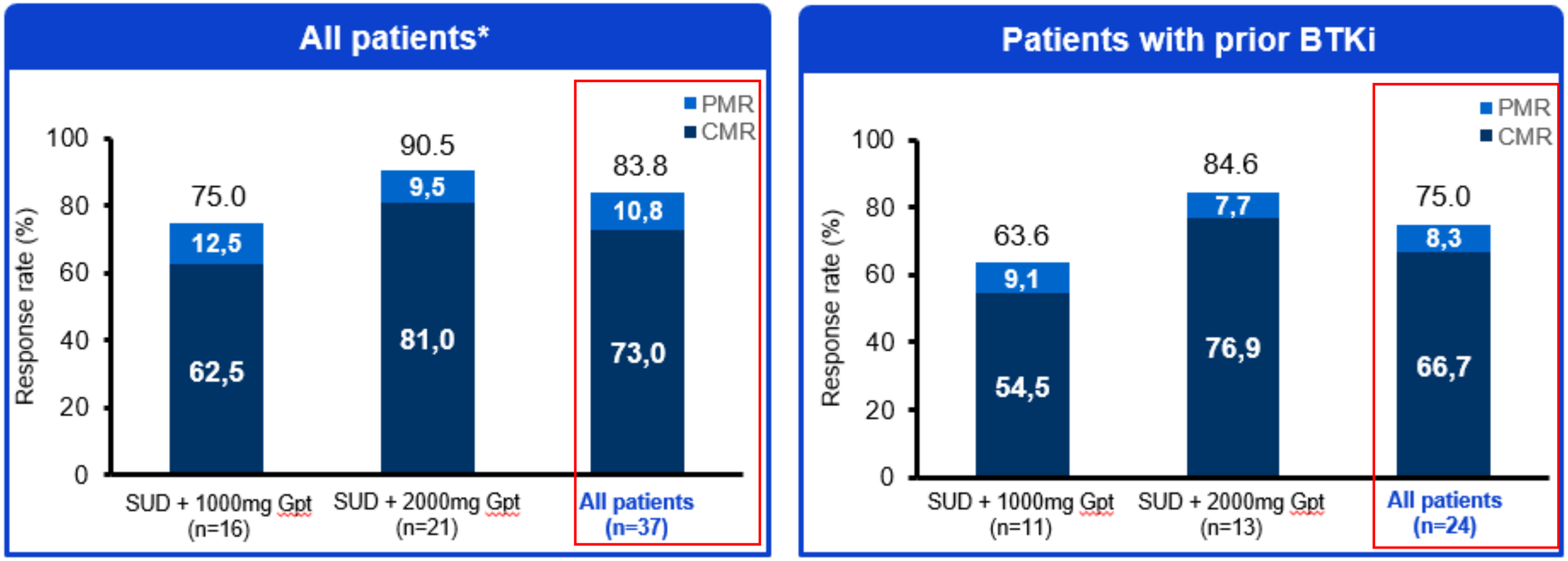
Zilo+Ibr is well-tolerated with a safety profile that is very similar compared with Ibr alone

ORR 85.2%, CR 40.7%

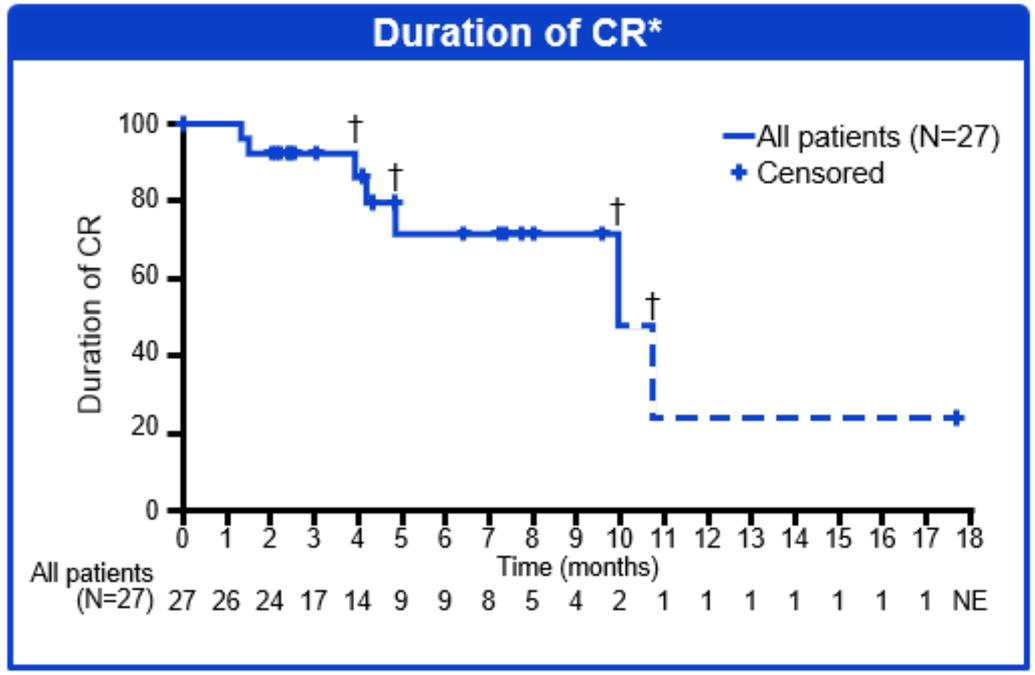
Promising activity in TP53 mutated (n=6)

Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma. **Phillips TJ et al.**

N=37; Median age 72 (41-84)



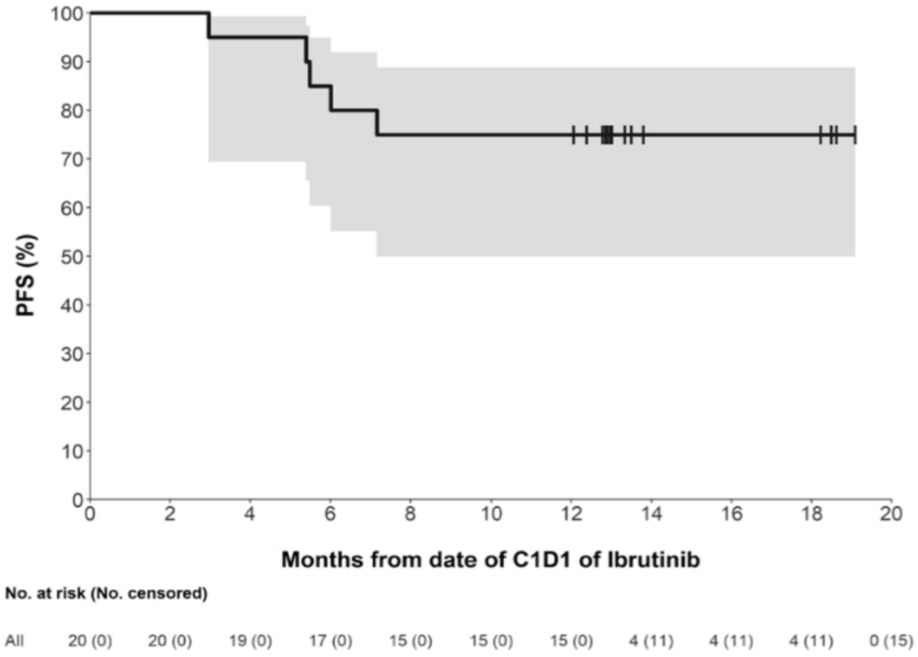
Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma. Phillips TJ et al.



- Median DOCR follow-up: 5.1 months (range, 0.0–18.0)
- Median DOCR: 10.0 months (95% CI: 4.9–NE)
- At data cut-off, **74.1%** (20/27) of patients with a CR remained in remission
- Durable CRs were maintained after cessation of therapy
- Four events due to COVID-19 deaths; when excluded, median not reached and 87% (20/23) CRs were ongoing

- Fixed-duration treatment: maximum 12 cycles (21-day cycles)

Time-Limited Ibrutinib and Tisagenlecleucel Is Highly Effective in the Treatment of Patients with R/R MCL: First Report of the Tarmac Study. Minson et al.



Ibrutinib lowers CRS and
increases Car-T cells expansion

N=21.
Prior Tx 2 (1-5); 44% TP53 mut
Ibru 7 days prior to leukapheresis,
then 6 months after reinfusion

CR 80%. No difference by risk factors
High CarT cells expansion and peak

Lisocabtagene maraleucel, R/R MCL, studio fase I TRANSCEND NHL 001 (NCT02631044) (Palomba et al, Blood 2020, 32 pazienti MCL)
Coinvolgimento SNC non era criterio di esclusione, risposte anche in un paziente con coinvolgimento SNC, minore evidenza di CRS e neurotossicità rispetto a brexucabtagene

Prospettive future

Trial a Verona

- I linea
  - Giovane: Triangle (chiuso)
  - Anziano:
    - Zanubrutinib+R vs Bendamustine+R (fase III, Mangrove: chiuso)
    - VRBAC (fase II FIL, chiuso)
    - **VIRAL (fase III, in attivazione)**: BR+ibrutinib+R mant vs R Venetoclax+Ibrutinib+R Ibr mantenimento

- **R/R**
  - **FIL_COLUMN** (fase II)
  - **BTKi degraders** (fase 1)
  - **Zanubrutinib+Bcl2i vs Bcl2i**
  - Zilovertamab+ibrutinib vs Ibrutinib (**ZILO301, fase III randomizzato in attivazione**)
  - **MALT1 inhibitor** (fase 1)

In pazienti BTKi refractory→pirtobrutinib compassionevole

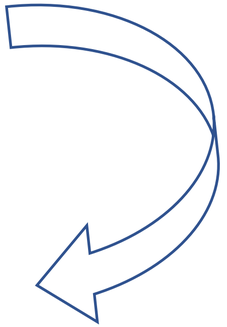
- **Early-POD in the elderly MCL**: approvazione del CE (Verona, Piacenza, FIL, centri Lymphoma Forum)

FONDAZIONE ITALIANA LINFOMI

- **Mantle First BIO**

MANTLE-FIRST^{BIO}

FIL_MANTLE-FIRST BIO Study
PI: F.M. Quaglia
https://clinicaltrials.gov/



ESH 2023 London: *Different infiltration patterns within the tumor microenvironment can identify mantle cell lymphoma patients with different clinical outcomes. Results from a pilot clinical-pathological study*

SIES 2022 Roma*: B-cell receptor signaling profiles identify subsets of mantle cell lymphoma patients with different clinical outcomes*

SIE 2023 work in progress….

Conclusioni

Conclusioni

- Nonostante gli avanzamenti terapeutici sottogruppi di pazienti con malattia aggressiva hanno ancora ***outcome* infausto**

- Quali **combinazioni**? Quale **sequenza** di trattamento?
- Gli approcci attuali non consentono remissioni durature → **nuovi farmaci**

- Combinazioni di terapie target e CIT in I linea: in studio, per il loro potenziale di consentire remissioni durature e sfidare il **ruolo dell'ASCT nei giovani**
- Nuovi BCL2i e strategie basate sulle **CAR-T** hanno il potenziale di continuare questa strada…

- Strumenti diagnostici/prognostici basati su IHC (Ki-67, SOX11,…) e genetica molecolare (TP53) stanno aprendo la strada ad una **valutazione personalizzata** del rischio e ad una personalizzazione del trattamento