# Cell Collection & Autologous Transplantation

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Sheba Medical Center

# על מה נדבר?

- ✓ איסופי תאים:
  - ✓ STEM CELLS - CD34
  - ✓ לימפוציטים – DLI , CART
- ✓ ECP

- ✓ השתלות עצמיות:
  - ✓ עקרונות
  - ✓ אינדיקציות

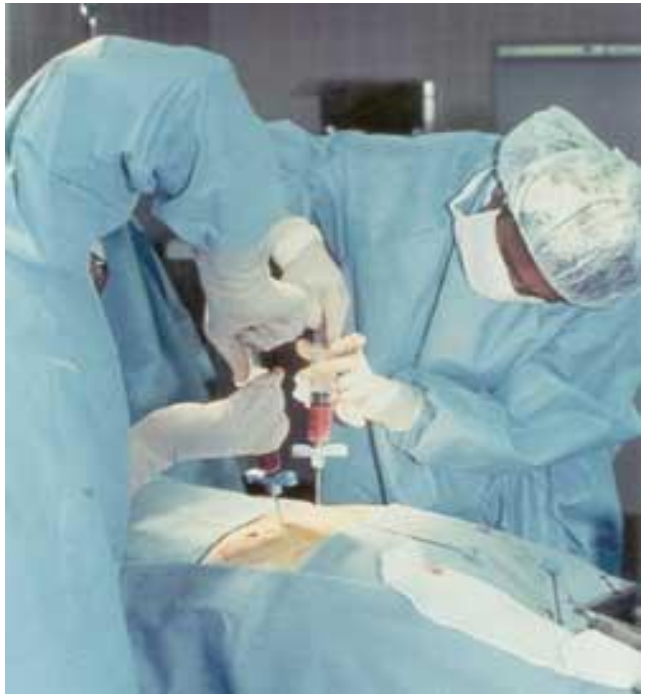
# Stem Cell Collection

- Auto-HCT = stem cell support to enable recovery from very high dose chemotherapy.
- Sufficient collection is mandatory.
- CD34+ cells number = indicator of HSC content.

- Two ways to collect stem cell:
  - BM - repeated aspiration from pelvic crest
  - PBSC - leukapheresis after mobilization of HSC into the PB.

- PBSC – favored, SOC:
  - Less stressful
  - Faster engraftment and hematologic reconstitution, improve patient outcomes.
  - Cost effective

## Bone marrow harvest



- הרדמה מלאה
- 2X10^8 TNC

- מבחינת נוזל מח עצם:

דרוש 10 מ"ל/לק"ג משקל גוף מטופל.

אסור לשאוב מעל 20 מ"ל/ק"ג משקל גוף תורם.

- ת"ל - כאבים, איבוד כמנת דם

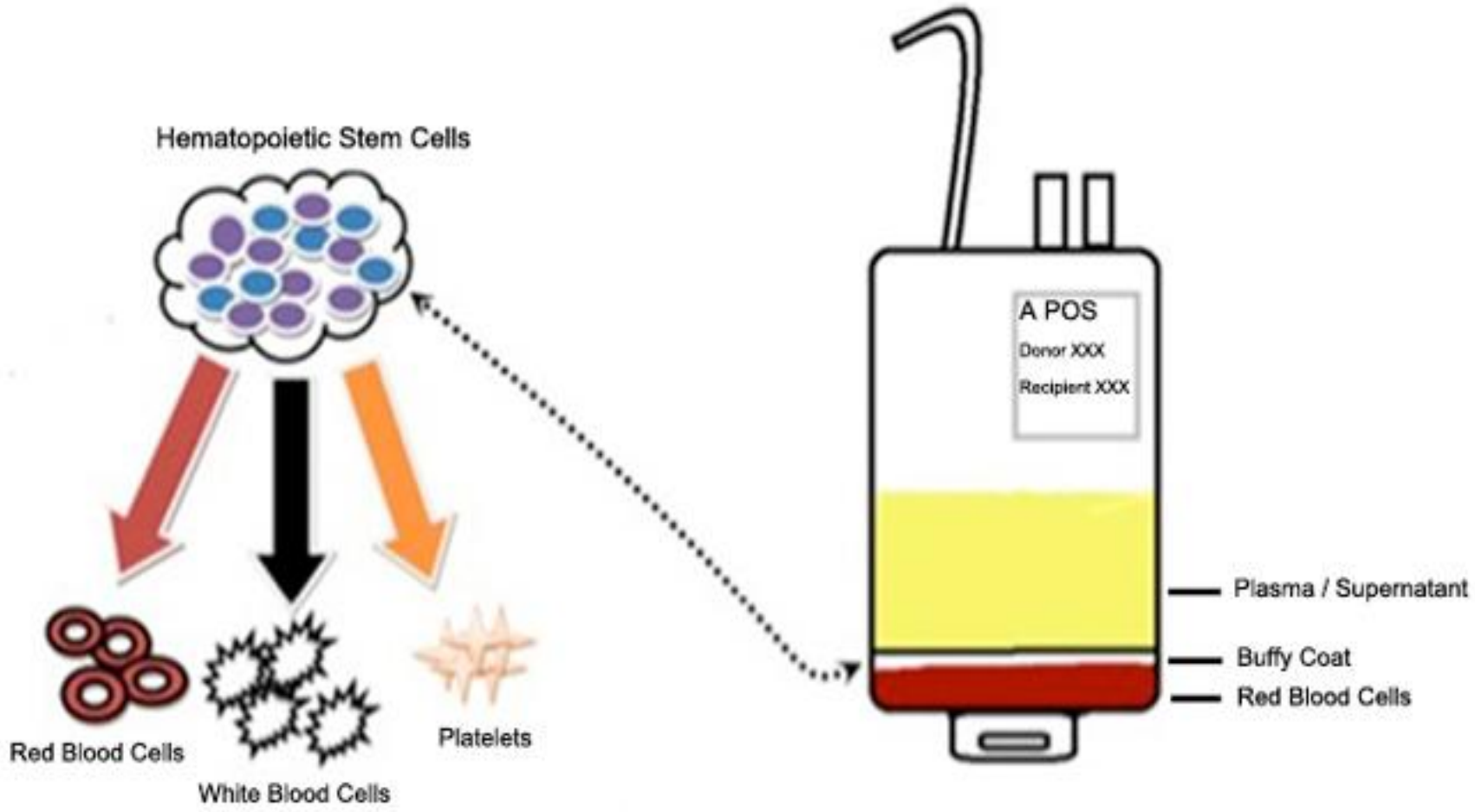
- Indications (Less cGvHD):
  - Allo sibling Pediatrics
  - Aplastic Anemia

# Definitions

- **Mobilization** of HSC from BM to the PB.
- **Apheresis** = "Taking away" a targeted cell type or substance from blood.

- **Centrifugation**:
  - RBC's at the bottom
  - Buffy coat of platelets and WBC's in the middle
  - Plasma on top

**Processing Fundamentals:** Clinical stem cell transplant processing typically involves the manipulation of plasma / supernatant and/or red blood cell layers, while maximizing the recovery of the buffy coat layer (containing stem cells) for infusion.

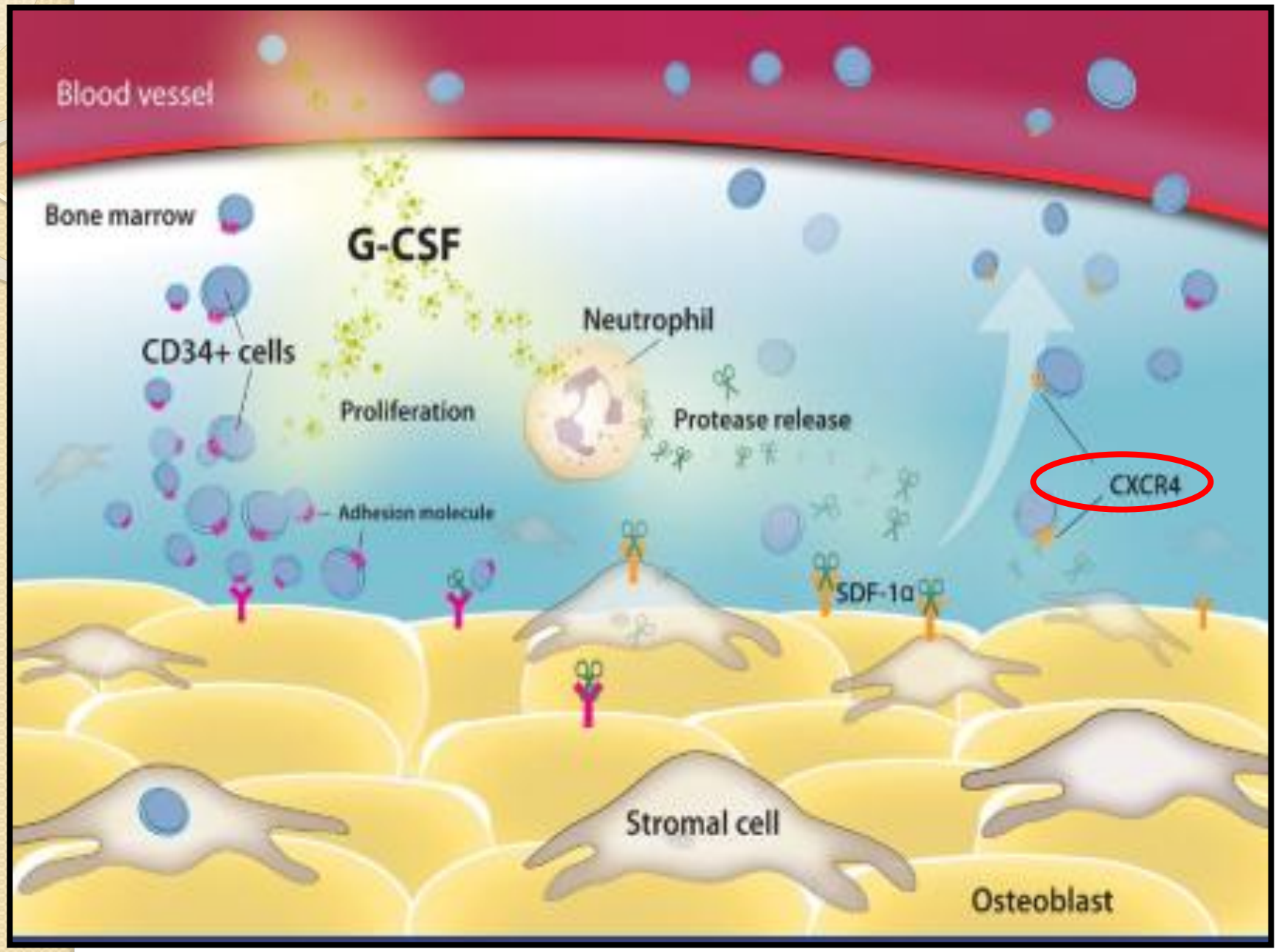


# Mobilization Without Chemotherapy ("Steady State")

- HSC is mobilized only by the use of cytokines:
  - G-CSF the only recommended cytokine.
  - GM-CSF - no longer available.

- G-CSF induces myeloid hyperplasia and release of CD34+ cells into the circulation through proteolytic cleavage of adhesion molecules (Lapidot 2002).

- 10 μg/kg/day SC for 4–5 consecutive days.
  Leukapheresis performed on day 5.
  Mobilization - continued for 1–2 days.


Blood vessel
Bone marrow
G-CSF
CD34+ cells
Neutrophil
Proliferation
Protease release
CXCR4
Adhesion molecule
SDF-1α
Stromal cell
Osteoblast

## Advantages

- Low toxicity
- Predictable time of leukapheresis
- Outpatient administration
- Reduced costs

## Disadvantages

- Higher mobilization failure rates
- Lower CD34+ cell yields
- Only in patients without further need of chemotherapy

# Mobilization with Chemotherapy

- Recovery from cytotoxic chemotherapy

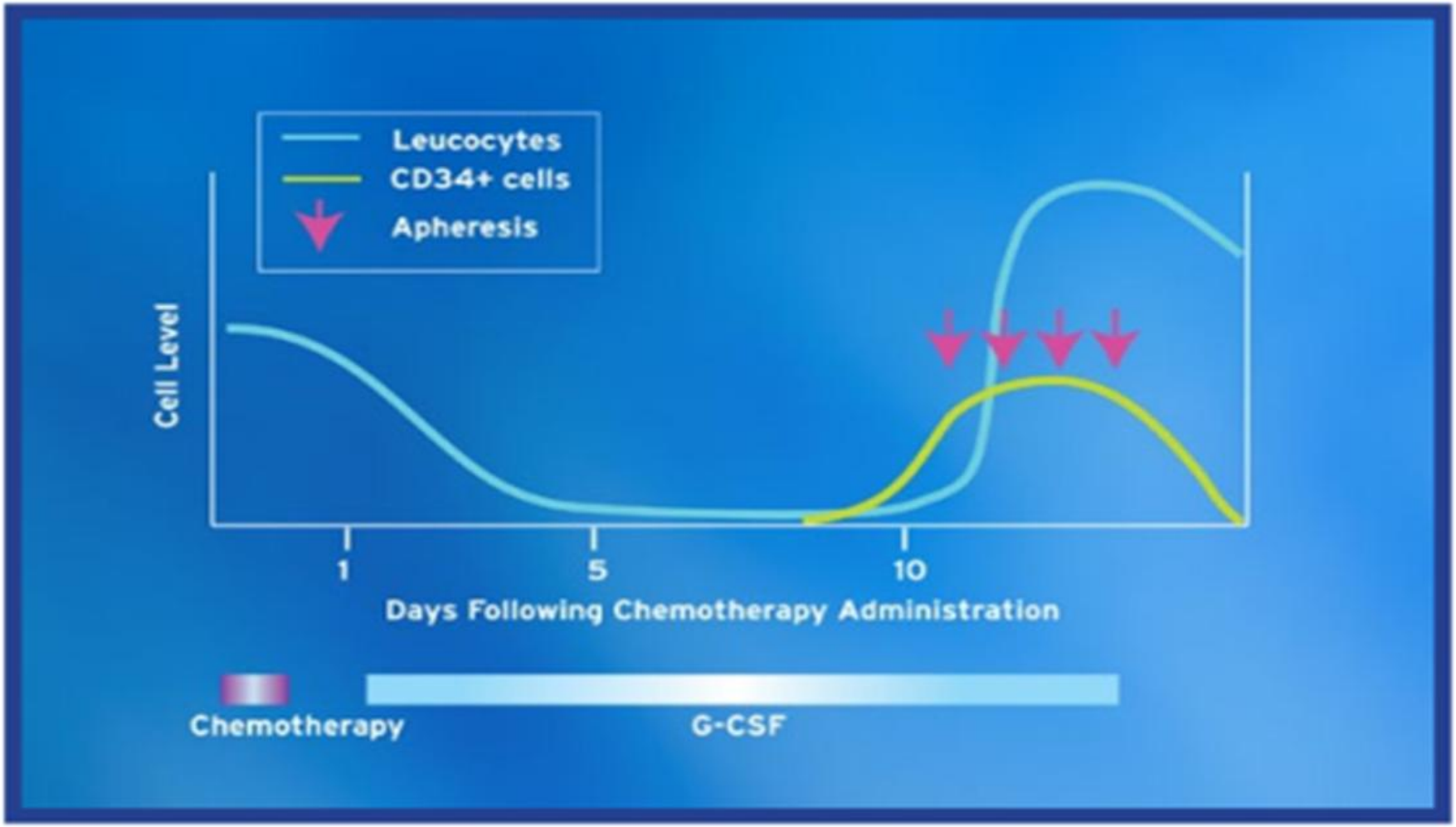
HD G-CSF

synergistic effect

- Preferred way of mobilization for all patients who will need further decrease of tumor burden and/or who have to collect a high number of HSC.
  - Part of disease-specific chemotherapy

  (DHAP or ICE) in lymphoma patients.
  - CY in a dose of 2–4 g/m2 in MM patients.

- SC G-CSF 5-10 μg/kg/day SC within 1–5 days after end of chemotherapy.
- Apheresis on day 10 ….



## Advantages

- Effect on the tumor.
- Improvement of the collection yield

## Disadvantages

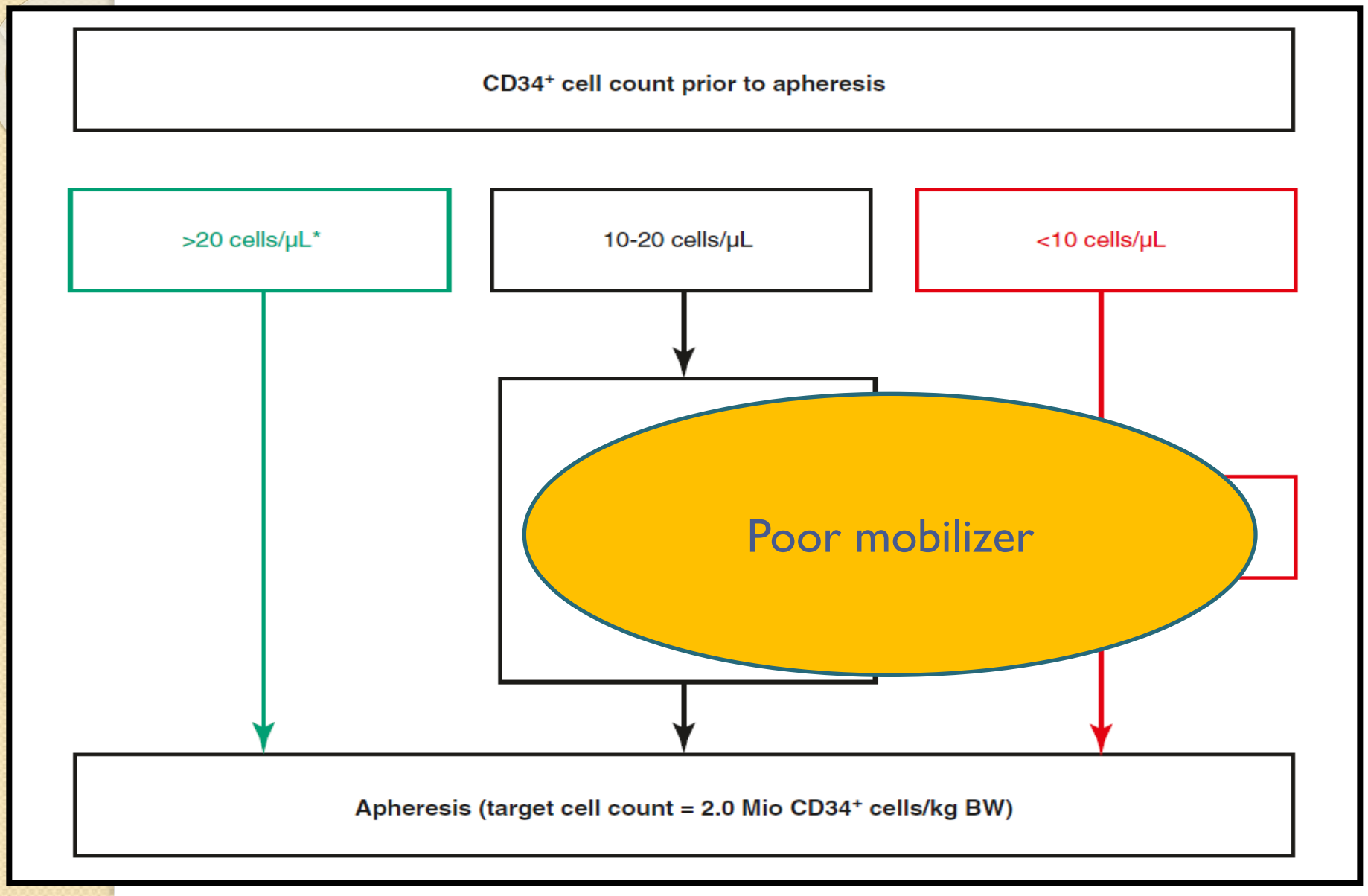
- Therapy-related toxicity →
  infections, neutropenic fever, blood products, hemorrhagic cystitis.
- Requirement of in-hospital treatment.
- Bone marrow damage.
- Higher costs
- Difficult to predict start of leukapheresis, require daily monitoring of CD34 cells.

# Target HSC Collection Count

- The target quantity of HSC:
  - Minimum - 2X10^6  CD34+ cells/kg (Mohty 2014)
  - Aim - higher yields of 4–5X10^6 associated with faster neutrophil and platelet recovery, reduced hospitalization, blood transfusions, and antibiotic therapy (Stiff 2011, Giralt 2014).

# Pre-collection PB CD34 by FACS →

# Estimation of expected collection yield and duration



# Poor mobilizers

- Patients collecting < 2X10^6 CD34 cells/kg.
- PB CD34 < 10–20 cells/μl.

| Risk factors for poor mobilization |
| --- |
| Age >60 years |
| Advanced stage of underlying disease |
| High number of prior treatment lines |
| Therapy with fludarabine, melphalan, and lenalidomide *(controversial)* |
| Low CD34+ cell count before apheresis |
| Low platelet count before mobilization *(controversial)* |

Radiation
Prior transplant

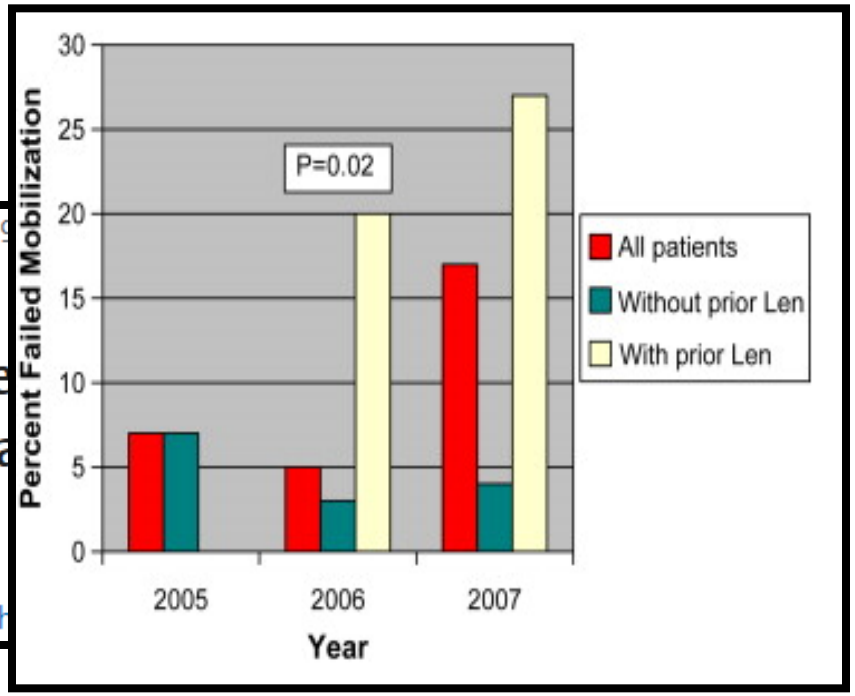
Extensive bone marrow involvement / cellularity <30%
Female>Male
Lymphoma>MM
Diabetes
Smoking

# Lenalidomide

Biol Blood Marrow Transplant. 2009 Jun;15(6):718-23. doi: 10.1016/j.bbmt.2009
Epub 2009 Apr 8.

## Impairment of filgrastim-induced stem ce mobilization after prior lenalidomide in pa with multiple myeloma

Uday Popat [1], Rima Saliba, Rupinderjit Thandi, Chitra Hosing, Muzaffar Qazilbash




- 26/302 (9%) of myeloma patients, stem cell mobilization failed:
  - 25% of patients who had previously received lenalidomide
- In a multivariate analysis:
  - prior lenalidomide use
  - mobilization more than 1 year after diagnosis

  significantly associated with failed mobilization.

Last decade – LEN included in all myeloma induction combinations

# How to manage poor mobilizers?

- Larger volume Leukapheresis
- PEG-Filgrastim
- Increased-dose G-CSF
- Twice daily G-CSF
- Re-mobilization
- Bone Marrow Harvest

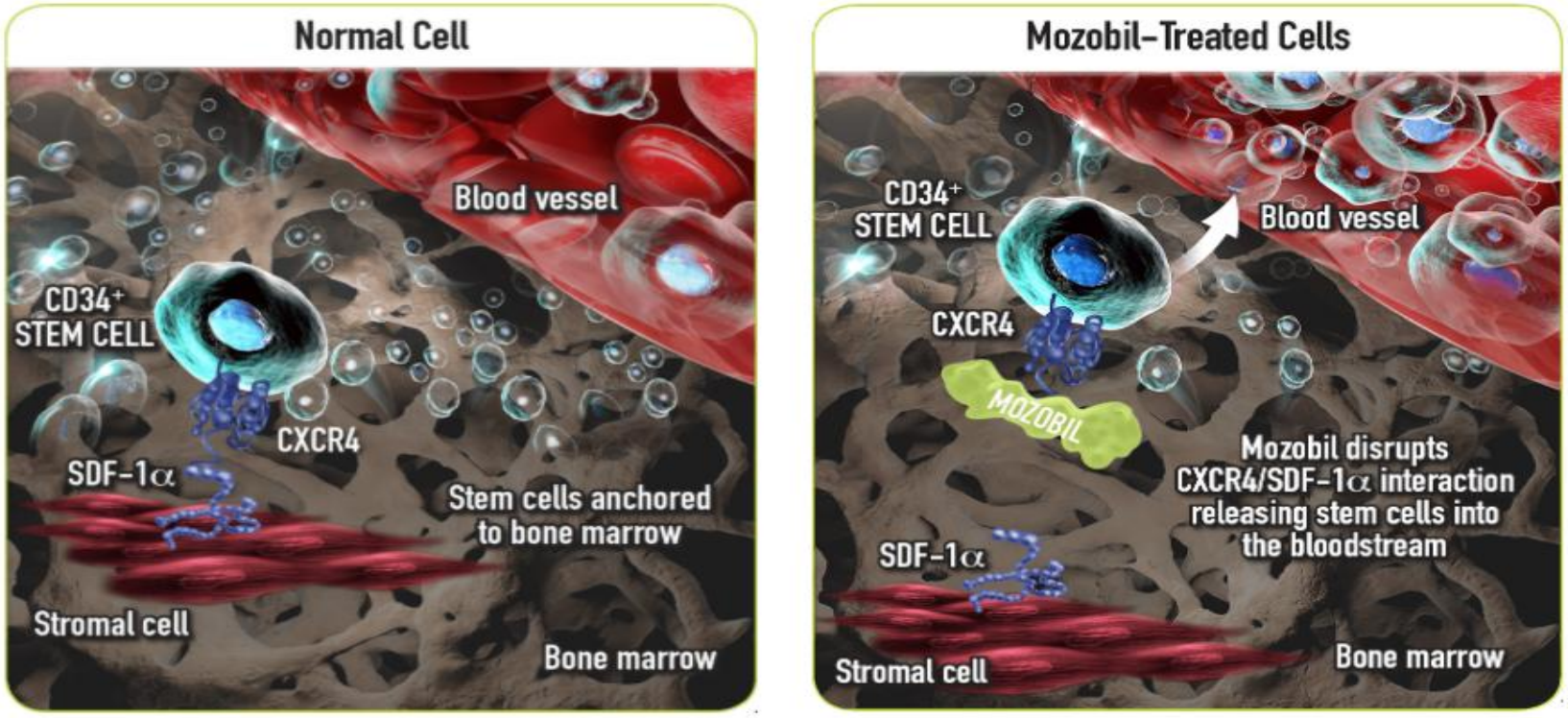
- Plerixafor

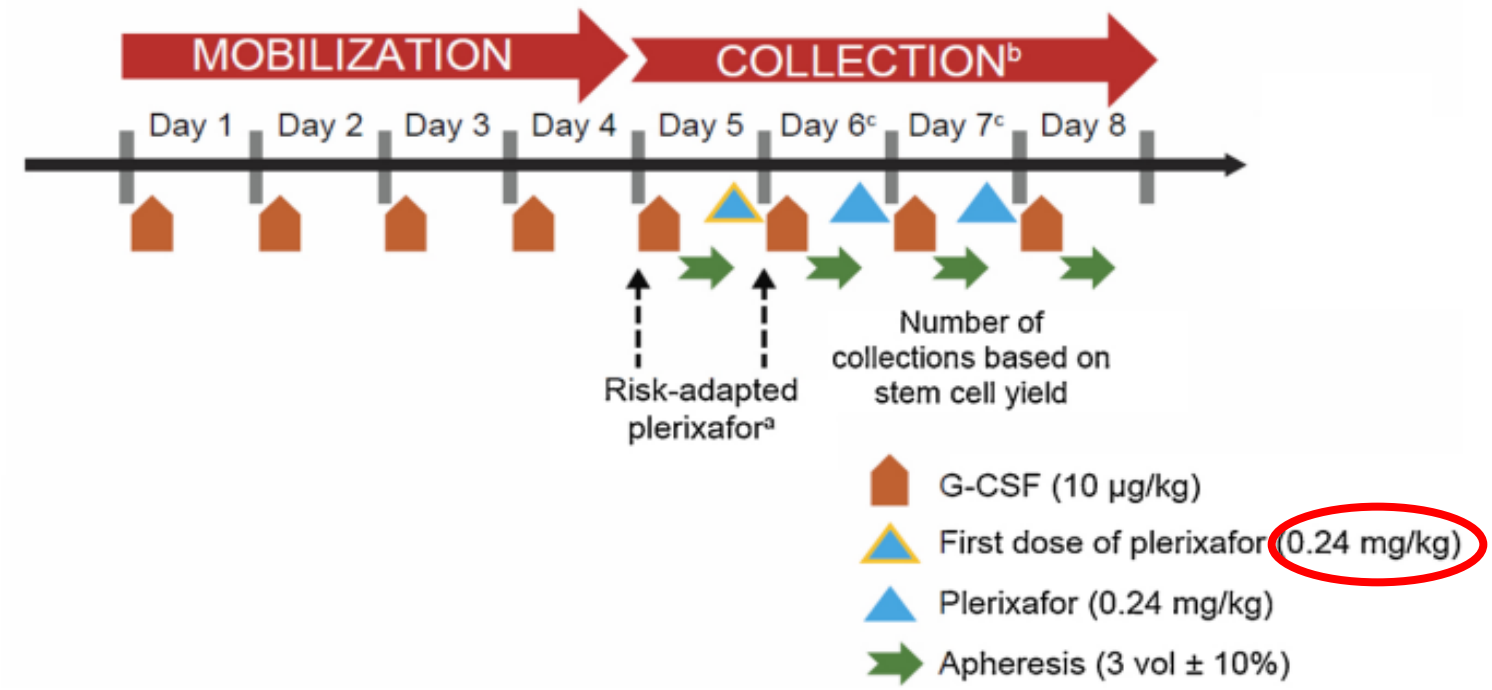
# Plerixafor - Mozobil

FDA APPROVED

## Mozobil Reversibly Blocks the CXCR4/SDF-1α Interaction[2]

2008






Multiple phase III studies [DiPersio 2009, Calandra 2008]- Addition of P to G-CSF:

- Higher CD34+ cells
- Fewer apheresis procedures
- No additional toxicity.

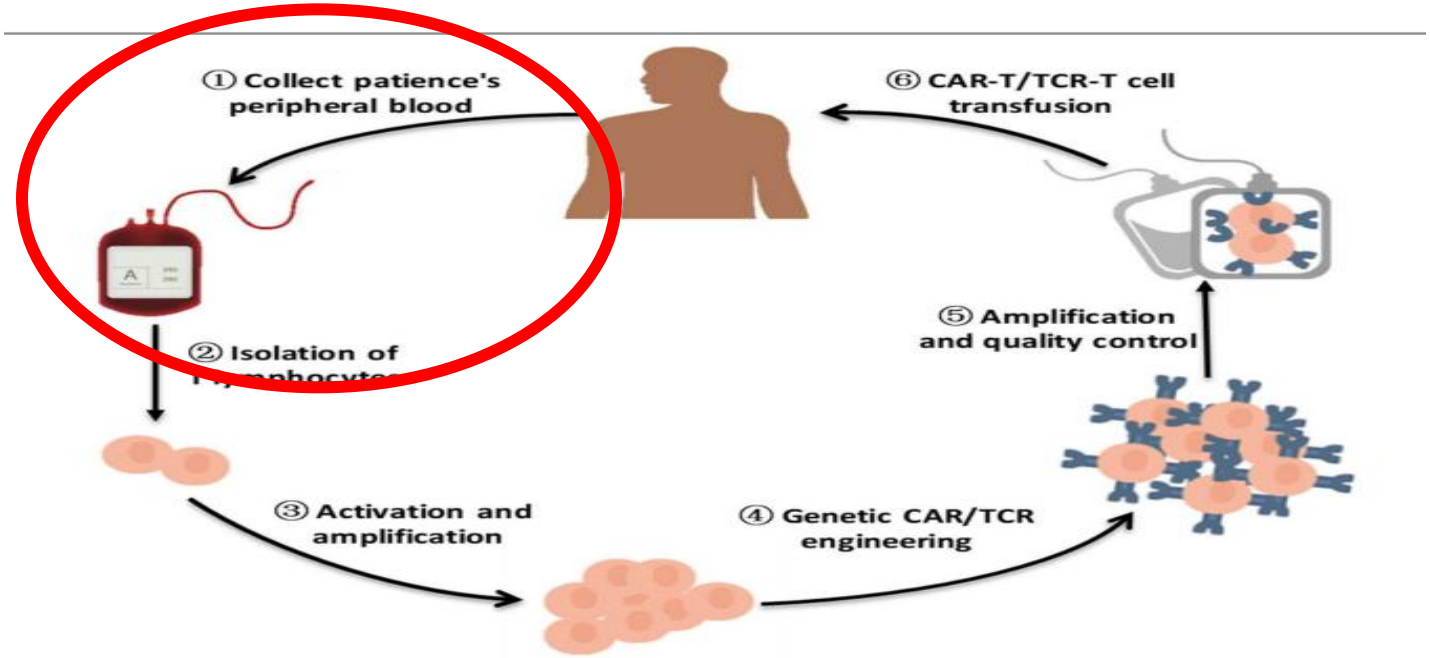
COST vs. Higher TOXICITY

# לסיכום

- חולי מיאלומה המטופלים בlenalidomide – מעקב צמוד,
  איסוף לאחר מחזור 2-3 –
  ברגע שהושגה תגובה טובה, גם אם חלקית ....

- חולי לימפומה –
  להשתדל מאוד לנצל טיפול הצלה שני,
  וכל עוד רושם לתגובה קלינית לטיפול הצלה,
  לאסוף עם כימותרפיה (בSS קשה ורובם יזדקקו ליומיים ..)

- מוזוביל – בחולה עם CD34 בדם פריפרי נמוך מ10 למיקרוליטר ...
- בין 10-20 – 2 ימי איסוף ...




- Apheresis of mononuclear cells (MNCs) from non-stimulated PB.
- Challenges:
  - Difficult patients:
    - Wide range of ages (paediatrics and elderly)
    - Different diseases
    - Heavily pretreated and frequently have lymphopenia
    - High numbers of circulating malignant cells (ALL, MCL)
  - Identify procedural and clinical factors affecting collection
  - Optimize the yield of  T cells

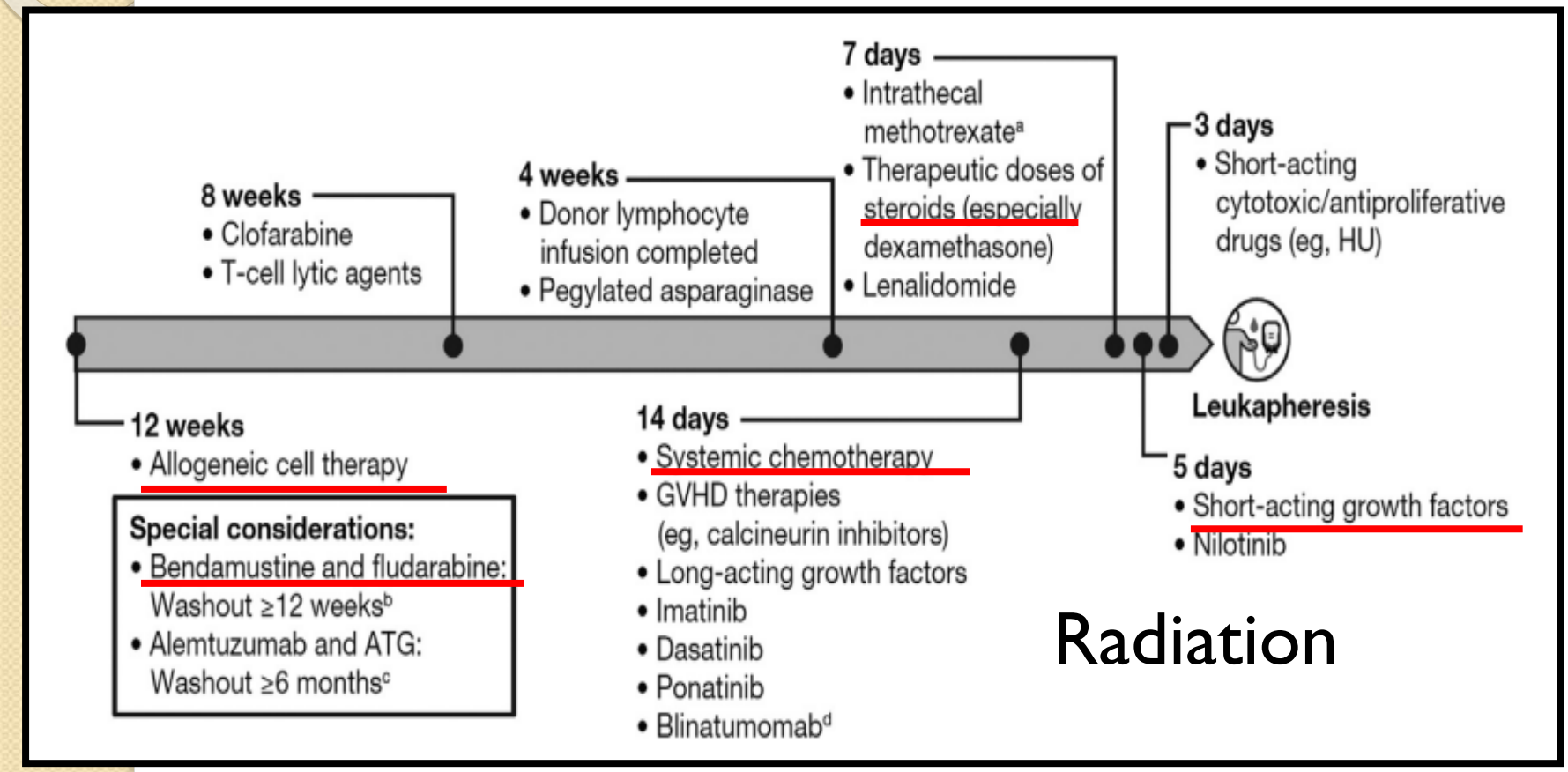
**Table 6.4** Collection requirements of different manufacturers of CAR-T therapies

| Product | Axicabtagene ciloleucel | Brexucabtagene autoleucel | Tisagenlecleucel | Lisocabtagene maraleucel | Idecabtagene vicleucel | Ciltacabtagene autoleucel |
|---|---|---|---|---|---|---|
| Registered name | Yescarta® | Tecartus® | Kymriah® | Breyanzi® | Abecma® | |
| Manufacturer | Gilead | Gilead | Novartis | Juno-Celgene-BMS | BlueBird Bio-Celgene-BMS | Legend Therapeutics-Janssen |
| Antigen recognized | CD19 | CD19 | CD19 | CD19 | BCMA | BCMA |
| Target cell dose during apheresis[a] | $5–10 \times 10^9$ MNCs | | $1–4 \times 10^9$ $CD3^+$ cells<br>$\geq 2 \times 10^9$ TNCs<br>≥3% CD3+ of TNCs<br>(rounding rules apply) | $5–10 \times 10^9$ MNCs | | |
| Target volume to be processed[a] | 12–15 L | | 6–10 L | 12–15 L | | |

- Tisa-Cel – Require specific collected cell counts (CD3, TNC)
- Axi-Cel, Brexu-cel, Liso-cel - specify blood volume
  - Liso-cel – 1-2X10^9 CD3 → To produce 50X10^6 CD4 & CD8 CART cells

# Pre Apheresis Check-list

- Wash-out Period




Qayed M. et al. Leukapheresis guidance and best practices for optimal chimeric antigen receptor T-cell manufacturing. Cytotherapy 2021

# Hepatitis / HIV

Though excluded from pivotal studies, patients with controlled infection under preventive therapy can be treated with Axi-Cel.


**TO THE EDITOR:**

Safety of CAR T-cell therapy in patients with B-cell lymphoma and chronic hepatitis B or C virus infection

Paolo Strati, Loretta J. Nastoupil, Luis E. Fayad, Felipe Samaniego, Sherry Adkins, and Sattva S. Neelapu

# DLI = Donor Lymphocyte Infusion

- Transfusion of Unmodified Donor Cells to increase GVL reactivity.
- Complications:
  - GVHD
  - DLI-induced aplasia – 2-5% - prolonged
  - Predicted by the extent of residual host hematopoiesis, (higher incidence in case of mixed chimerism – d/t destruction of original host hematopoietic elements by allogeneic donor lymphocytes).
- Improve results:
  - Delay DLI until establishment of complete donor chimerism
  - Repeated DLI in escalating doses

# Indications:

- Therapeutic DLI - Post-transplant relapse
- Pre-emptive DLI - persisting mixed or decreasing donor chimerism or by persisting MRD.
- Prophylactic DLI - high-risk disease based on genetics and/or advanced stage at SCT.

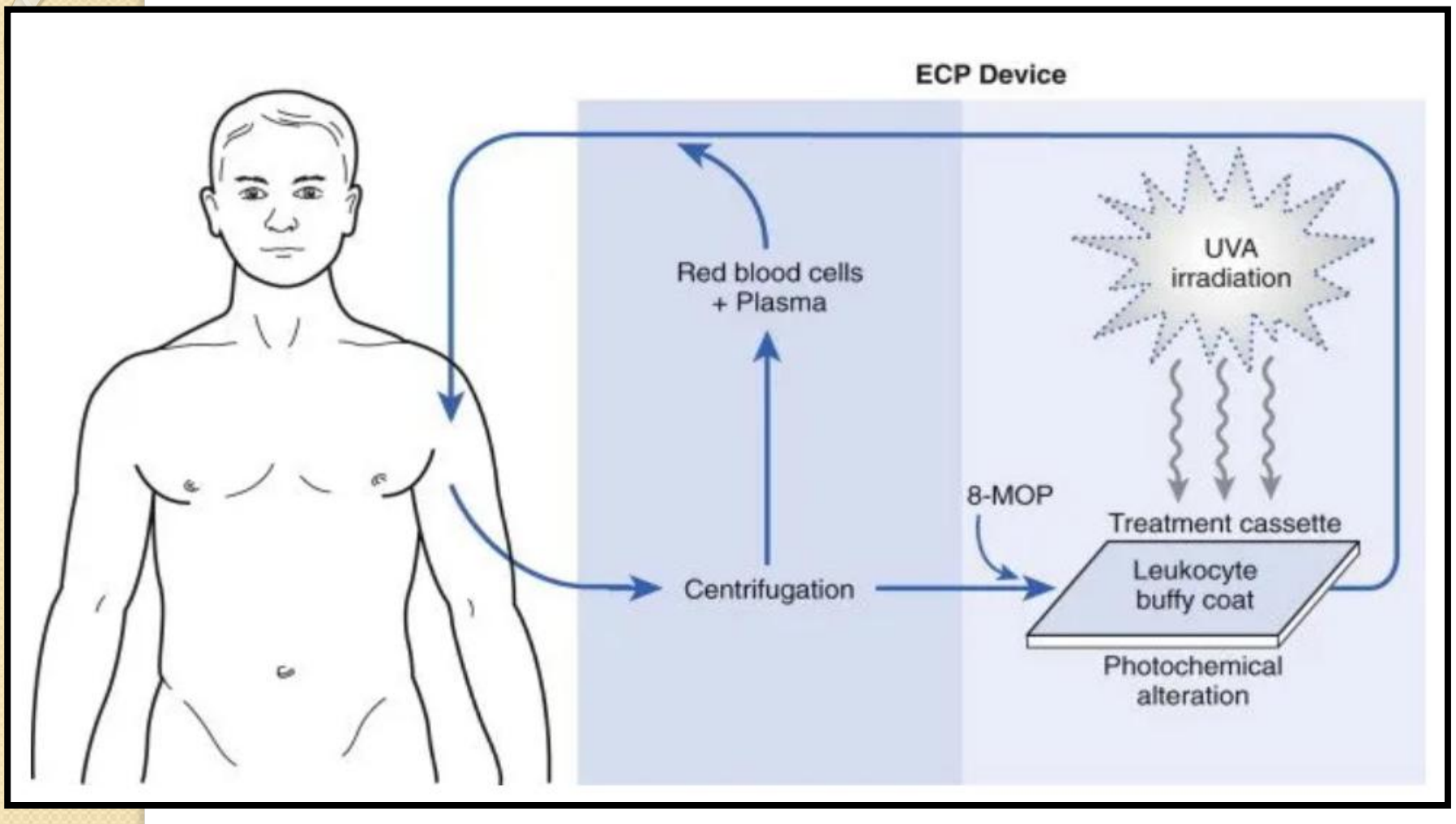
*Schmid C. Prophylactic donor lymphocyte infusion after allogeneic stem cell transplantation in acute leukaemia - a matched pair analysis ALWP EBMT. BJH 2019*

--> Improved OS in high-risk, but not standard-risk, AML or ALL

# Modifications of Classic DLI

- Allogeneic CAR T cells – Freshly collected donor cells or from the SCT recipient (pseudo-allo).
- Viral-specific cytotoxic T-lymphocytes

# Extracorporeal photopheresis



- Since 80's Immunomodulatory therapy:
  - Sézary syndrome – 1st and only FDA approved
  - GvHD
  - Systemic sclerosis
  - Prevention of solid organ transplant rejection

off-label

- Exact mechanism – unknown
- Unlike IST - No increased risk of opportunistic infections.
- Unlike PUVA - No skin complications.

- Side-effects - Fluid shifts, need for central catheter.

# ECP and GVHD

- Until Jakavi, ECP was the OFF LABEL 2nd line for steroid Ref. a & cGVHD
- Acute – 2 treatments per week for 4 weeks
- Chronic – 1 cycle every 1-2 weeks

- Proposed immunomodulatory mechanism:
  - Autoreactive NK and T apoptosis
  - Induction of T-regulatory cells

# Stages of AutoHCT


**Patient support during aplasia**

- Irradiated blood products
- Wide spectrum antibiotics prophylaxis & neutropenic fever
- G-CSF
- Symptoms' relief morphine (mucositis), antipyretics, anti-diarrheals

**Factors influencing recovery**:

Cell dose

Damaged marrow/stroma

Infection

Medications

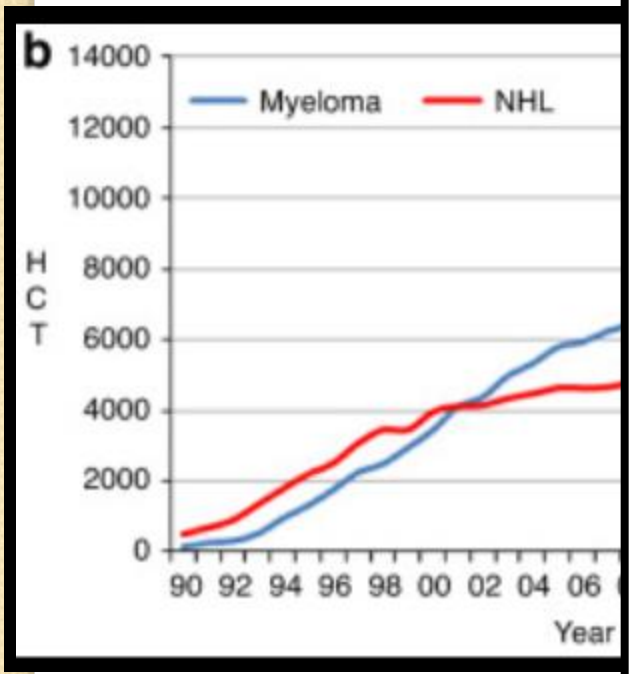
# Implications

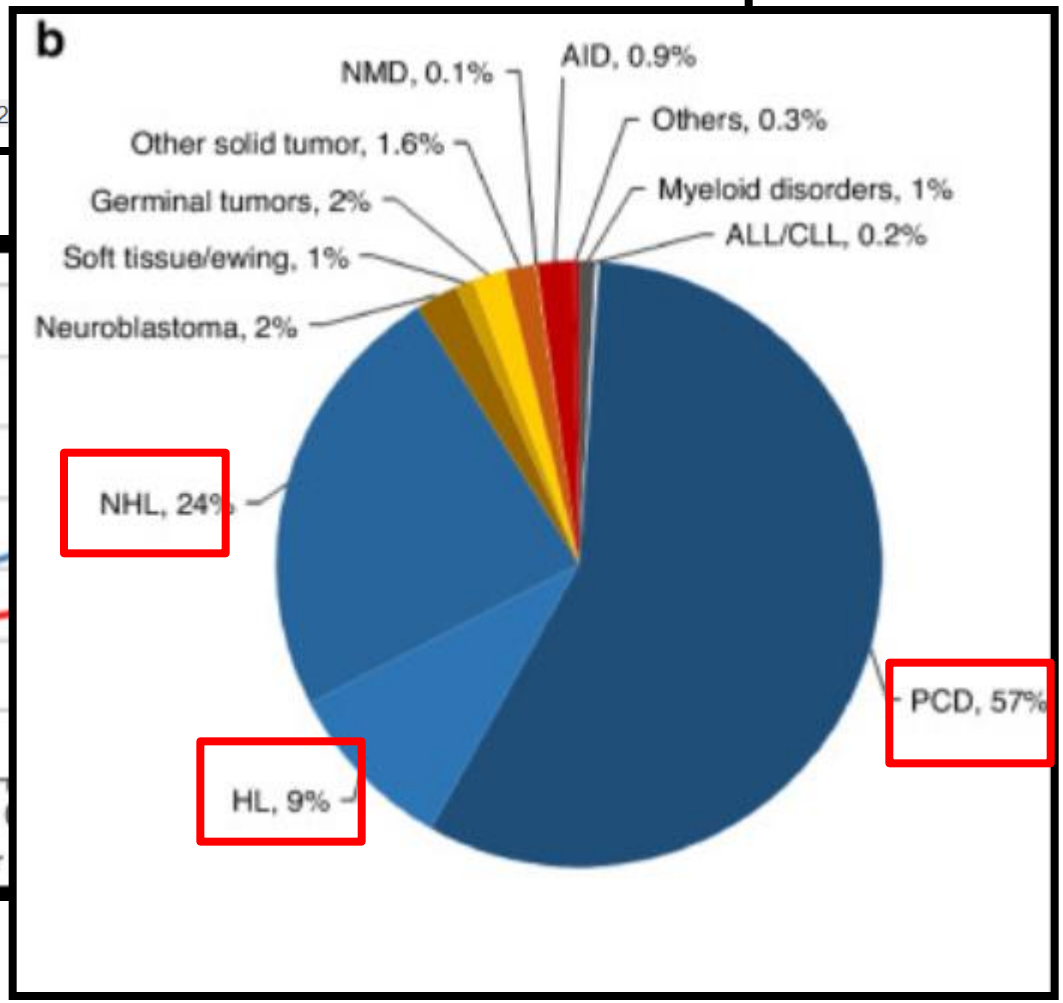
- Delayed toxicity - BCNU lung toxicity
- Infertility
- Secondary malignancy → **t-MN**
  - Global incidence 3-5%
  - Median time from ASCT to t-MN - 3.2 years.
  - Lymphoma >> MM
    - Higher burden of previous antineoplastic treatments including radiation.
    - Lymphoma - 2nd/3rd Line, whereas MM 1st Line …

Multicenter Study > Bone Marrow Transplant. 2024 Jun;59(6):803-812.
doi: 10.1038/s41409-024-02248-9. Epub 2024 Mar 4.

# Hematopoietic cell transplantation and cellular therapies in Europe 2022. CAR-T activity continues to grow; transplant activity has slowed: a report from the EBMT

Jakob R Passweg [1], Helen Baldomero [2]



# Multiple Myeloma

- Leading indication
- Incidence ↑ (elderly)

- ASCT in MM – concepts:
  - 90's - HD MEL improved PFS & OS
  - 20's:
    - OS of HCT in CR2 = CR1 following IMID-based induction.
    - TANDEM - For HR cytogenetics.
  - 2010's – 2nd HCT after at CR2

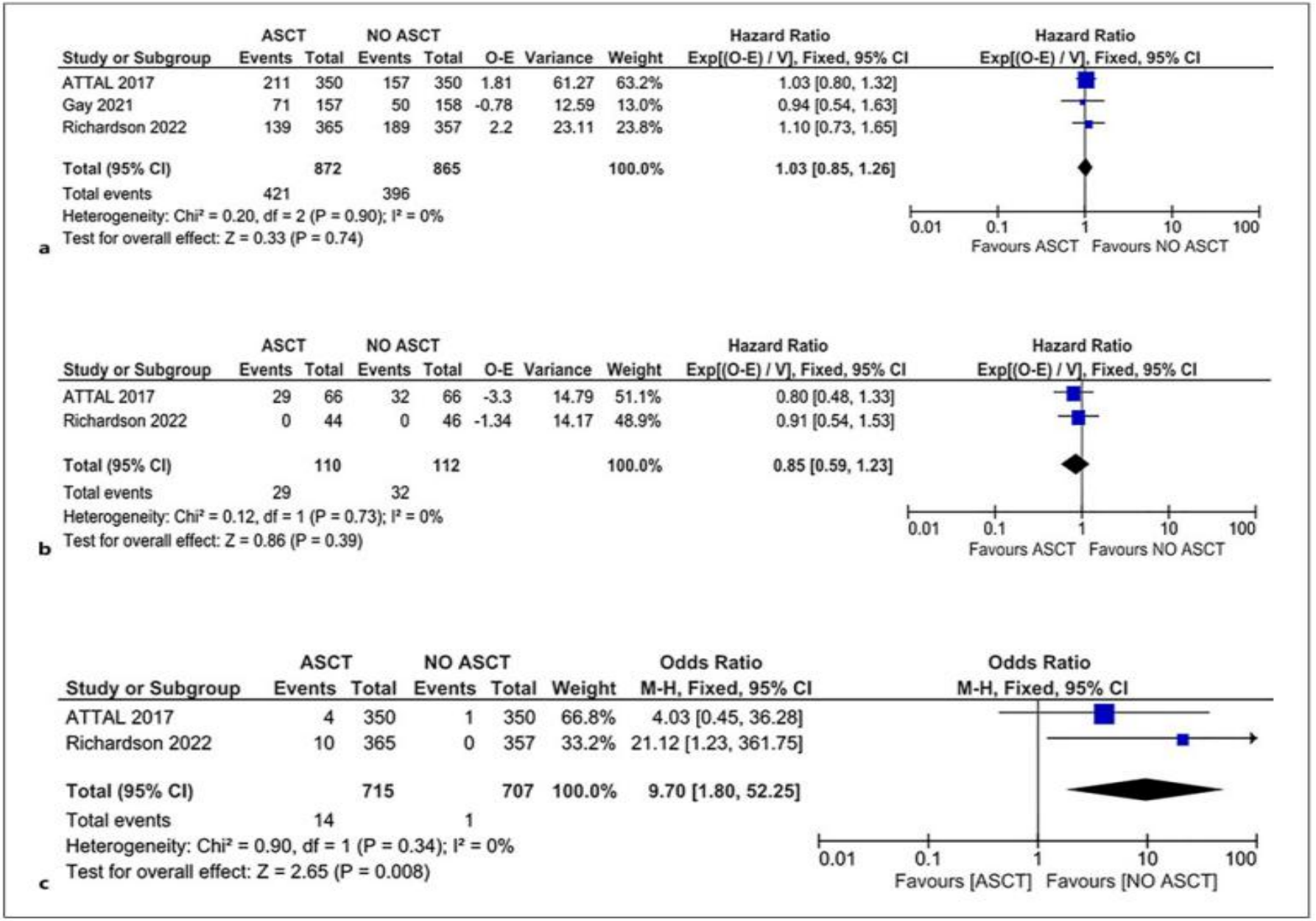



**Fig. 2.** Forest plot analyses. **a** Overall survival. **b** Overall survival in high-risk cytogenetics. **c** Secondary myeloid neoplasms.

# Current Recommendations

- All fit patients should undergo SC collection

- Auto-HCT at 1st CR should be discussed with all patients:
  - Pros (longer 1st PFS, less intensive maintenance)

    Vs
  - Cons (Toxicity)

- 2nd HCT after relapse – only for patients having prolonged PFS after 1st HCT ( 2-3y ).

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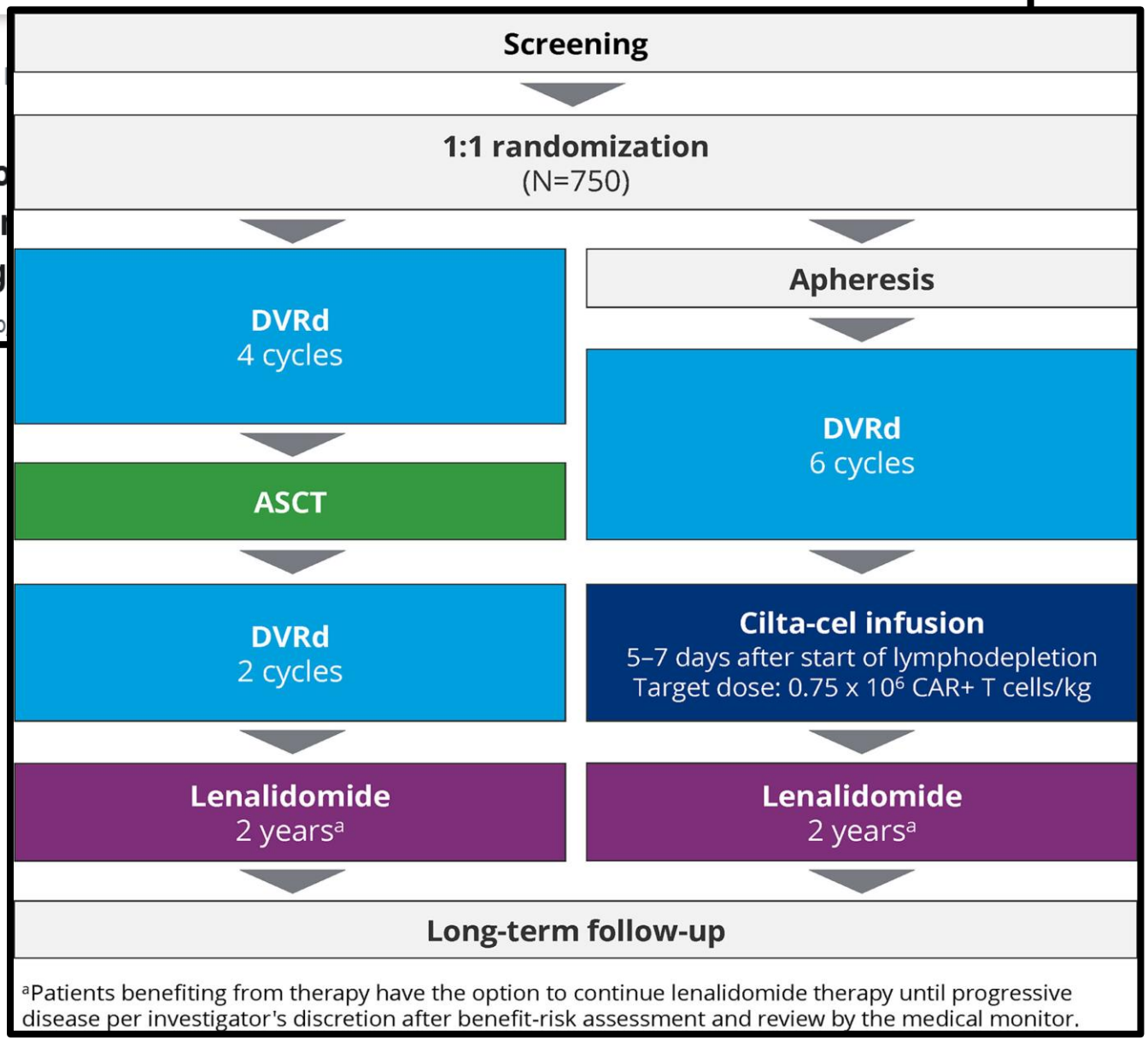
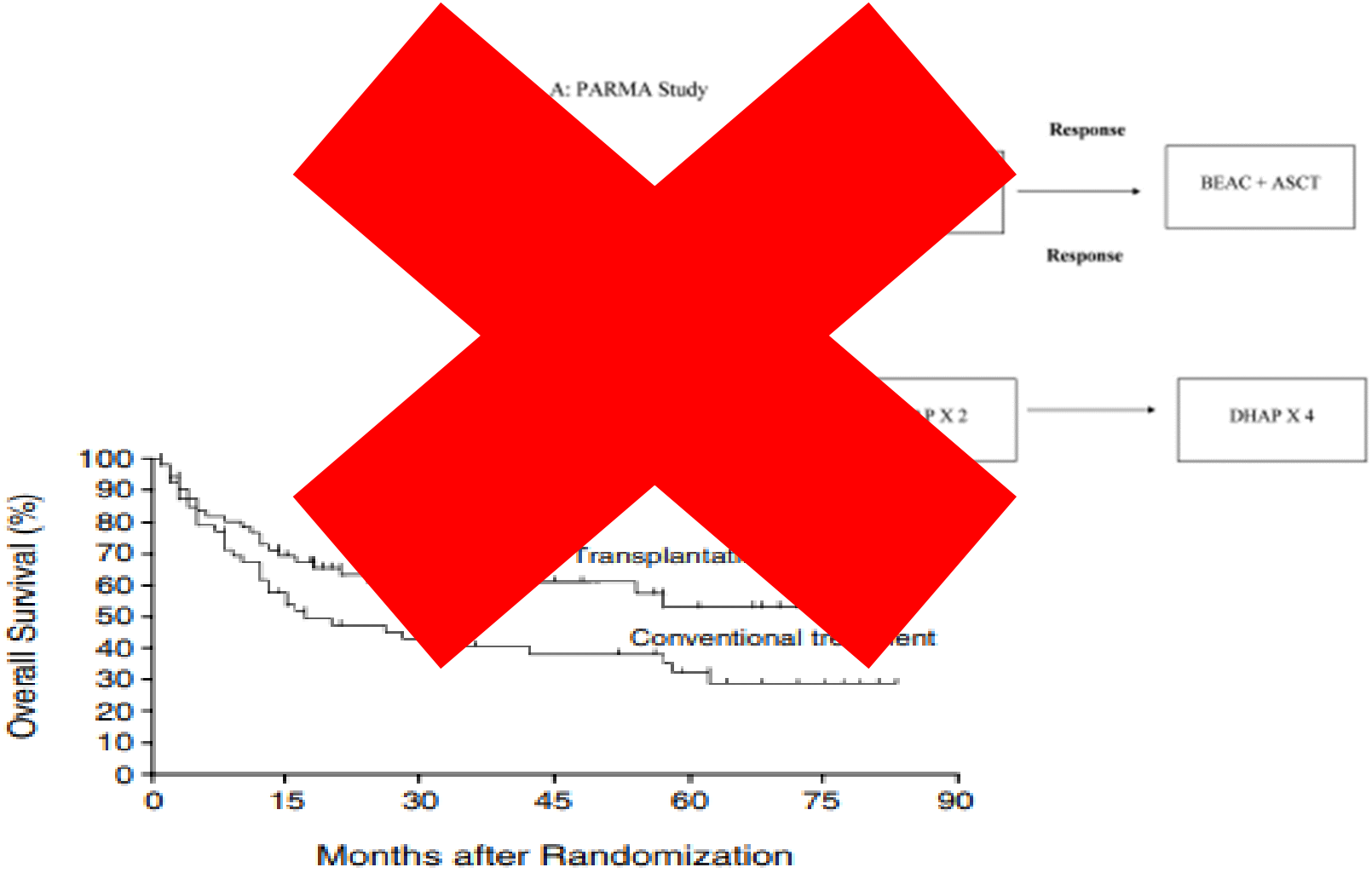
# DVRd Follo in Patie Elig

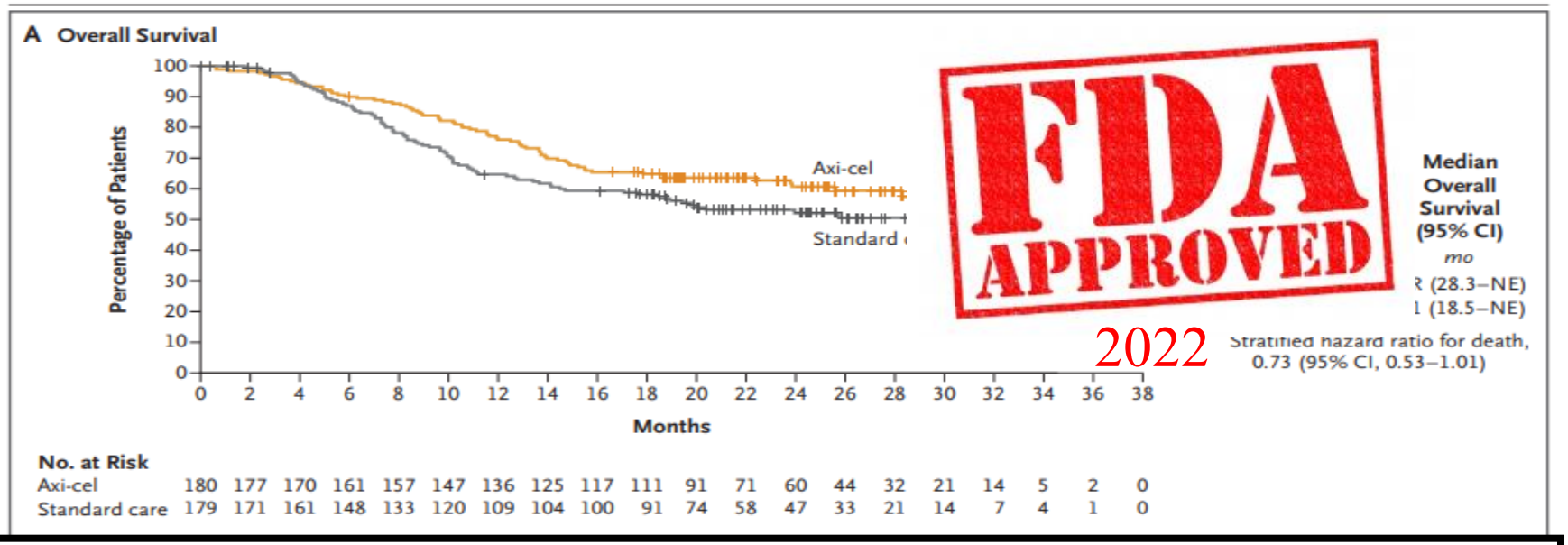
Mario Boccadoro



# DLBCL

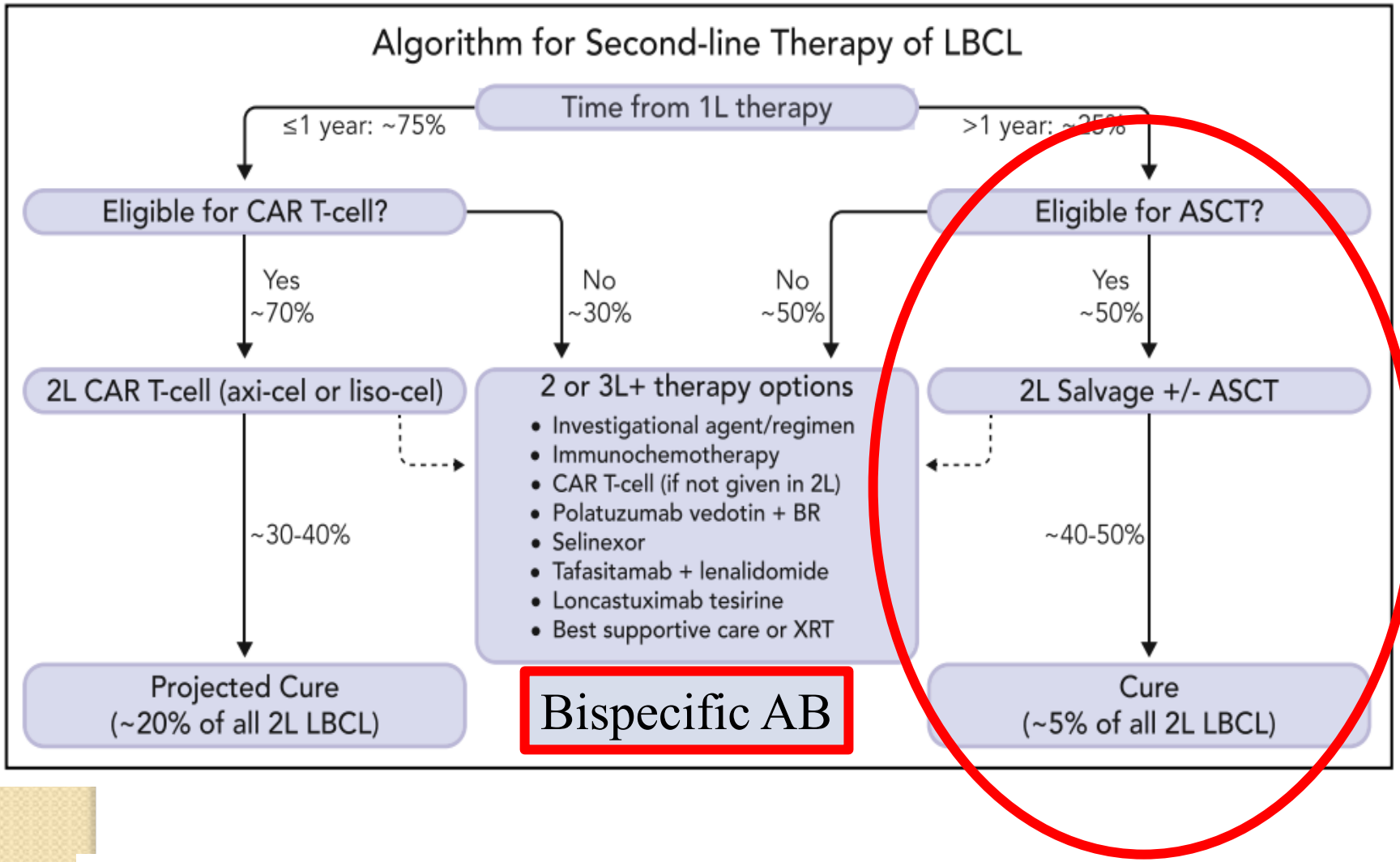
## PARMA study NEJM 1995






# PRIMARY OVERALL SURVIVAL ANALYSIS OF THE PHASE 3 RANDOMIZED ZUMA-7 STUDY OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE IN RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

- Median OS was longer with axi-cel vs SOC (not reached vs 31.1m)
- 4y OS estimates were higher with axi-cel (54.6% vs 46.0%).
- OS benefit consistent in prespecified key subgroups,
  - Age > 65 years, primary refractory, early relapse, high-grade B-cell lymphoma




*CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift? Westin j. BLOOD 2022.*

# HODGKIN'S LYM

- Relapse/Refractory HL:–

  Auto HCT –

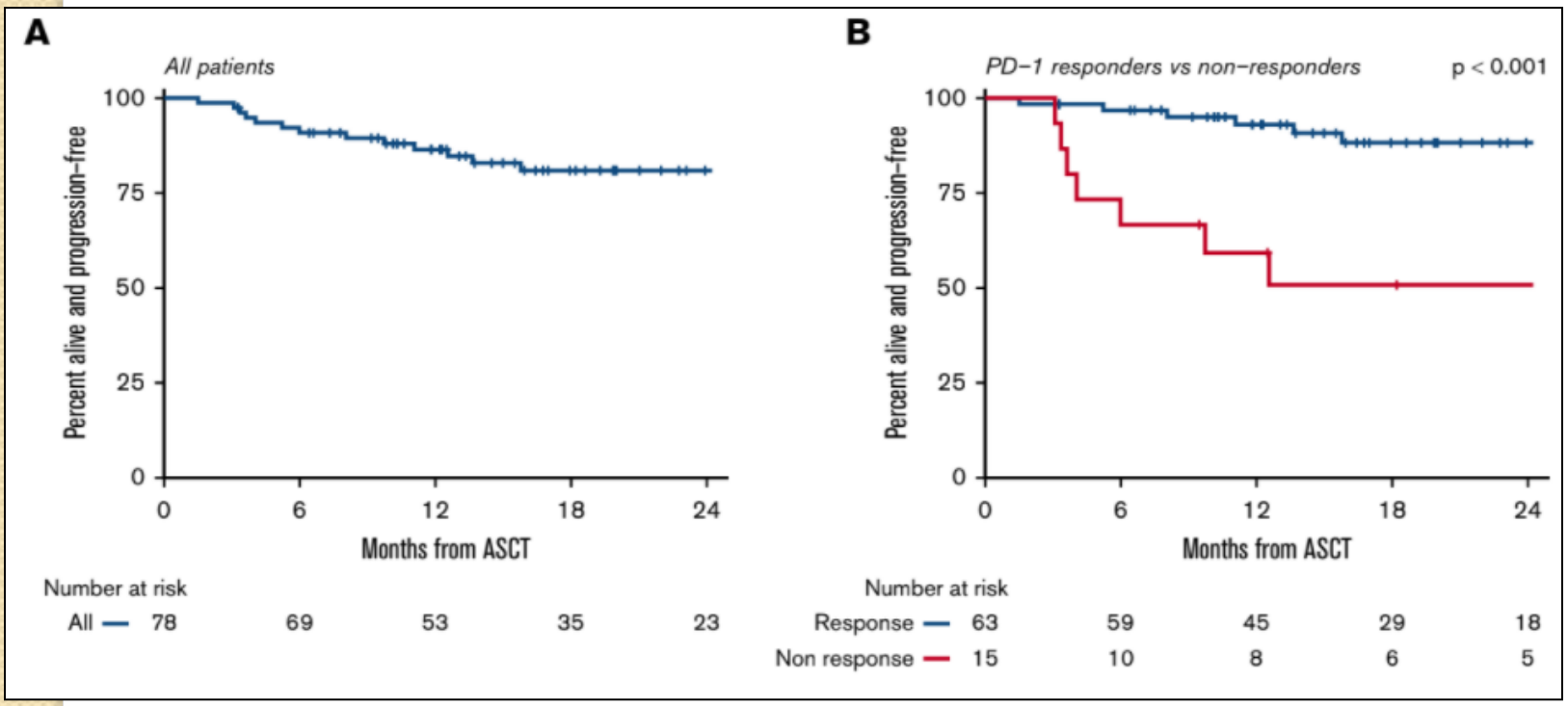
  SOC in patients achieving CR after salvage chemotherapy.

Is it relevant also at the era of BV and anti-PD1?

## Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma.

Merryman RW, et al. Blood Ac

- רב מרכזית
- 78 מטופלי anti-PD1 שעברו השתלה.
- תוצאים טובים יותר למטופלים שהגיבו ל PD1.



Clinical Trial > Blood. 2021 Aug 12;138(6):427-438. doi: 10.1182/blood.2020009178.

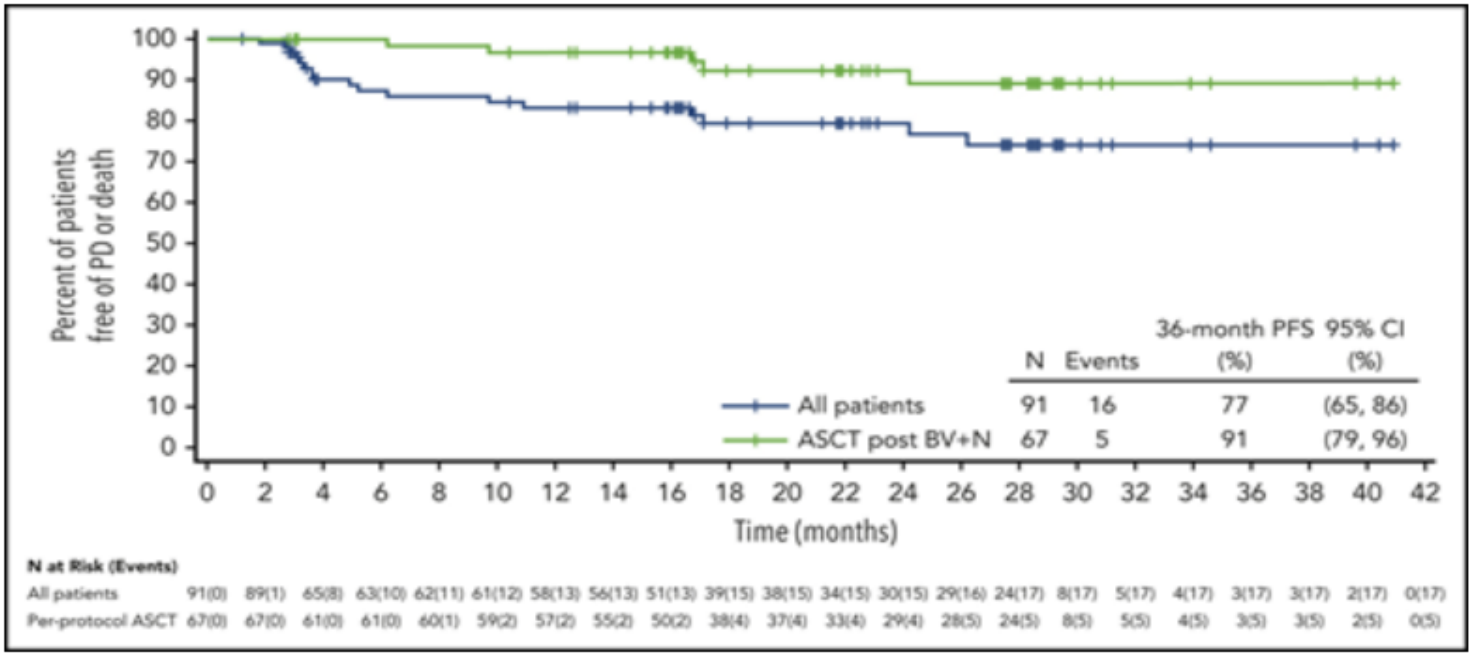
# Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results

Ranjana H Advani [1]

91 חולים

4 B – NIVO מחזורים, ASCT+/-

תוצאות טובות יותר למושתלים ...



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Volume 142, Supplement 1, 2 November 2023, Page 182

Oral Abstracts

624.Hodgkin Lymphomas and T/NK cell Lymphomas: Clinical and Epidemiological

# PD-1 Blockad
# Stem Cell Tra
# Outcomes in
# Classic Hodg
# from a Multi

Sanjal H. Desai MBBS [1 2], Re

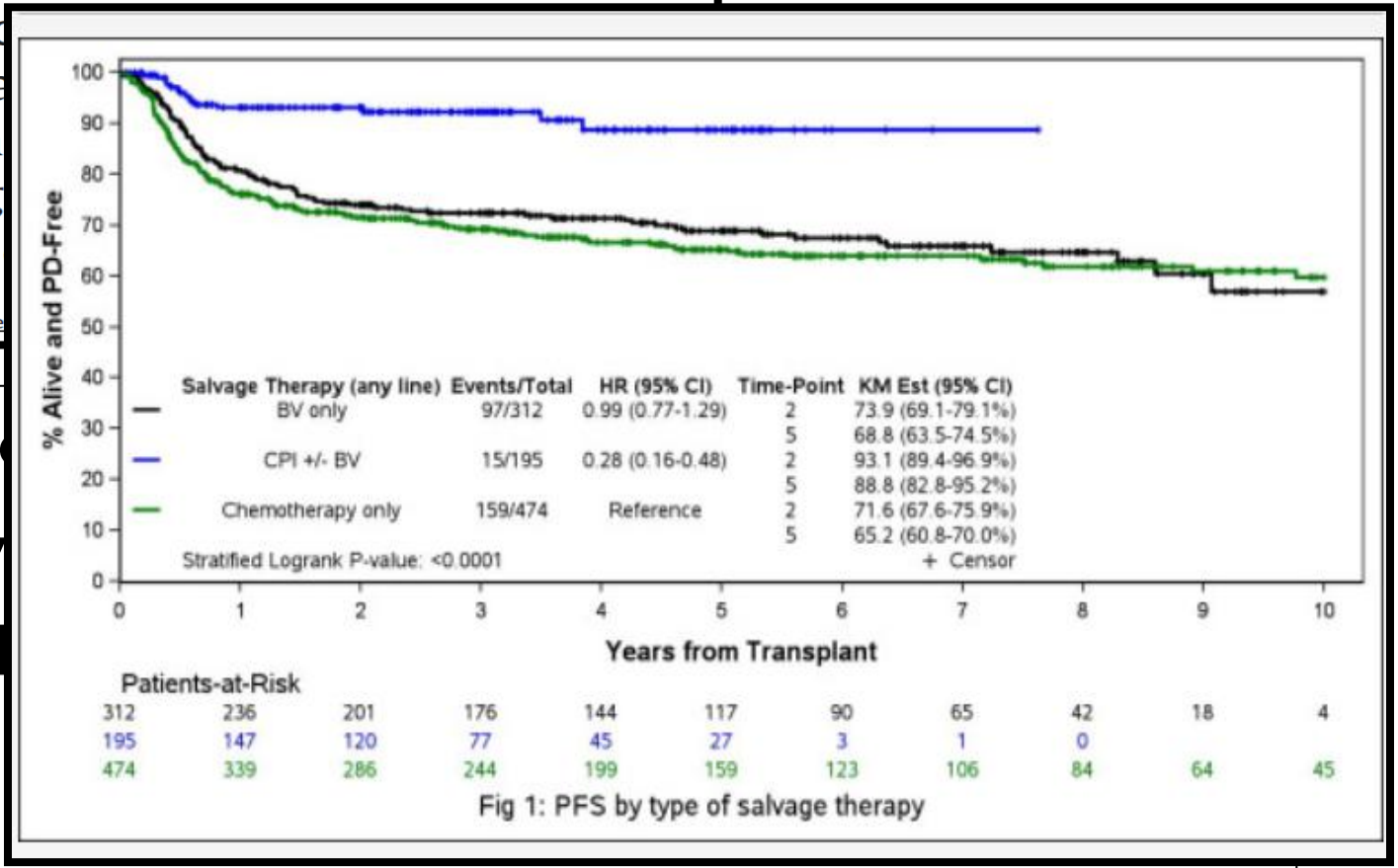


Fig 1: PFS by type of salvage therapy

- 5 MC, retr
- 31% receiv
- 195 Anti P
- 2y PFS 93,

- Results strongly support use of anti-PD1 salvage for R/R cHL

# Peripheral T-cell Lym

- Dismal outcomes compared to B-NHL…

- CHOP not enough:

  1) Addition of Etoposide –

  modestly improves PFS for patients under 60y, without impact on OS

  2) Consolidation with HSCT → ASCT

Clinical Trial > J Clin Oncol. 2012 Sep 1;30(25):3093-9. doi: 10.1200/JCO.2011.40.2719. Epub 2012 Jul 30.

**Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01**

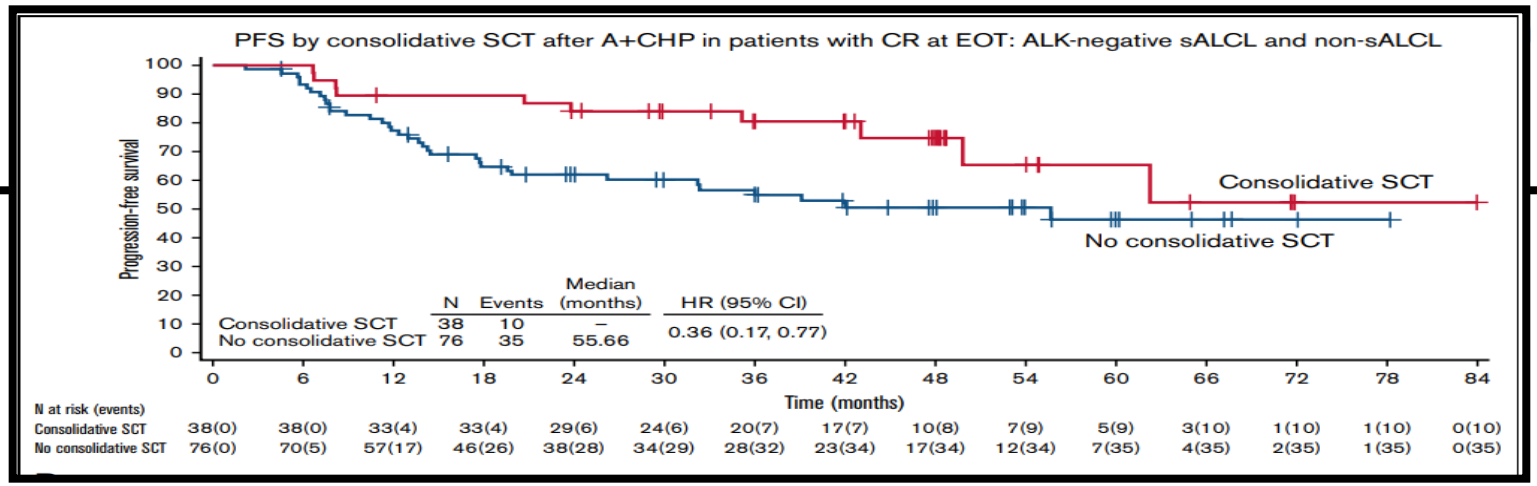

Francesco d'Amore [1], Thomas Relander, Grete F Lauritzsen, Esa Jantunen, Hans Hagberg, Harald Anderson, Harald Holte, Anders Österborg, Mats Merup, Peter Brown, Outi Kuittinen, Martin Erlanson, Bjørn Østenstad, Unn-Merete Fagerli, Ole V Gadeberg,

# Addition of BV 2019


The **ECHELON-2** Trial: 5-year results of a randomized, phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma.

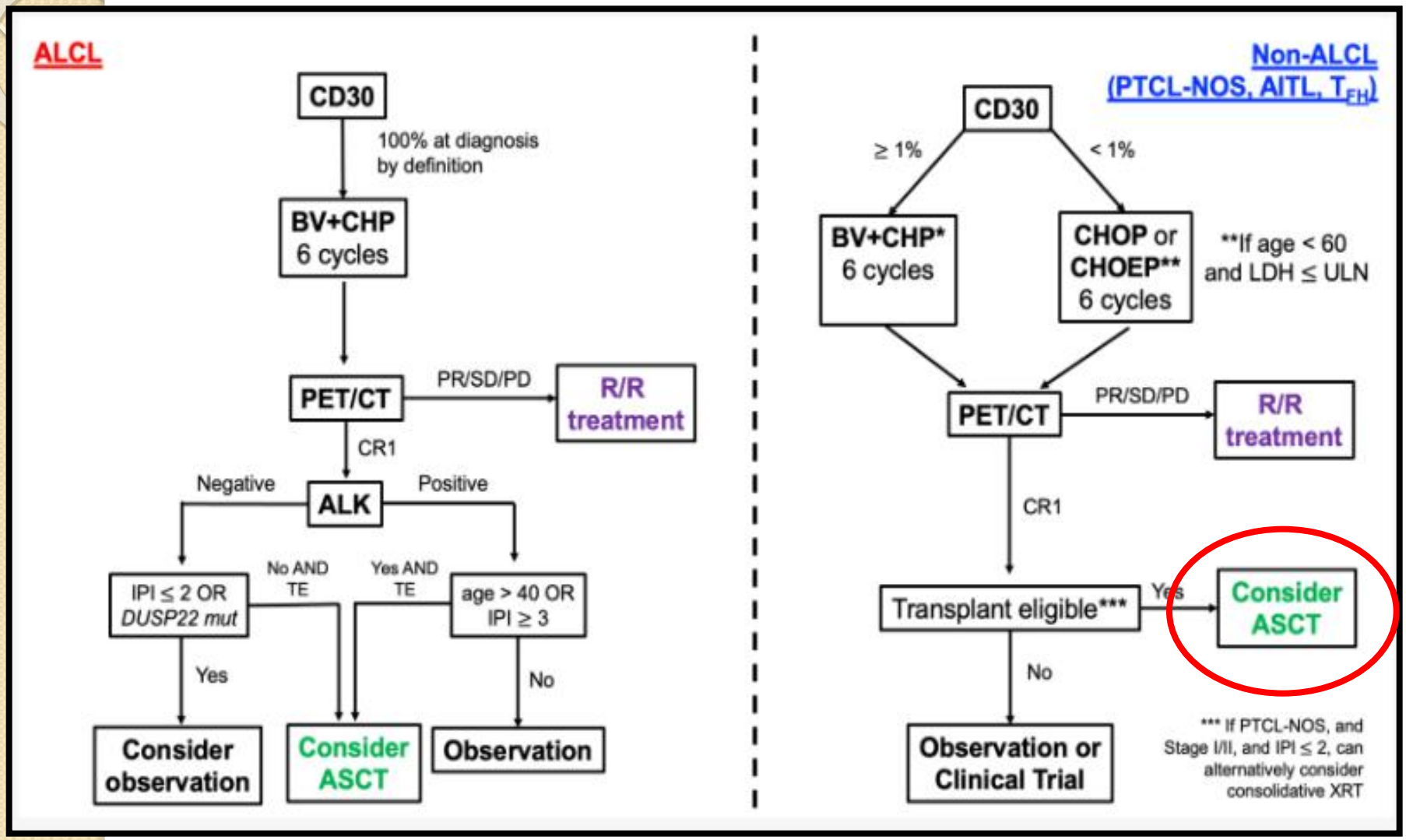

Role of stem cell transplant in CD30+ PTCL following frontline brentuximab vedotin plus CHP or CHOP in **ECHELON-2**.

Savage KJ, Horwitz SM, Advani R, Christensen JH, Domingo-Domenech E, Rossi G, Morschhauser F, Alpdogan O, Suh C, Tobinai K, Shustov A, Trneny M, Yuen S, Zinzani PL, M,




Median PFS with SCT not reached, vs 55m …

# Peripheral T-cell Lym



# AUTO vs ALLO

Clinical Trial > Blood. 2021 May 13;137(19):2646-2656. doi: 10.1182/blood.2020008825.

## A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL

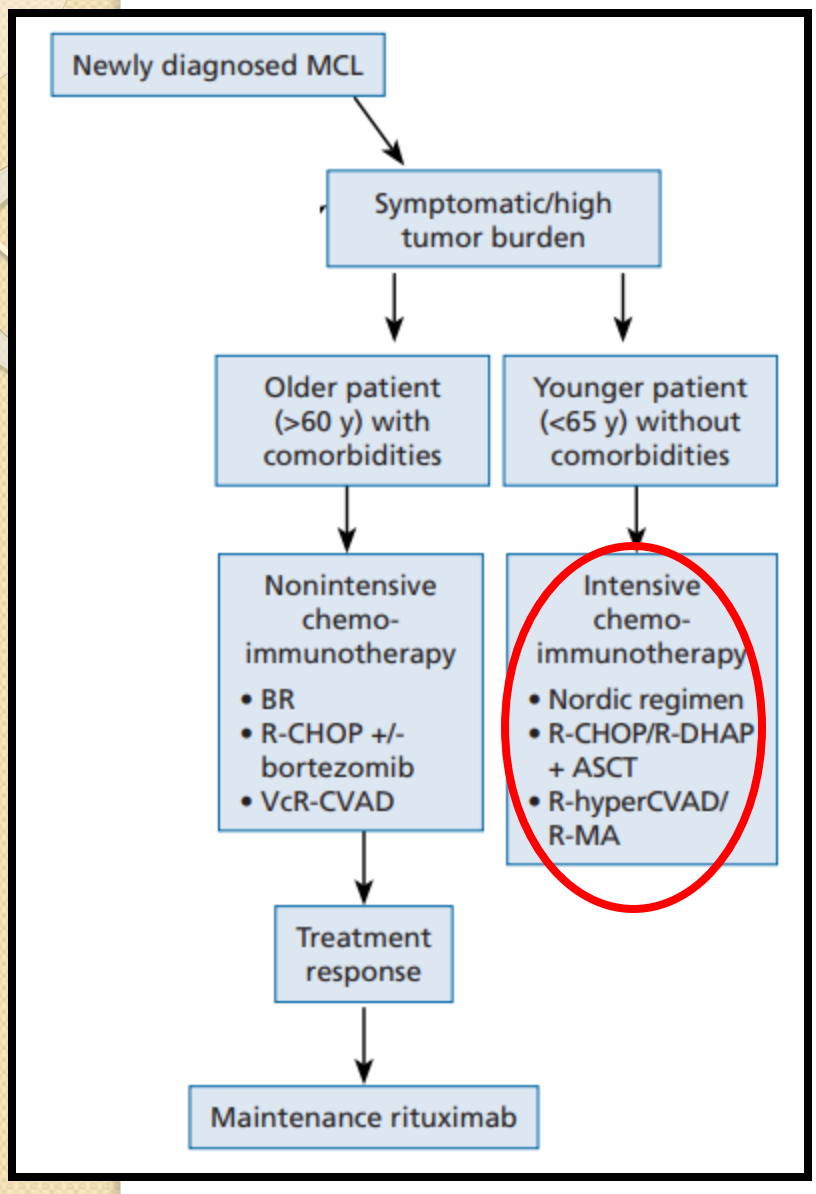

Norbert Schmitz [1], Lorenz Truemper [2], Krimo Bouabdallah [3], Marita Ziepert [4],

100 p, CHOEPx4→DHAP→ Allo Vs. Auto

3y EFS – Allo 43%, Auto 38%

3y OS – Allo 57% vs Auto 70%.

Strong GVL effect at ALLO -- **counterbalanced** by TRM …




# MCL

**Table 1 Comparison of Intensive Treatment Strategies for Newly Diagnosed MCL**

| Trial | N | Age (y) | 5-y EFS | 5-y OS |
|---|---|---|---|---|
| GELA[12] | 60 | 57 | 65% | 75% |
| R-CHOP+ASCT[13] | 249 | 55 | 40% | NR |
| R-CHOP/R-DHAP+ ASCT[13] | 248 | 56 | 65% | NR |
| Nordic[10,11] | 160 | 56 | 60% | 74% |
| R-hyperCVAD/R-MA[7,8] | 97 | 61 | 48% | 68% |
| CALGB 59909[14] | 78 | 57 | 56% | 64% |

# *TRIANGLE*: Trial Design

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

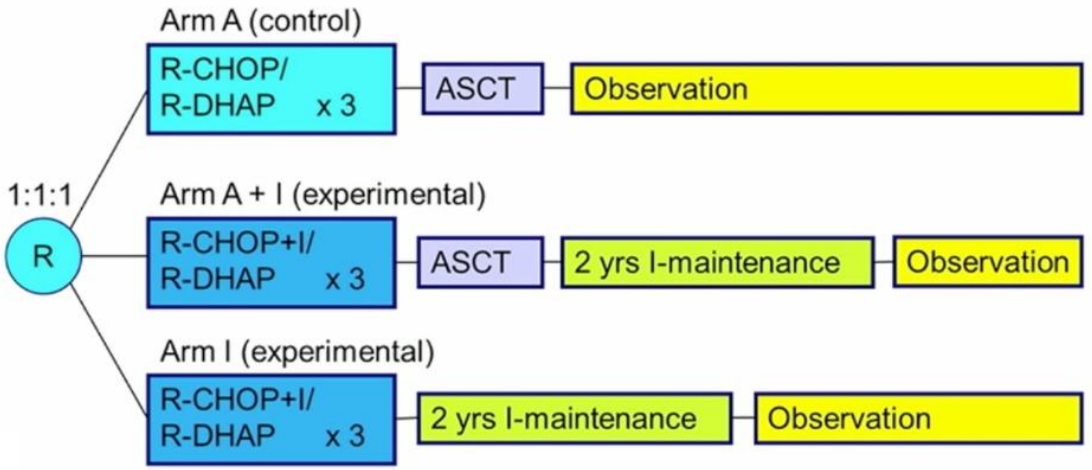
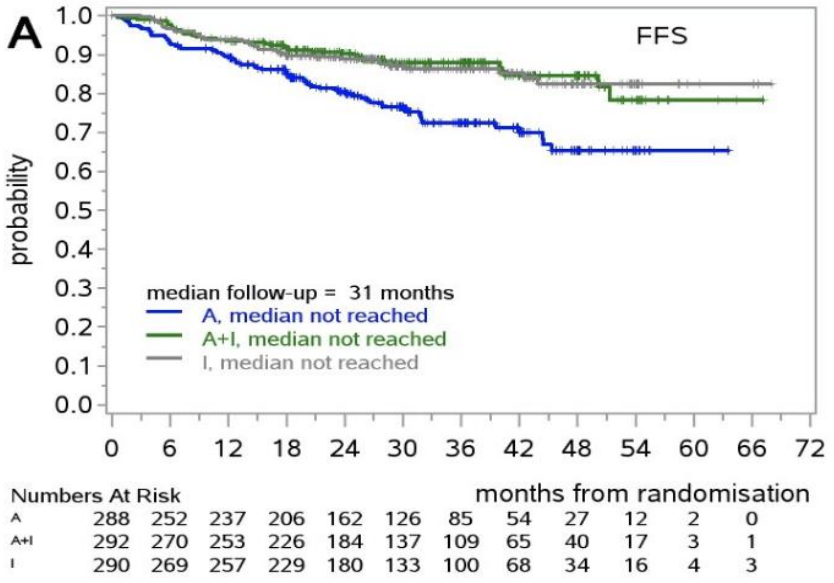
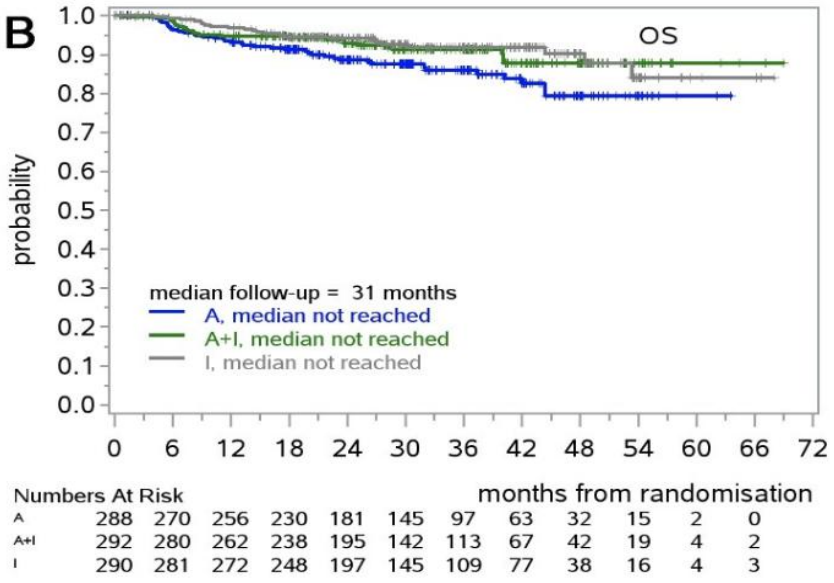
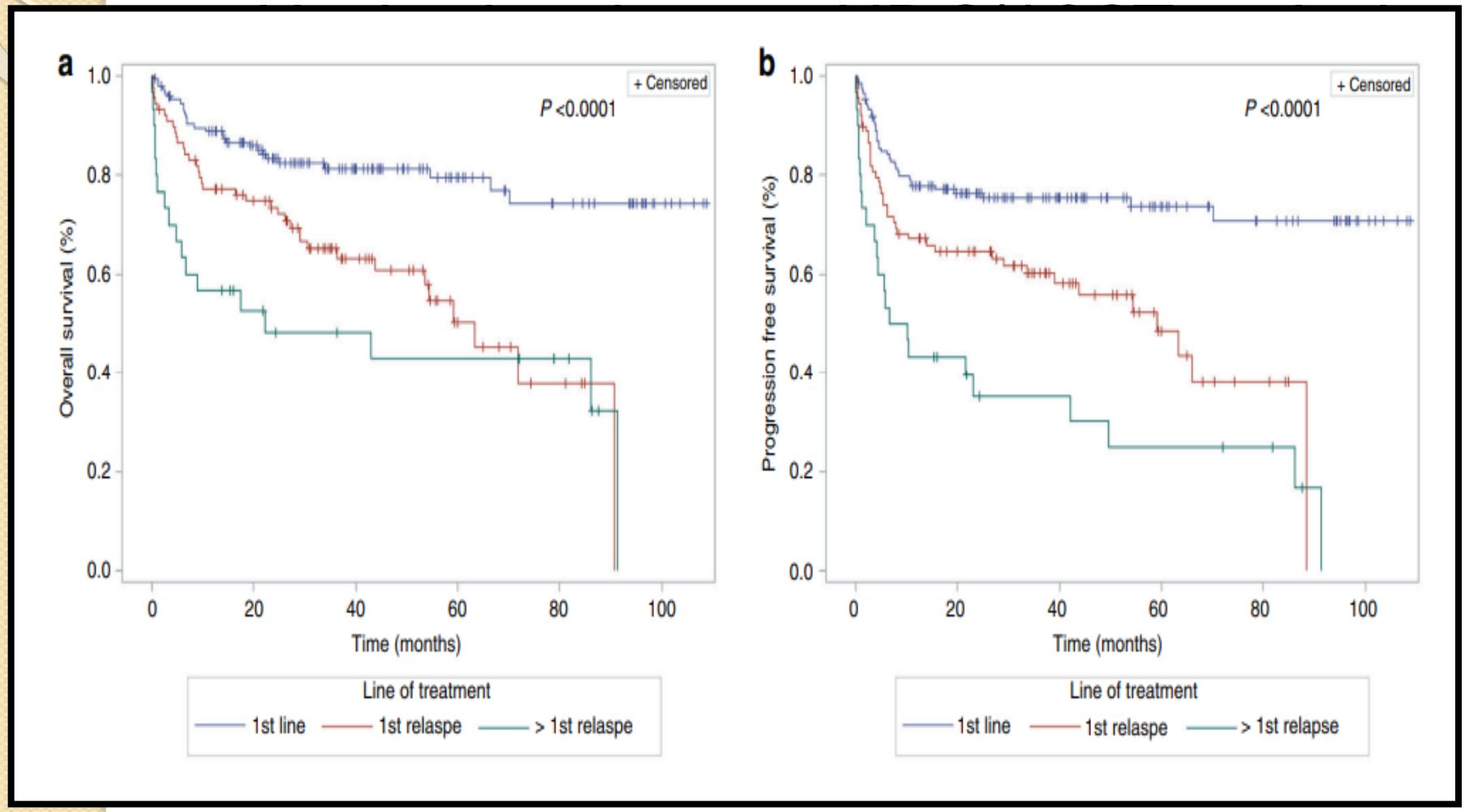



**Figure 1A: FFS (primary outcome) and B: OS according to randomized trial arm A (R-CHOP/R-DHAP followed by ASCT), A+I (ibrutinib-R-CHOP/R-DHAP followed by ASCT and ibrutinib maintenance) and I (ibrutinib-R-CHOP/R-DHAP followed by ibrutinib maintenance)**



# Primary CNS Lymphoma



Clinical Trial > J Clin Oncol. 2019 Apr 1;37(10):823-833. doi: 10.1200/JCO.18.00306. Epub 2019 Feb 20.

# Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study

Clinical Trial > J Clin Oncol. 2022 Nov 10;40(32):3692-3698. doi: 10.1200/JCO.22.00491. Epub 2022 Jul 14.

# Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients Age 60 Years and Younger: Long-Term Results of the Randomized Phase II PRECIS Study

8y OS – similar - ASCT 69% and WBRT 65%

Balance (52% *v* 10%, $P \leq 0.001$)

Neurocognition (64% *v* 13%, $P < .001$)

**Significantly deteriorated after WBRT**

# CAR T-cell Therapy for Central Nervous System Lymphoma

Houillier C, Choquet S.

Curr Oncol Rep. 2024 Nov;26(11):1521-1529. doi: 10.1007/s11912-024-01609-3. Oct 28.

**Table 1** CAR T-cells in CNS lymphomas, review of the litterature: main characteristics before CAR T-cells

| Name of 1st author | Type of study | *N* | PCNSL (*N*) vs. SCNSL (*N*) | *N* of previous lines: median (range) | Previous ASCT (%) | Age before CAR T-cells: median (range) |
|---|---|---|---|---|---|---|
| Siddiqi [15] | Retrospective | 5 | PCNSL | UK | UK | 49 (42–53) |
| Ahmed [14] | Retrospective | 7 | SCNSL | 4 (2–4) | 29 | 50 (39–72) |
| Frigault [13] | Retrospective | 8 | SCNSL | 5 (3–6) | 12.5 | 50 (17–79) |
| Frigault [17] | Prospective | 12 | PCNSL | 4 (2–9) | 25 | 63 (34–81) |
| Alcantara [16] | Retrospective | 9 | PCNSL | 3 (2–5) | 78 | 67 (48–75) |
| Choquet [18] | Retrospective | 25 | PCNSL | 3 (2–6) | 52 | 68 (34–76) |
| Karschnia [19] | Retrospective | 45 | PCNSL (18)<br>SCNSL (27) | 3 (1–10) | 11 | 32 (UK-UK) |
| Nayak [20] | Prospective | 18 | PCNSL (13)<br>SCNSL (4)<br>Systemic + VRL (1) | 3 (1–7) | 33 | 62 (33–81) |
| Yu [21] | Retrospective | 22 | PCNSL (12)<br>SCNSL (10) | 2 (1–5) | 4.5 | 56 (29–70) |
| Epperla [22] | Retrospective | 61 | SCNSL | 3 (1–5) | 23 | 56 (18–82) |
| Ayuk [23] | Retrospective | 28 | SCNSL | UK | UK | 58 (33–78) |
| Saidy [24] | Retrospective | 88 | SCNSL (78)<br>PCNSL (10) | 63%: ≥3 prior lines | 34 | 63 (31–81) |
| Alsouqi [25] | Retrospective | 86 | SCNSL | 3 (1–8) | 20 | 62 (52–71) |
| Cook [26] | Metaanalysis | 30 | PCNSL | 3.75 (3–5) | UK | 56 (44.5–67) |
| Cook [26] | Metaanalysis | 98 | SCNSL | 4 (3–7) | UK | 50 (38–58) |
| Elgohary [27] | Metaanalysis | 141 | PCNSL (29)<br>SCNCL (88)<br>UK (24) | UK (1–15) | UK | UK (17–85) |

# תודה על ההקשבה

# ובהצלחה