



Rapidly Evolving Targeted and Immunotherapies

Focusing

On Lymphomas and Plasma cell Myelomas

**Real life experiences in 2019
what we do
when and the Future**



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NHS
Mid and South Essex
University Hospitals Group
one team, working together



NHS **70**
YEARS
OF THE
1948 - 2018
University College London Hospitals
NHS Foundation Trust



Queen Mary
University of London



Anglia Ruskin
University

Faculty of Medical Science
School of Medicine



Conflict of interest

- ▶ Conference attendance: Sponsored by Haematology Society of Bangladesh

INTRODUCTION

Targeted and Immunotherapies in haematological malignancies
Evolving rapidly

Changing the way we treat our patients
Made many disease curable

- ▶ Monoclonal antibodies
- ▶ TKIs
- ▶ PI3K inhibitors
- ▶ Check point inhibitors
- ▶ CAR T CELL therapies
- ▶ And more adding each year


GOAL OF THERAPIES

- ▶ Finding optimal treatment strategies to

Improve long-term outcome

Minimizing the impact of treatment-related toxicity

Here I will discuss some real life cases

- ▶ **How we selected upfront therapies**
 - ▶ **How we treated in relapsed settings**
 - ▶ **Role of stem cell transplantations and indications**
 - ▶ **Clinical trial options**
- 

Diffuse Large B cell Lymphomas

55 years old male

- ▶ Stage 4B DLBCL with high IPI, **BCL6, BCL2 positive**
- ▶ RCHOP x6 CMR- PET negative
- ▶ CNS prophylaxis IV MTX preferred
- ▶ For Watch

DLBCL

- ▶ Relapsed 12 months after with Extensive extrnodal disease: left thigh, tonsils, stomach (C-myc,BCL2) **double hits**
- ▶ Salvage chemo with R-ESAHPX3 PET : CMR (Options: R- GDP, R- IVE, R- IVAC, R- DHAP)
- ▶ ASCT- Consolidation (**standard**)
- ▶ Offered Allograft : declined as mortality >20%

DLBCL

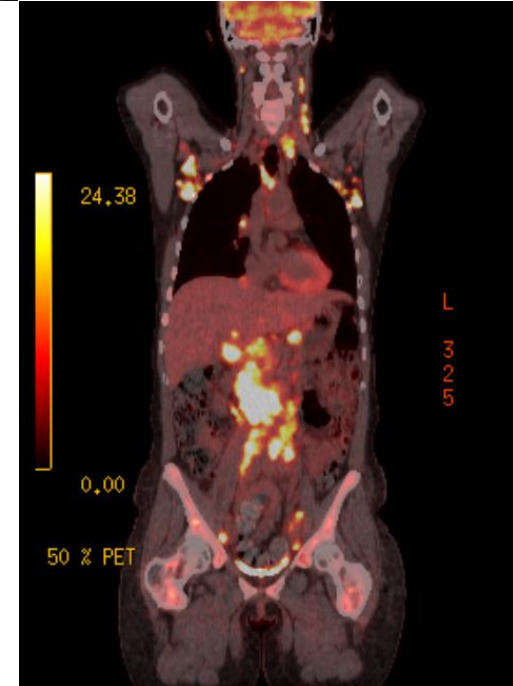
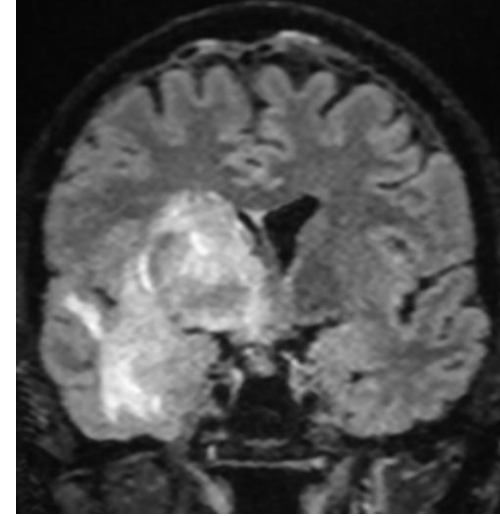
6 months post ASCT

- ▶ Headache and cerebellar signs
- ▶ PET CT and MRI brain: Biopsy CNS and synchronous systemic DLBCL

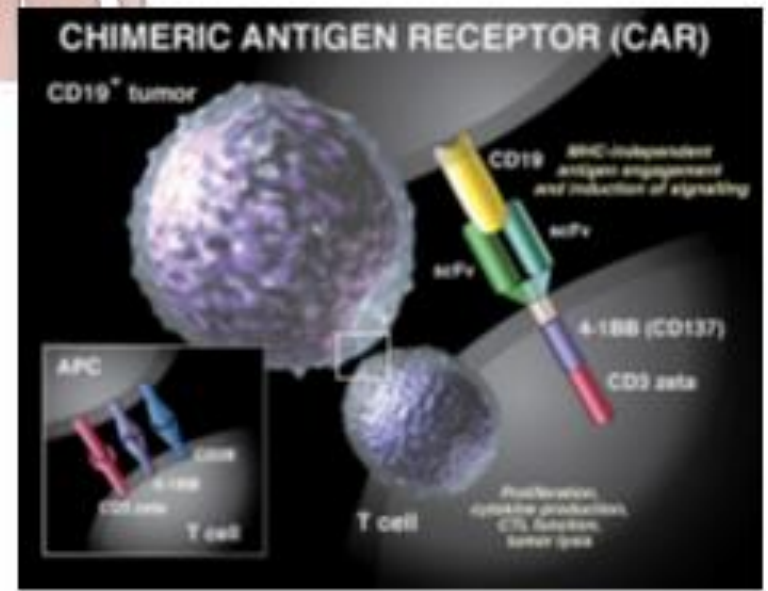
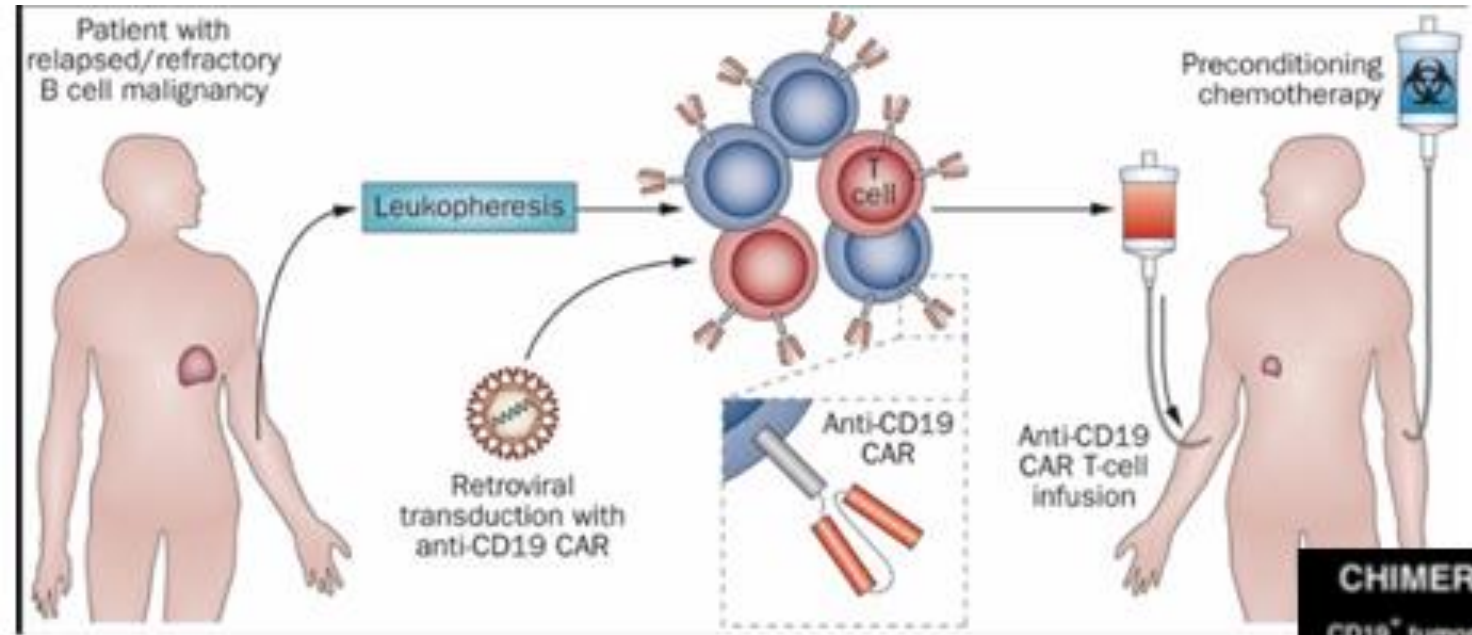
Triple hit (BCL2, BCL6, C-Myc positive)

Outcomes : very poor in this setting

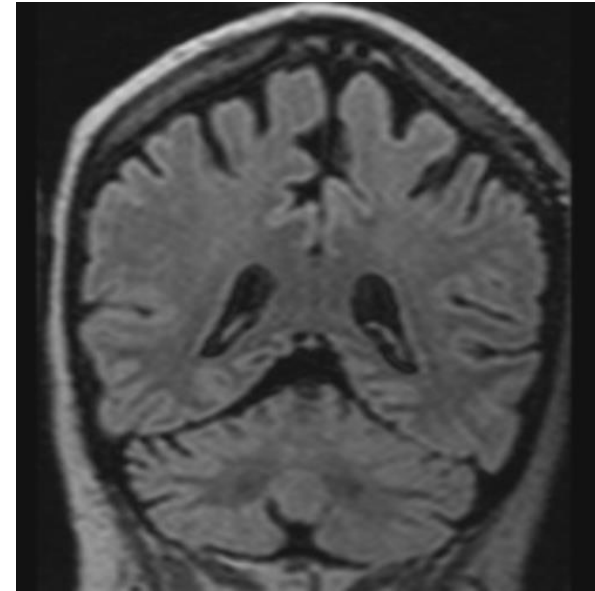
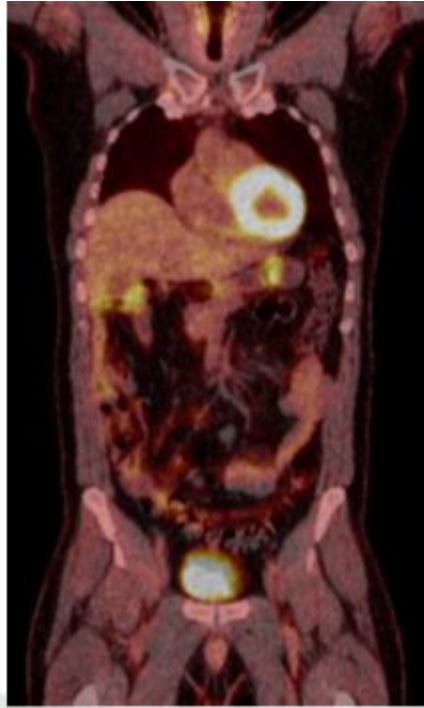
UCLH MDT : Opted for CAR T cell therapies



DLBCL CAR T



3 Months post CAR- T: CMR



DLBCL/BURKITS or Burkitts like

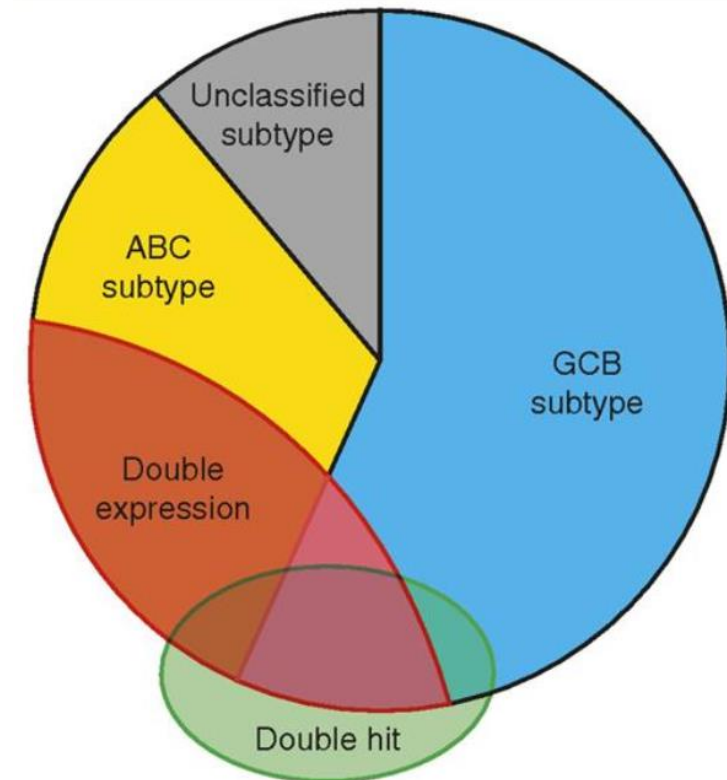
- ▶ C- MyC , BCL2, BCL6 (triple hit)
- ▶ Treat like Burkitts?

Denovo BURKITS: RCODOX/M IVAC protocol

- ▶ High risk of TLS
- ▶ Follow TLS pathway
- ▶ Rasburicase
- ▶ High Mortality with TLS

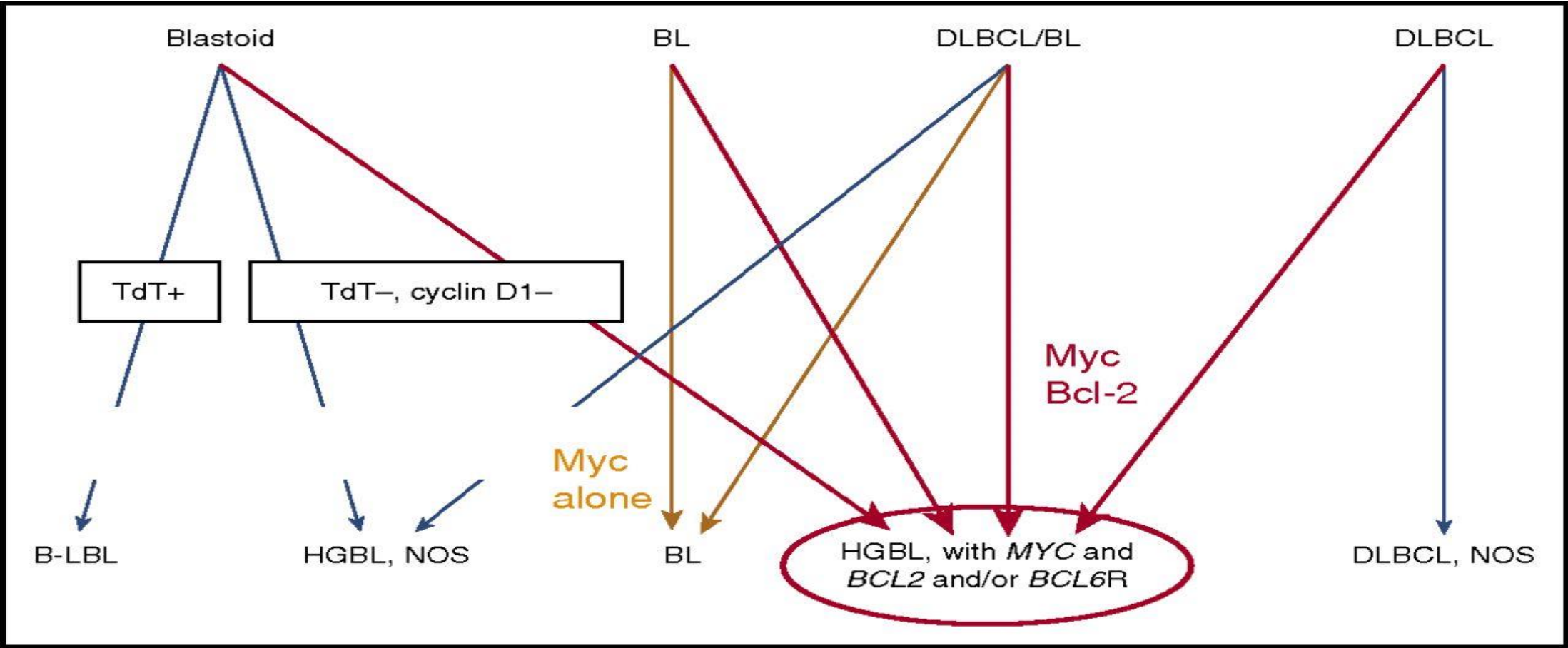
Relapsed Double and triple hit lymphomas

- ▶ Aggressive disease
- ▶ 4 years PFS with salvage therapies and ASCT **only 4%**
- ▶ This patient should be considered for CAR- T
If available



Herrera AF, Mei M, Low L, et al. Relapsed or refractory double-expressor and double-hit lymphomas have inferior progression-free survival after autologous stem-cell transplantation. *J Clin Oncol.* 2017;35(1):24-31.

How I treat double-hit lymphoma



Jonathan W. Friedberg, How I treat double-hit lymphoma, Blood, 2017, Figure 1.

Clinical trial options and CAR -T cell

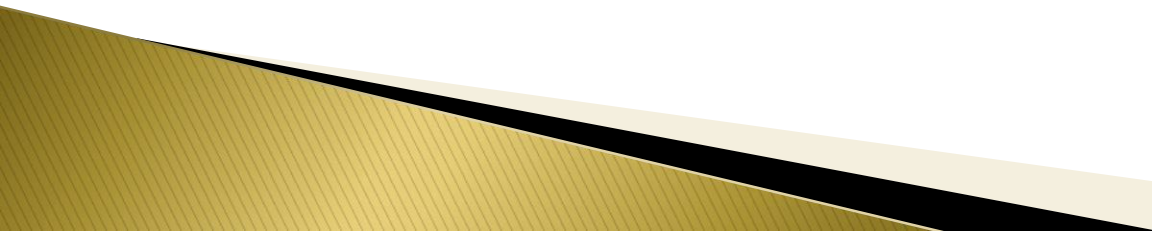
- ▶ Clinical trials options available

Exploring noble

- ▶ **PI3K/Ibrutinib/lenolidomide/BCL2 inhibitors**
- ▶ B Mind study- phase 3: Bendamustine+ MOR208 (CD19ab) or Bendamustine +Rituximab

POLARIX: A PHASE 3 STUDY OF POLATUZUMAB VEDOTIN (POLA) PLUS R-CHP VERSUS R-CHOP IN PATIENTS (PTS) WITH UNTREATED DLBCL

CAR T- DLBCL

- ▶ Available under clinical trial as **second and subsequent lines**
 - ▶ Excellent PFS and ORR
 - ▶ Certainly an option for patient NOT suitable for ASCT/Allo SCT
 - ▶ Recent huge investment and interest in developed world
 - ▶ Strict selection criteria
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Primary Mediastinal B Cell Lymphomas

34 years old female

- ▶ Huge mediastinal mass
- ▶ Evaluation confirmed PMBCL
- ▶ Pleural and pericardial effusion

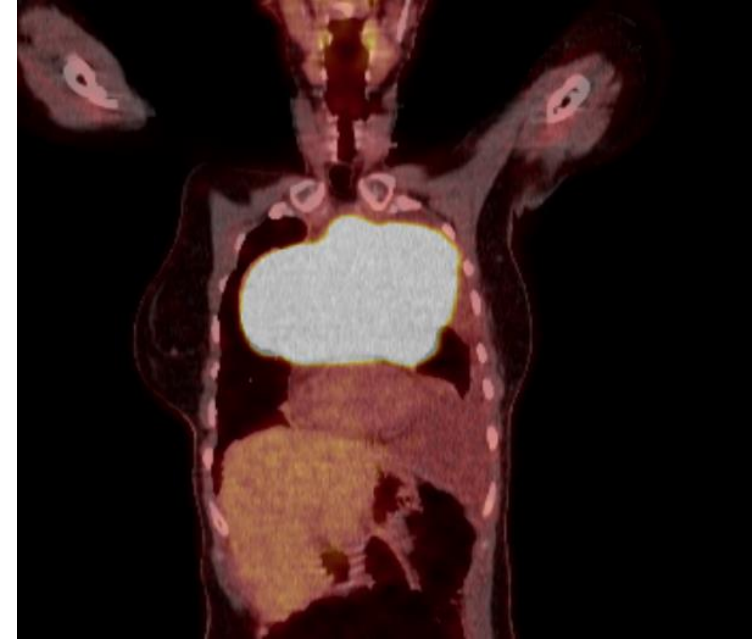
PMBCL a New entity, poor outcomes then DLBCL

- ▶ CD20 and CD30 positive
- ▶ Overlap between cHL and DLBCL
- ▶ NFkB anti-apoptotic survival pathway and the JAK-STAT signalling pathway
- ▶ PDL1 and PDL2 translocation



PMBL

- ▶ MDT
- ▶ RCHOP 21 X6 with interim PET CT
- ▶ PET after 2 RCHOP inadequate response
- ▶ Escalated to Dose adjusted R- EPOCH
- ▶ PET negative after 2
- ▶ Total 4 DA R- EPOCH
- ▶ RT to main bulk
- ▶ RT can not be omitted outside clinical trial IESLG37 Aw results



Clinical trial options

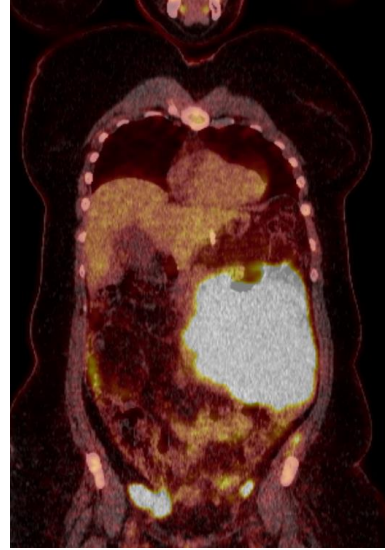
- ▶ R-CHOP 21 vs R-CHOP 14
- ▶ Da R-EPOCH
- ▶ R-CHOP 21 + Brentuximab
- ▶ Consolidation with RT vs NO RT after CR
- ▶ On going **IESLG 37 trial**
- ▶ Patients involvement in decision making regarding RT
- ▶ Risk/benefit discussions
- ▶ Pembrolizumab phase 1 trial USA/Europe
- ▶ CAR- T in refractory patients

FOLLICULAR LYMPHOMAS

37 years old lady

- ▶ Abdominal pain
- ▶ Evaluation PET/CT biopsy: FLIPI 2- Follicular NHL
- ▶ Obinutuzumab+CHOP **as standard**
- ▶ NO response after 3 cycles (**Primary refractory**)
- ▶ Escalated to salvage R- ESAHP- Inadequate response
- ▶ R- IVE X2 - Poor response

Gallium study : Marcus et al NEJM 2017



Follicular NHL contd

- ▶ Idelalisib to VGPR
- ▶ Not suitable for CAR T cell therapies
- ▶ Allograft BUT RIP with sepsis

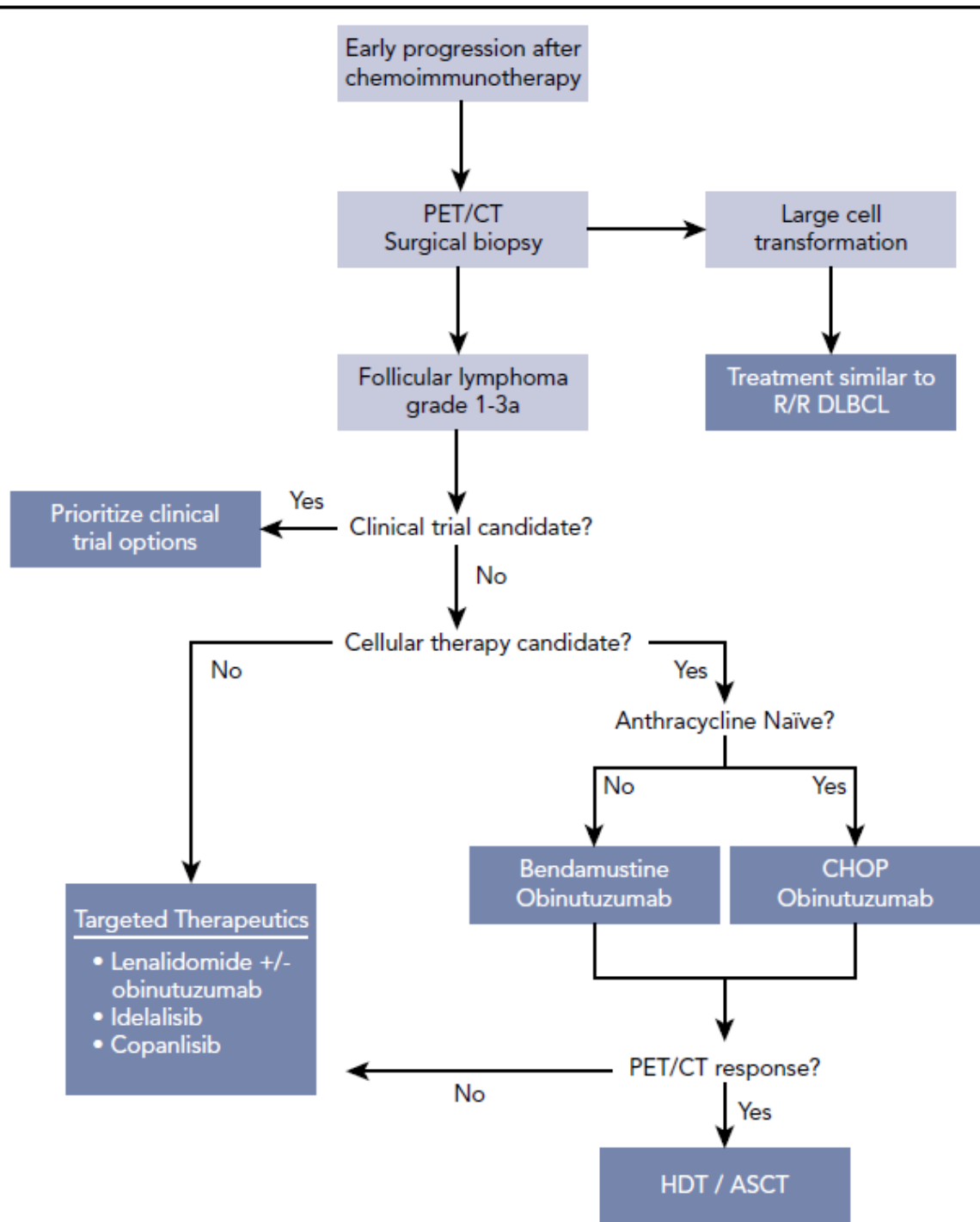
- ▶ ACCEPT trial : R-CHOP+Acalabrutinib upfront options available

Follicular relapsed or primary refractory

- ▶ Salvage therapies
- ▶ R- ESHP for fit –ASCT

Not for ASCT patients

- ▶ Obinituzumab+Bendamustine then O maintenance
(GADOLIN STUDY)
- ▶ Follicular CAR- T
- ▶ Idelalisib single agent



Chronic Lymphocytic Leukaemia's

52 years old gentleman

- ▶ B symptoms ,huge abdominal and neck mass
- ▶ Evaluation CLL : TP53 Normal 13 q deletion
- ▶ FCR **standard**
- ▶ FCR X3 POOR RESPONSE
- ▶ Venetoclax + rituximab CR **second line standard**
- ▶ On watch NOT for stem cell transplant as yet
- ▶ Next lines: Ibrutinib, Idelalisib, ACALIBRUTINIB, CAR T cell therapies available



CLL

- ▶ CLL standard risk: FCR fit (Less fit Obinituzumab+Clb
- ▶ TP53/17P mutated/deleted: Rituximab/idelalisib, Ibrutinib single agent, Venetoclax/Ritux
- ▶ **Allograft NOT advocated any more**
- ▶ **Allo SCT not considered as curative in the era of targeted therapies**
- ▶ High mortality >30% in some centres in the west

Clinical trial options

Upfront combinations

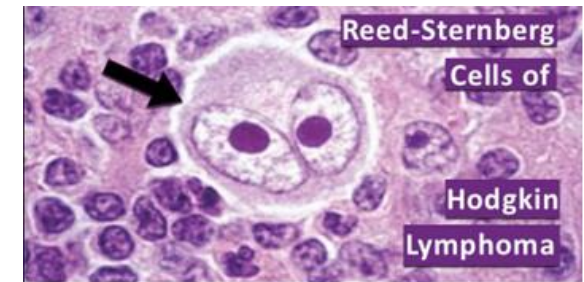
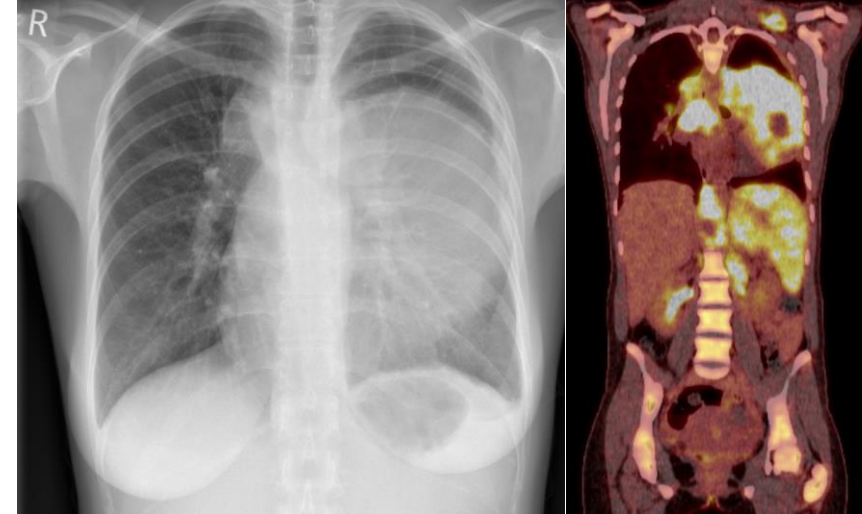
- ▶ Venetoclax/Rituximab
- ▶ Ibrutinib/Rituximab
- ▶ Idelalisib/acalaibrutinib combinations
- ▶ CAR T cell trial

HIGH EFFICACY OF VENETOCLAX PLUS OBINUTUZUMAB IN PATIENTS WITH COMPLEX KARYOTYPE (CKT) AND CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A PROSPECTIVE ANALYSIS FROM THE CLL14 TRIAL

Hodgkin's Lymphomas

27 years old lady

- ▶ SOBE
- ▶ Pleuritic chest pain
- ▶ Evaluation : Classical NS HL (huge mediastinal mass)
- ▶ ABVD agreed **standard** (omit bleomycin if PET negative after 2ABVD Rathal study)
- ▶ Post 2 ABVD: Poor response



HL

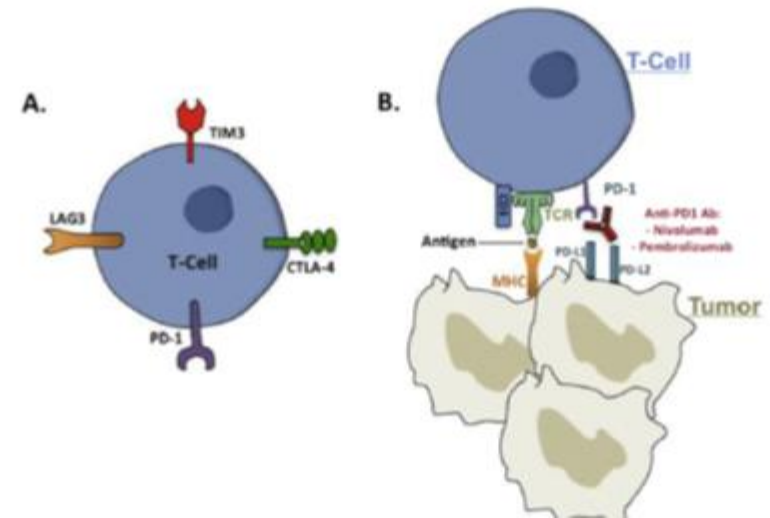
- ▶ Escalated to Es-BEACOPP
- ▶ Residual PET positivity after 4 cycles
- ▶ Biopsy: Persistent NS HL
- ▶ GDP: Poor response
- ▶ Brentuximab to CR
- ▶ ASCT as consolidation
- ▶ Currently under watch

Clinical trials

- ▶ ABVD vs A+brentuximab+vinblastine/decarbazine
- ▶ PDL1 blocker: Pembrolizumab/Nivolumab
- ▶ We use this as third or fourth lines therapy in the UK
- ▶ Nivolumab + Brentuximab Vedotin: phase 2 trial: ORR 81% in R/R HL

PD1 and PD L1 checkpoint inhibitor

L.M. Juárez-Salcedo et al. / Critical Reviews in Oncology/Hematology 113 (2017) 52-62



Mantle Cell Lymphomas

75 years old man

- ▶ B symptoms
- ▶ Dyspeptic symptoms
- ▶ PET/Biopsy - OGD: MCL Ki67 45%
- ▶ Not suitable for R- MAXI CHOP (NORDIC protocol) **standard**
- ▶ BR X6 CR post CR was on MR
- ▶ Relapsed at 6 months
- ▶ On Ibrutinib CR after 3 months

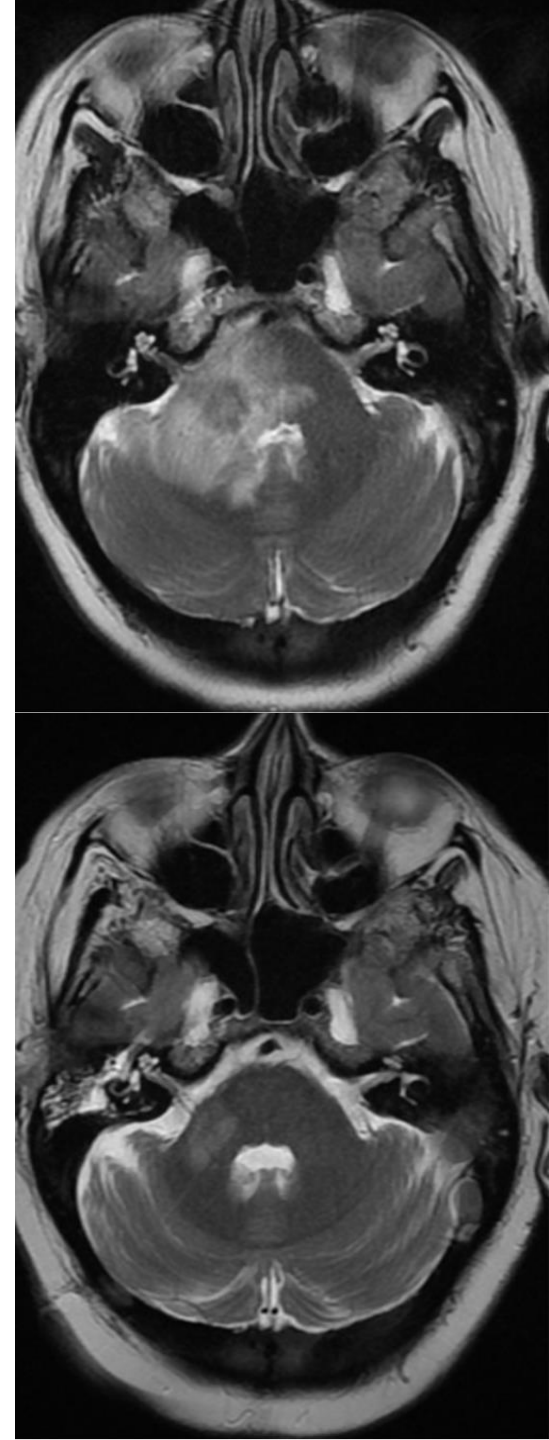
MCL

- ▶ Fit and young: NORDIC-ASCT **OS AND PFS benefit (14 years data)**
- ▶ Allograft for relapsed post ASCT patient
- ▶ ASYMPTOMATIC LOW VOLUME : WATCH IS AN OPTION

- ▶ **Primary refractory or relapsed options**
- ▶ R- ESHP-ASCT
- ▶ Clinical trials, Rituximab+lenolidomide
- ▶ Rituximab+Ibrutinib (ENRICH)
- ▶ Venetoclax /Rituximab
- ▶ Allograft in selected cases under clinical trial

PCNS lymphoma

- ▶ Unsteady gait
- ▶ Visual impairment
- ▶ Headache
- ▶ Evaluation CT /MRI PET/ biopsy: PCNS DLBCL
- ▶ MATRIX protocol
- ▶ CR after 4
- ▶ ASCT- CR



POST MATRIX 1

PCNS lymphoma

- ▶ Important to exclude synchronous Peripheral DLBCL
- ▶ Intercalating with MATRIX/R-CHOP
- ▶ ASCT under clinical trial
- ▶ RT as palliative in elderly and frail NOT For MATRIX
- ▶ Needs to exclude HIV/CMV/EBV
- ▶ Folinic acid rescue and MTX level 24 hrs and 48 hrs respectively

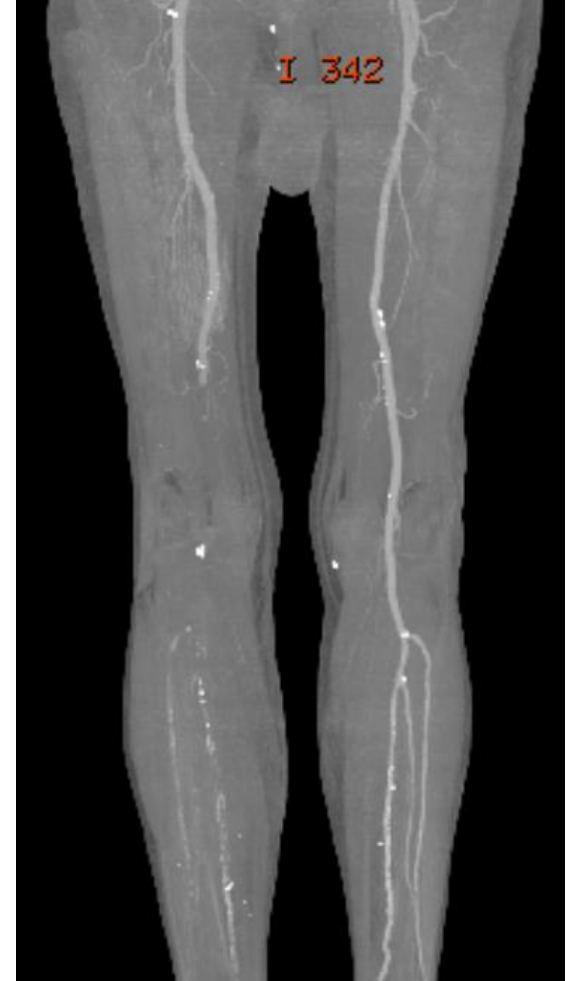
Angioimmunoblastic T Cell Lymphomas (AITCL)

71 years old man

- ▶ SOBE
- ▶ Jaundiced
- ▶ Neck nodes for 3 months
- ▶ Evaluations: Autoimmune haemolytic anaemia HB 40, DAT IgG4+, LDH 4500
- ▶ Biopsy: AITCL
- ▶ CHOEP chemo – ASCT **standard**
- ▶ After 2 months pulseless foot and chest pain: Arterial clots and PE
- ▶ Below knee amputation,: RIP PD

AITCL

- ▶ CHOEP **standard**
- ▶ ASCT standard in 1st CR
- ▶ Relapsed setting: ESAHP
- ▶ Consider Allograft
- ▶ Highly prothrombotic condition and
- ▶ Immune mediated symptoms very common
- ▶ Clinical Trial option: RomiCar

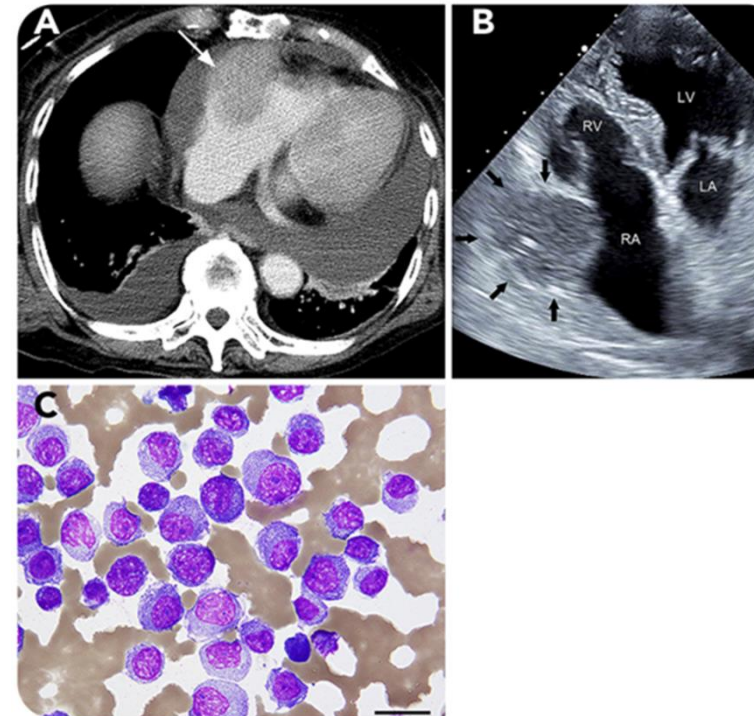


RomiCar: RomiCar: Phase I/II study to determine the MTD and overall response rate of the combination of romidepsin and carfilzomib in relapsed / refractory peripheral T-cell lymphoma

MYELOMA

81 years old female

- ▶ AKI , Creatinine 500
- ▶ Bloods , free light 2000, lambda, PP 34g/l HB 67, PLT 25, WCC Normal, Bone marrow 56% clonal plasma cells
- ▶ Valcade/dex/cyclo started- No response
- ▶ Dara/Valcade/Dex 2 months-No response
- ▶ Ixazomib/Revlimid/Dex 2 cycles: poor response
- ▶ Currently on Ponabinostat/Valcade and dex



Myeloma INITIAL TREATMENT IN PATIENTS ELIGIBLE FOR TRANSPLANTATION

Typically

Patients are treated with approximately 4 to 6 cycles of induction therapy with bortezomib, lenalidomide, and dexamethasone (VRd) prior to stem cell harvest (6 X VTd in UK)

Low dose Dexamethasone are preferred 20mg 4 days or 40 mg Weekly

- ▶ 5. Rajkumar SV, Jacobus S, Callander NS, et al. *Lancet Oncol.* 2010;11(1):29-37. ■

MM- ASCT as Consolidation

- ▶ After harvest,

Patients can either undergo frontline autologous stem cell transplantation (ASCT)

or

Resume induction therapy delaying ASCT until first relapse

As data are showing **NO OS** benefit in the Era of Newer therapies

Myeloma- INITIAL TREATMENT IN PATIENTS NOT ELIGIBLE FOR TRANSPLANTATION

- ▶ Initial therapy with VRd

Approximately 8 to 12 cycles, followed by maintenance therapy with lenalidomide.

Alternatives to VRd include VCd and VTd can be used

Myeloma-STEM CELL TRANSPLANTATION

- ▶ The Intergroupe Francophone du Myelome trial compared

Early versus delayed ASCT in patients treated with VRd followed by lenalidomide maintenance for 1 year.

Patients were randomized to receive

Either VRd (3 cycles) followed by ASCT and then VRd consolidation (2 cycles) versus VRd × 8 cycles with ASCT reserved for relapse.

Myeloma-STEM CELL TRANSPLANTATION

- ▶ Both arms received lenalidomide maintenance for 1 year.

A significant improvement in progression-free survival (PFS) was seen as expected with early ASCT

This has so far not been translated into a difference in overall survival (OS).

Allogeneic transplantation is still investigational in Myeloma

Can be considered for young patients

with high-risk disease in first relapse or

Exclusively patients choice after risk benefit discussion

30-40% Mortality in some centres

Preferably under clinical trials if available

RELAPSED MM options

- ▶ Almost all patients with MM eventually relapse

The choice of a treatment regimen at relapse affected by many factors

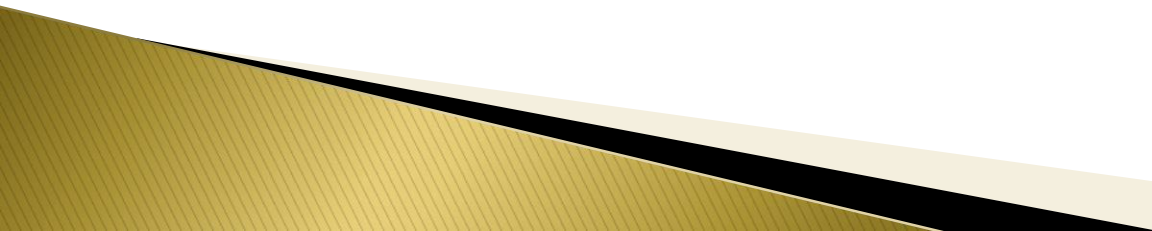
Timing of the relapse

Response to prior therapy

Aggressiveness of the relapse and

Performance status (TRAP)

Relapsed MM

- ▶ Other drugs to consider for relapse include
 - ▶ panobinostat, a pan deacetylase inhibitor
 - ▶ Bendamustine, lenalidomide, and dexamethasone; or bendamustine, bortezomib, and dexamethasone.
 - ▶ Venetoclax (BCL 2 inhibitor) appears to have single agent activity in patients with t(11;14) subtype of MM.
- 

Relapsed MM

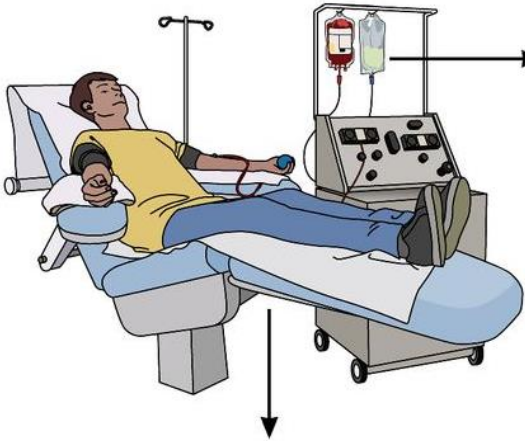
- ▶ Most exciting investigational options are chimeric antigen receptor T cells (CAR-T)

Targeting B-cell maturation antigen (BCMA) such as bb2121,9 and GSK2857916 (a humanized anti-BCMA antibody that is conjugated to monomethyl auristatin-F, a microtubule disrupting agent).

Berdeja JG, Lin Y, Raje N, et al. Durable clinical responses in heavily pretreated patients with relapsed/refractory MM: updated results from a multicenter study of bb2121 anti-BCMA CAR T cell therapy. *Blood*. 2017;130:740.

CAR T cell Cartoon

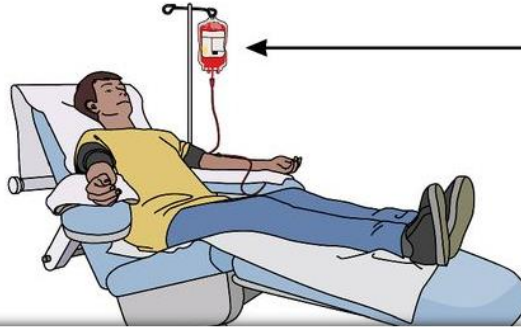
1. A patient's leukocytes are collected by apheresis



2. Patient receives lymphocyte-depleting chemotherapy prior to T-cell infusion



3. Patient receives CAR T-cell infusion



Ex-vivo cell processing

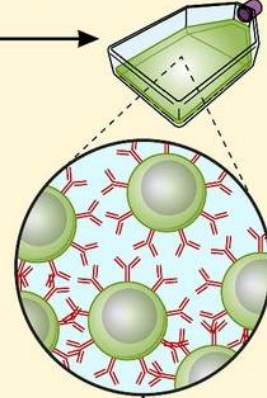
T-cell activation



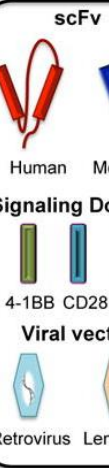
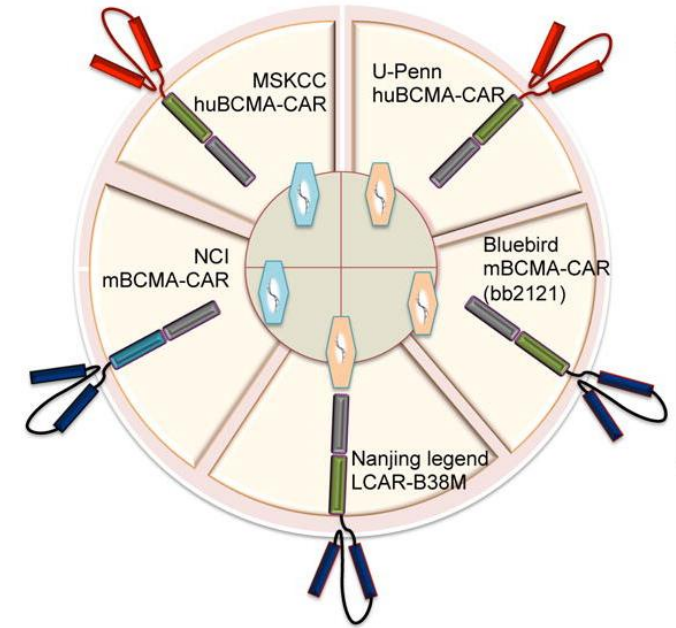
CAR transduction



T-cell proliferation



Virus: retrovirus, lentivirus
Electroporation: RNA/DNA



Type 1 cryoglobulin Case

78 years old man

- ▶ Skin rash and joint pain
- ▶ Pp 12 g/l lambda, free light chain 300 lambda, HB 100, UES NAD
- ▶ Evaluation : Confirmed Type 1 cryoglobulinaemia
- ▶ Needed emergency PEX and toe amputations
- ▶ Started Valcade/dex/cyclo-**No** response
- ▶ Switch to Rev/dex/ixazomib-**No** response
- ▶ Dara/valcade/dex- **Minor pp response** BUT needed PEX
- ▶ ASCT-after risk benefit discussion: 20 days post

Case of Amyloid

78 years old lady

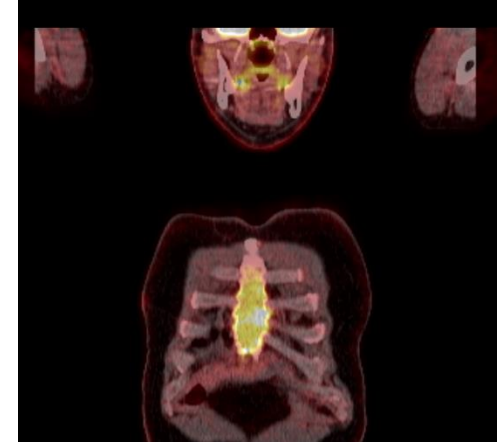
- ▶ Bilateral leg oedema
- ▶ Postural hypotension
- ▶ Creatinine : 80 normal
- ▶ Free light chain : slightly raised 200 lambda
- ▶ PP 7 gm/l
- ▶ BMAT: NAD
- ▶ Kidney biopsy: AL Amyloid
- ▶ NAC: Cardiac and renal amyloid for Valcade based treatment

Amyloid contd

- ▶ SAP scans
- ▶ Umbilical fat biopsy
- ▶ ECHO, C MRI
- ▶ Usually ASCT in CR **standard** if age permits
- ▶ High mortality with cardiac amyloid
- ▶ CVD **standard** approach

Solitary bone plasmacytoma-Myeloma

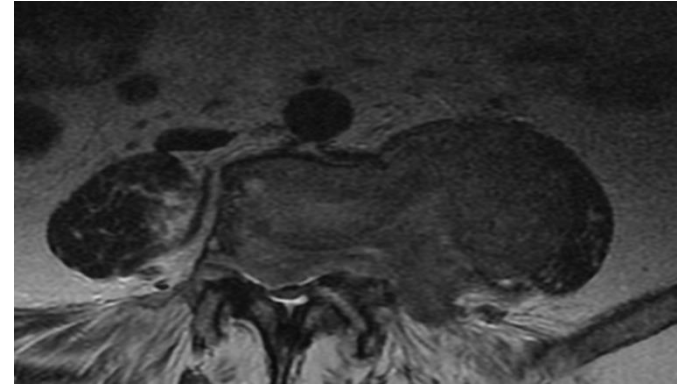
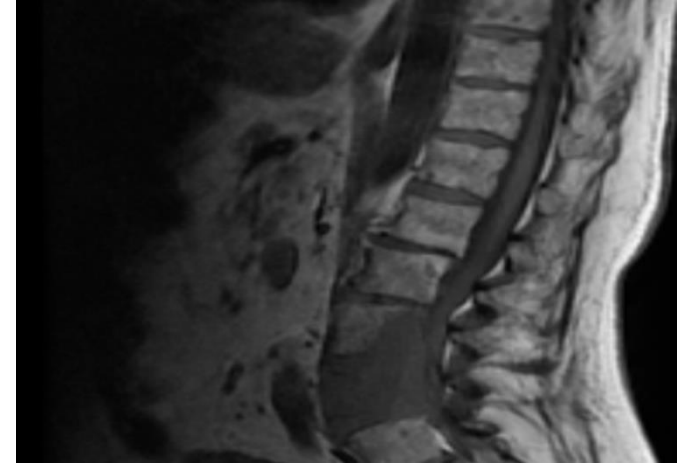
47 years old man



- ▶ Sternal bone pain: PET and Bloods: Solitary bone plasmacytoma
- ▶ RT -Curative intent
- ▶ Relapsed after 1 year with Serum free light chain 5,000
- ▶ VTDX6 then ASCT
- ▶ Exclusively asked for Sib Allo
- ▶ AlloHSCT October 2018
- ▶ Severe GVHD, viral infections BUT now well October 2019

Supportive care

- ▶ Assessment of Spinal stability- urgent if affected
IF Spinal cord Compression: Urgent RT is the KEY
- ▶ kyphoplasty and vertebroplasty in selected cases
- ▶ Zolindronic acid reduces Skeletal event in MM
- ▶ Usually 4mg monthly for 24 months (? 3 monthly)
- ▶ Some degree of anti myeloma effect (Myeloma 9 trial)



Summery

- ▶ Targeted therapies changed the way we treat cancers
- ▶ Made many conditions treatable and *curable*
- ▶ We are now treating many elderly and frail patients
- ▶ *CAR T cell* and check point inhibitors have shown the hope
- ▶ Many more immune and targeted therapies are in the development phase
- ▶ *Funding's remains an issue and price is a big challenge*
- ▶ *International collaboration essential*
- ▶ *Clinical trials should involve the developing world patients*

Thank you for your attention

Question?