Preserving the immune system of B-CLL and NHL patients with Blinatumomab expanded T cells

Alessandro Rambaldi

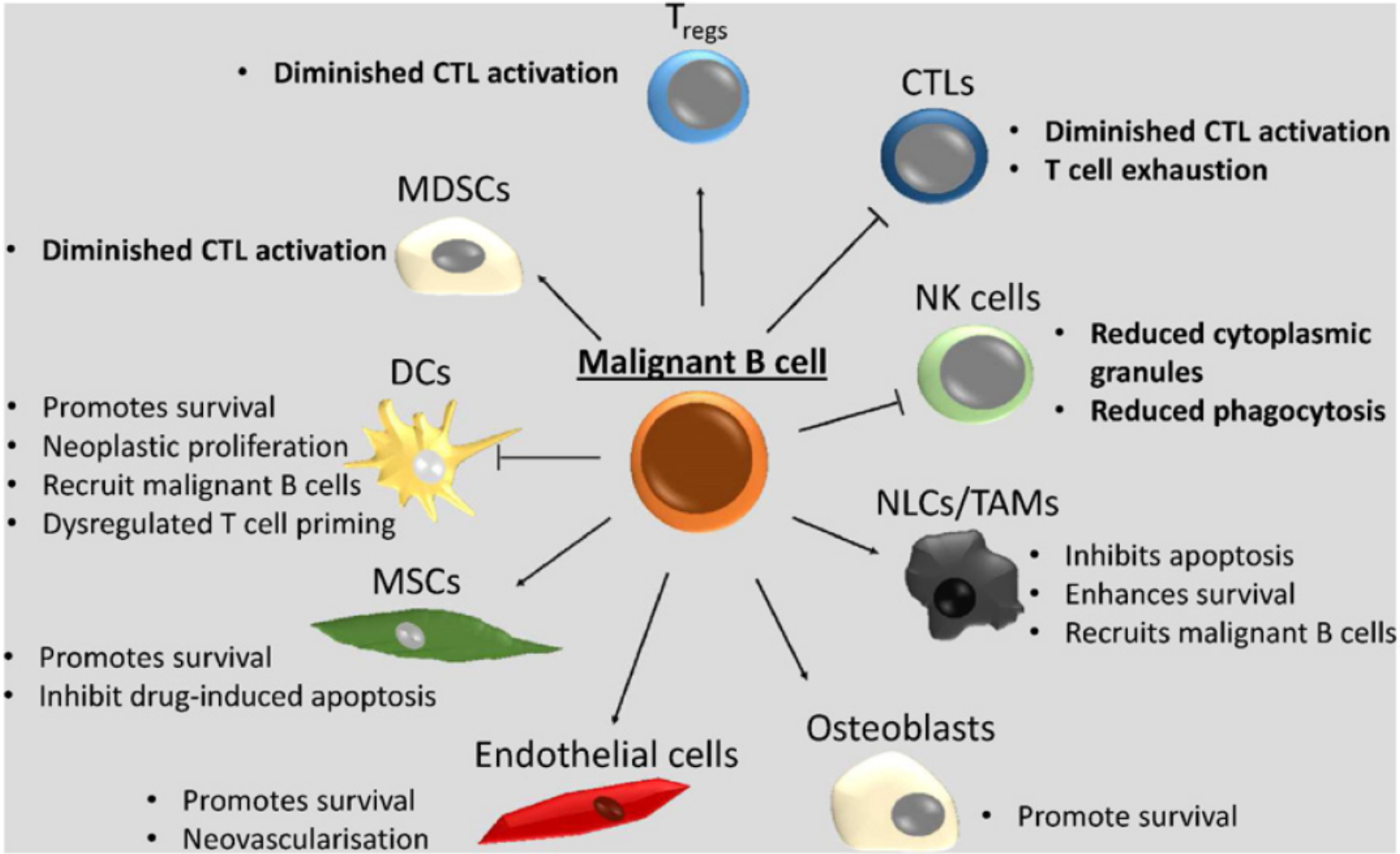
Cuneo, 18 Maggio 2018

Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Agenda

- CLL and indolent NHL: immune dysfunction at diagnosis and current treatment
- Infectious toxicity of chemo-immunotherapy and short and long term effect on immunological function
- Strategies to promote immune reconstitution after treatment

Immune dysfunctions in CLL and iNHL



las et al BBA 2016; Anderson et al Cancer 1981

Pathogenesis of infections in CLL and iNHL

Disease-Related Inherent Immune Defects
Hypogammaglobulinemia
Complement defects
Cell-mediated immune defects (T cells, delayed hypersensitivity)
Defects in neutrophil phagocytic/bactericidal activity
Deficiencies in monocyte enzyme levels
Potential mucosal immune defects
Therapy-Related Immune Defects
Neutropenia
Steroid-induced cell-mediated immune defects
Alemtuzumab-, purine analogue–related T-cell defects

rison, Clin Lymph Myeloma 2009

Treatment of CLL and iNHL

NCCN National Comprehensive Cancer Network®

Indolent NHL

First-line Therapy
- Bendamustine + rituximab (category 1)
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)

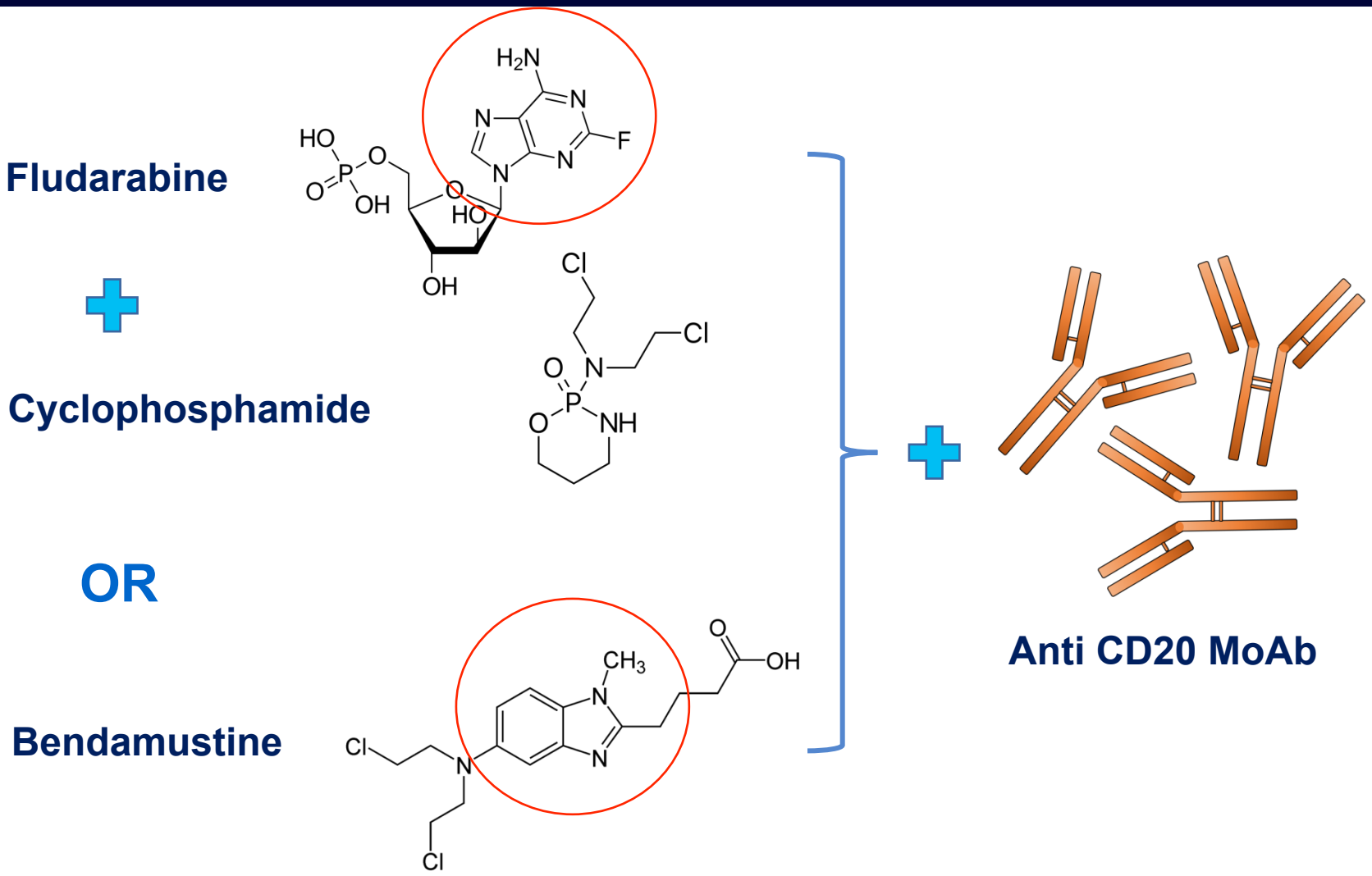
CLL without del(17p)/TP53 mutation

First-line therapy
- Age ≥65 y and younger patients with significant comorbidities
  - Preferred regimens
    - Obinutuzumab + chlorambucil (category 1)
    - Ibrutinib[c] (category 1)
    - Ofatumumab + chlorambucil
    - Rituximab + chlorambucil
    - Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± CD20 monoclonal antibody[d]

First-line therapy
- Age <65 y without significant comorbidities
  - Preferred regimens
    - FCR[f] (fludarabine,[g] cyclophosphamide, rituximab[h]) (category 1)[d]
    - Ibrutinib[c]
    - Bendamustine ± CD20 monoclonal antibody[d]
  - Other recommended regimens
    - FR[f] (fludarabine,[g] rituximab)[i]

NCCN Guidelines 2017

Treatment of CLL and iNHL



Gandhi, CCR 2009

Infections after first line FCR or BR in CLL

	Fludarabine, cyclophosphamide, and rituximab				Bendamustine and rituximab			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Adverse events per patient including all patients*								
Infections total	103 (37%)	97 (35%)	8 (3%)	6 (2%)	114 (41%)	61 (22%)	6 (2%)	7 (2%)
Bacterial infection	6 (2%)	5 (2%)	0	0	5 (2%)	5 (2%)	1 (<1%)	0
Fungal infection	6 (2%)	2 (1%)	1 (<1%)	0	5 (2%)	0	0	0
Viral infection	50 (18%)	22 (8%)	1 (<1%)	1 (<1%)	41 (15%)	9 (3%)	0	1 (<1%)
Unspecified pathogen	116 (42%)	67 (24%)	2 (1%)	2 (1%)	123 (44%)	38 (14%)	4 (1%)	1 (<1%)
Pneumonia	12 (4%)	29 (10%)	4 (1%)	1 (<1%)	13 (5%)	22 (8%)	0	2 (1%)
Sepsis	0	6 (2%)	1 (<1%)	2 (1%)	0	1 (<1%)	1 (< 1%)	3 (1%)

Severe infections (G≥3):

All pts: 40% FCR vs 26% BR

≤65 y: 37% FCR vs 28% BR

«*A significant number of severe infections in the triple combination therapy group occurred after the end of treatment until 5 months after treatment*»

Eichhorst Lancet Oncology 2016

Infections after first line BR in indolent NHL

Study	Treatment	N°	Infections %	G5 (Deaths)	Ref
STIL	BR	261	37% (G1-5)	<1%	Rummel et al., 2013
BRIGHT	BR	224	55% (G1-5)	3%	Flinn et al., 2014
GALLIUM	BR	338	7.7% (G3-5)	0.6%	Marcus et al., 2017
	OB	338	8% (G3-5)	2.7%	

Infections after first line BR in indolent NHL

Table 3. Adverse Events and Serious Adverse Events, According to Treatment Phase, and Selected Grade 3 to 5 Adverse Events during Treatment, According to Chemotherapy Agent and Treatment Phase in the Safety Population.*

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases		Follow-up	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)	Obinutuzumab Group (N=427)	Rituximab Group (N=428)
Grade 3 to 5 event, according to chemotherapy regimen — no./total no. (%)								
Neutropenia	—	—						
Bendamustine	—	—	73/338 (21.6)	87/338 (25.7)	49/312 (15.7)	29/305 (9.5)	6/270 (2.2)	1/263 (0.4)
CHOP	—	—	124/193 (64.2)	103/203 (50.7)	36/179 (20.1)	26/187 (13.9)	2/128 (1.6)	0
CVP	—	—	24/61 (39.3)	13/56 (23.2)	5/57 (8.8)	2/43 (4.7)	0	0
Infection¶	—	—						
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)	25/270 (9.3)	6/263 (2.3)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)	2/128 (1.6)	2/143 (1.4)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)	1/44 (2.3)	2/45 (4.4)
Second neoplasm‖	—	—						
Bendamustine	—	—	0	0	21/312 (6.7)	18/305 (5.9)	14/270 (5.2)	2/263 (0.8)
CHOP	—	—	0	0	8/179 (4.5)	8/187 (4.3)	1/128 (0.8)	1/143 (0.7)
CVP	—	—	0	0	0	1/43 (2.3)	0	0

Severe infections (G≥3):

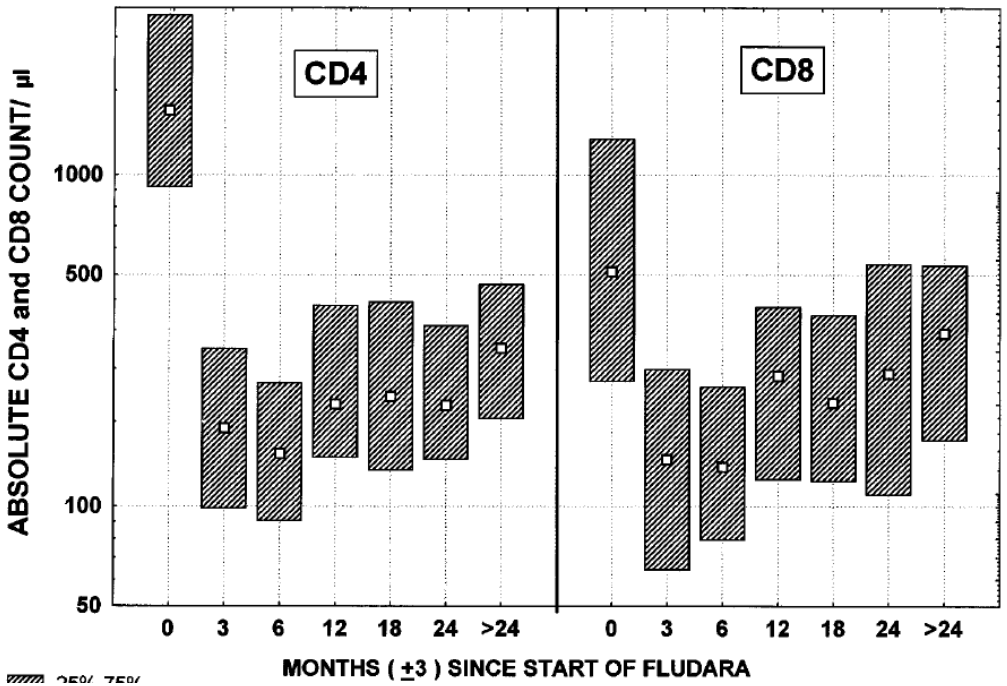
Maintenance: 14% B vs 5% CHOP/CVP

Follow up: 6% B vs 2% CHOP/CVP

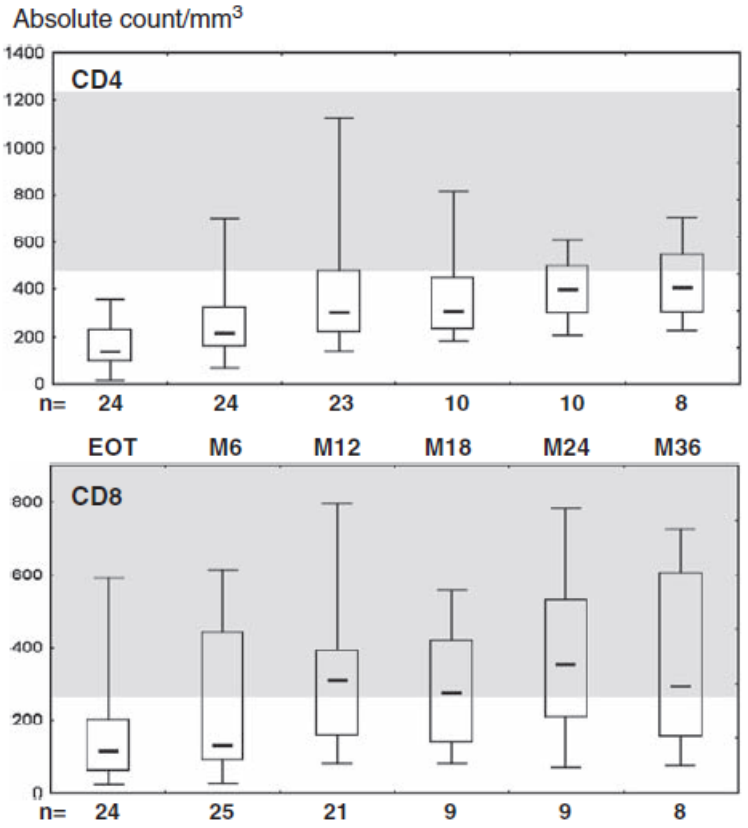
«Bendamustine was associated with higher rates of severe infections than CHOP or CVP during the maintenance and follow-up phases»

Marcus et al, NEJM 2017

T cell counts in CLL after Fludarabine based treatments

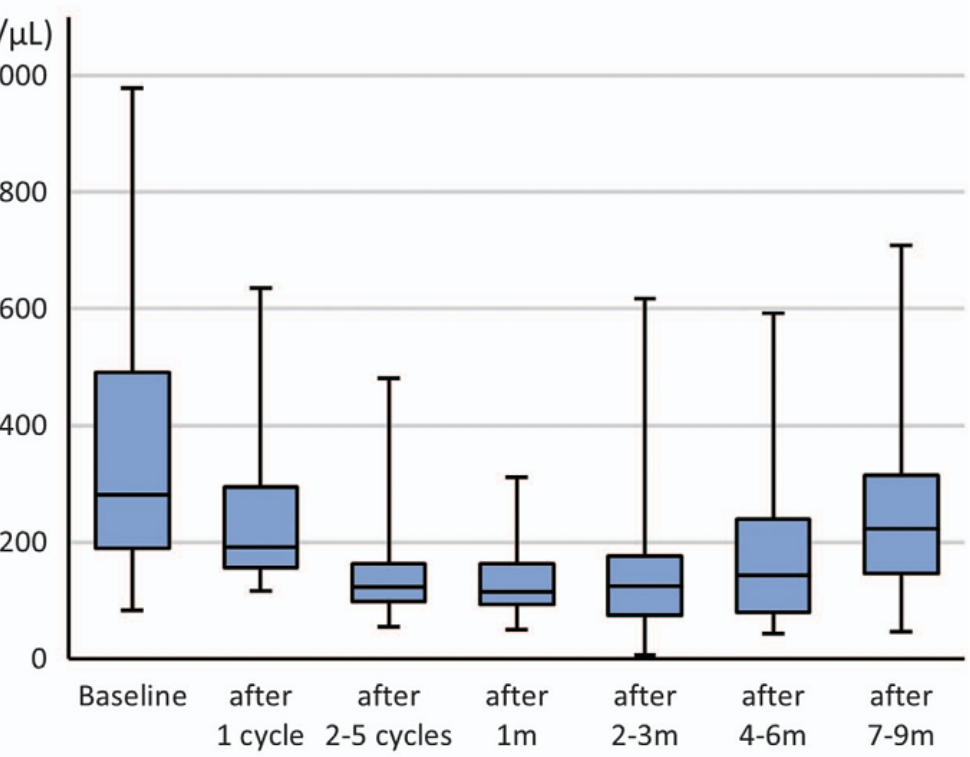


Keating Blood 1998

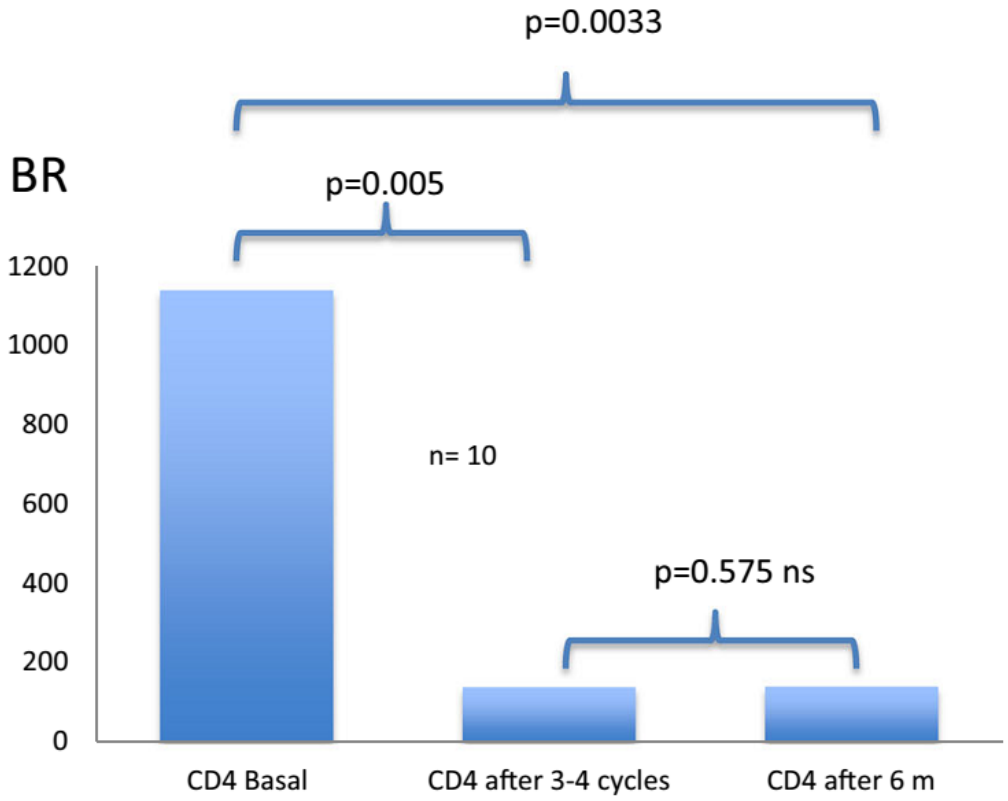


Ysebaert Leukemia 2010

T cell counts in NHL after Bendamustine based treatmen

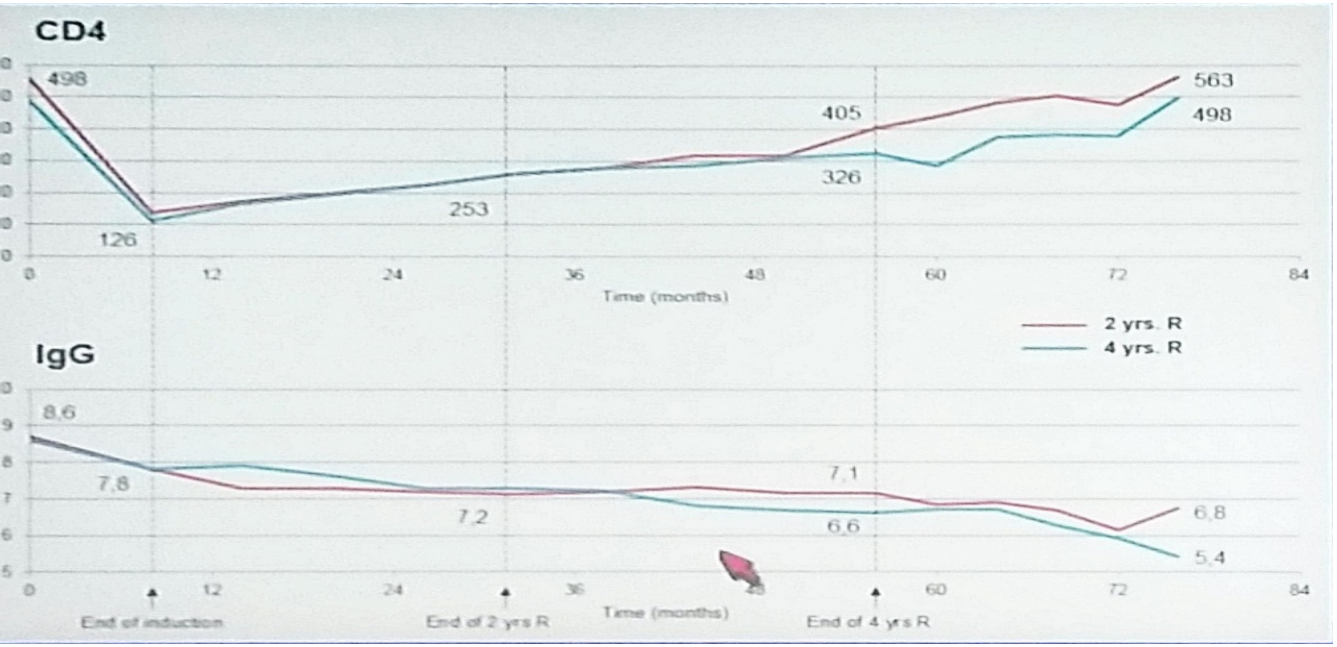


Saito BCJ 2015



García Muñoz Ann Hematol 2014

Immune reconstitution in indolent NHL after R-Benda (StiL NHL7-2008 MAINTAIN study)



HIV infection stage, based on CD4+ T-lymphocyte count

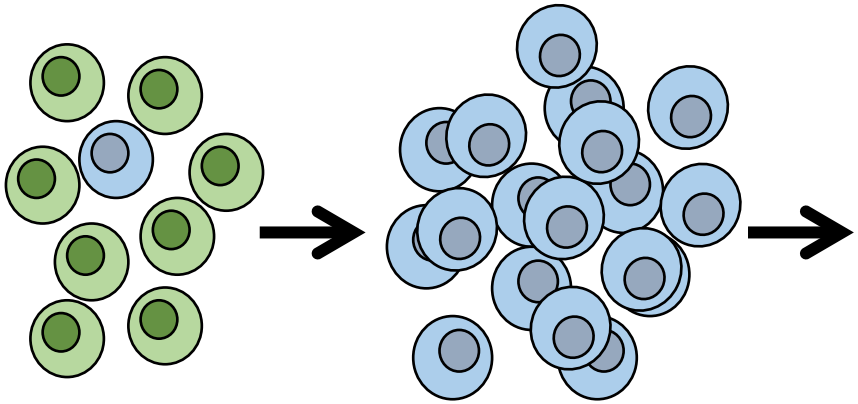
Stage	CD4+/mmc
1	≥500
2	200-499
3	<200

Rummel et al., Abs #483, ASH 2017

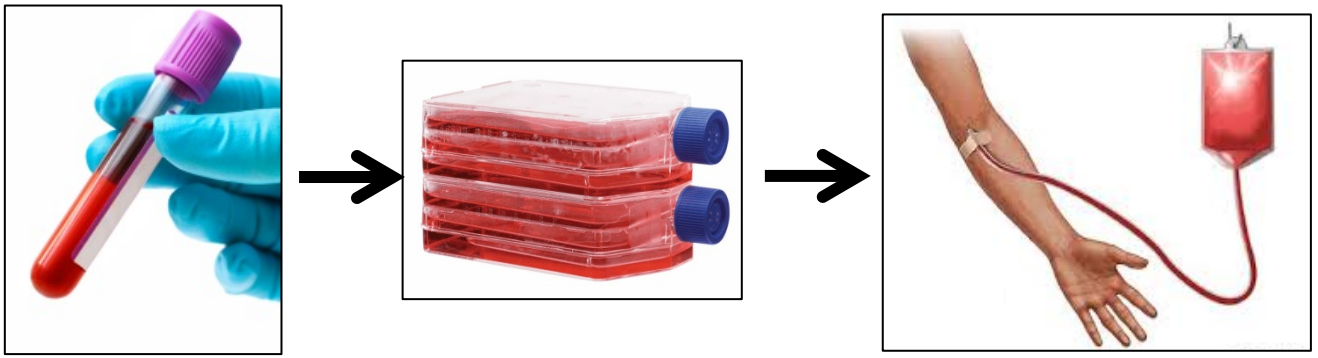
"HIV infection is classified as stage 3 (AIDS) when the immune system of a person infected with HIV becomes severely compromised (measured by CD4 cell count) and/or the person becomes ill with an opportunistic infection"

https://www.cdc.gov/hiv/statistics/surveillance/terms.html

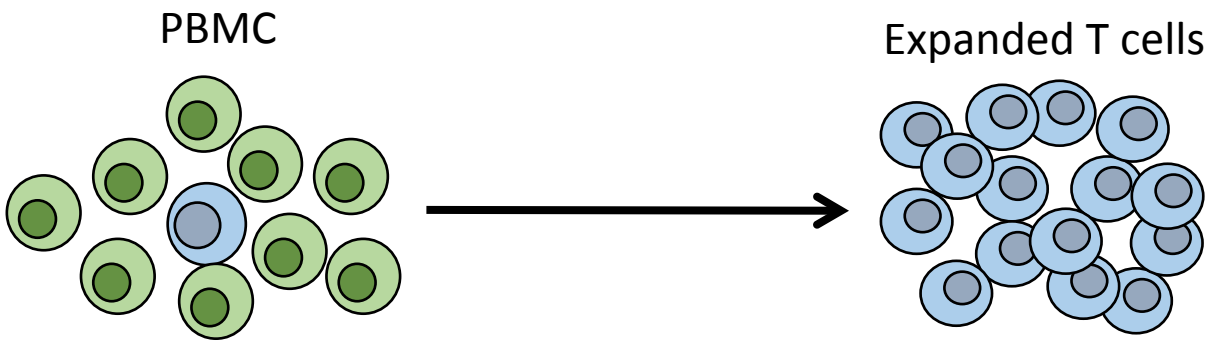
xpanding autologous polyclonal T cells in CLL for immunotherap



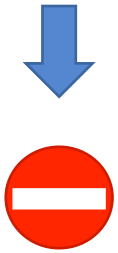
Immuno-reconstitution of CLL patients suffering life threatening infections after chemotherapy



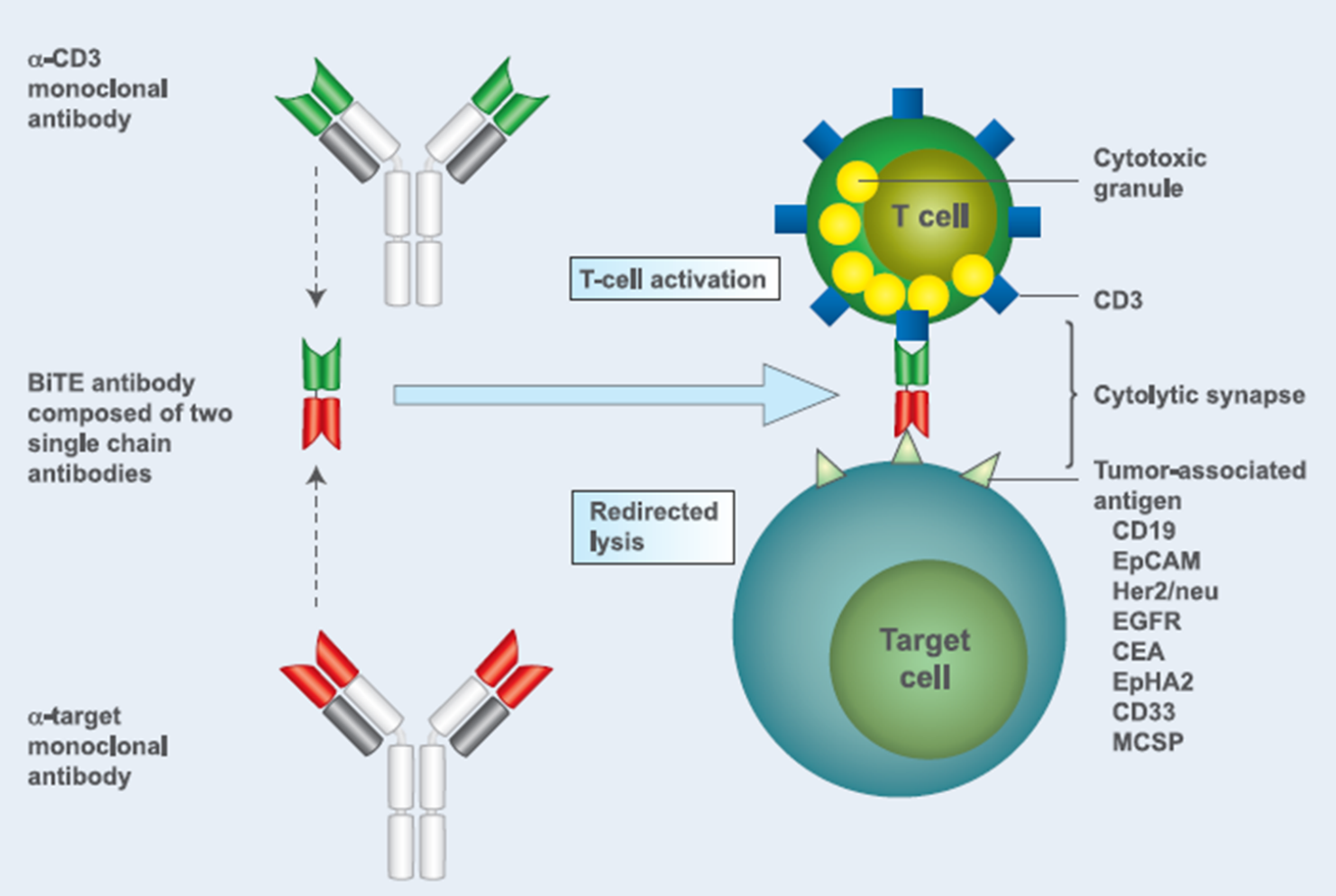
Challenge: expand few T cells and eliminate mass of CLL



- Need to deplete leukemic cells before expansion
- Ineffective expansion through inhibitory mechanisms
- Possible contaminating leukaemic cells in product

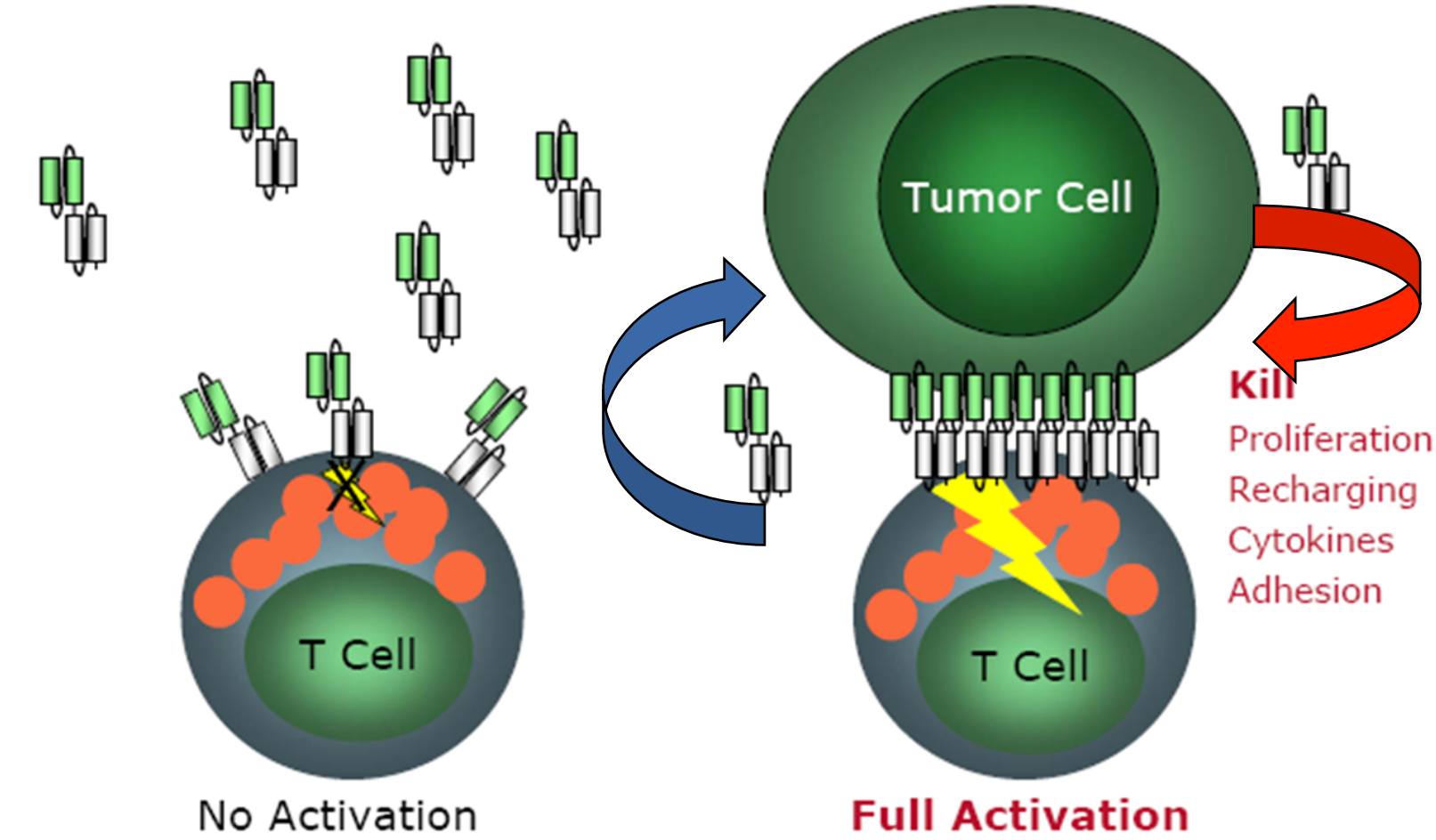


BiTE antibodies (bipsecific T cell engaging)

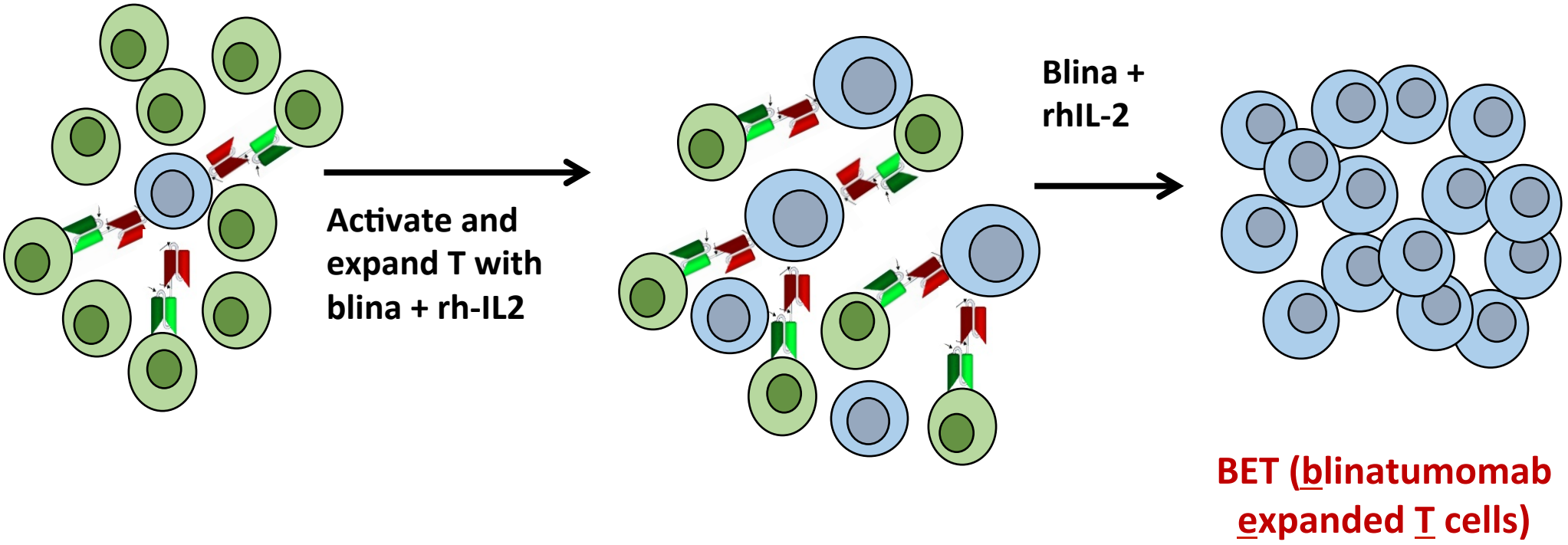


Baeuerle and Reinhardt Cancer Res 2009

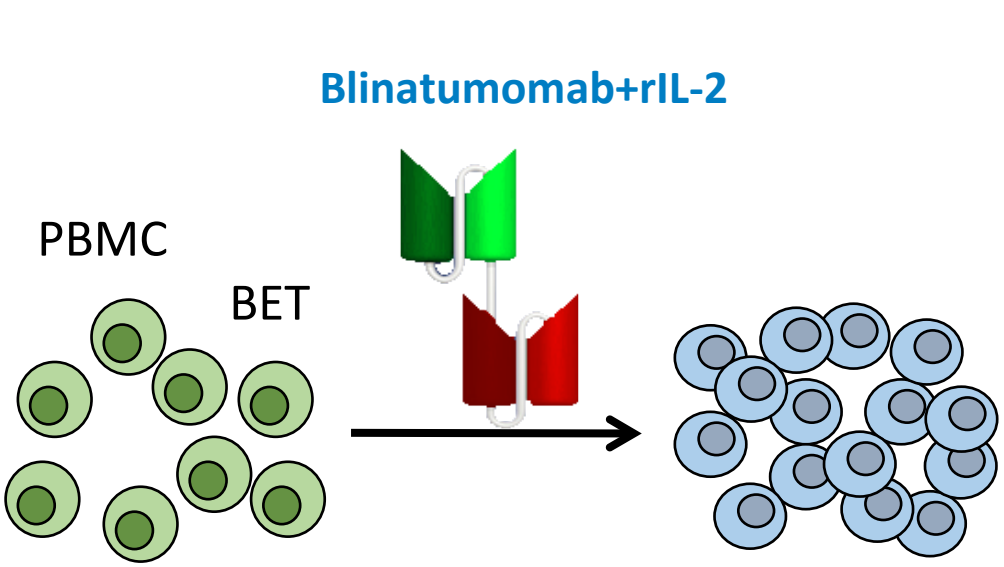
cells are activated and become cytotoxic only in presence of BiTE + target cells

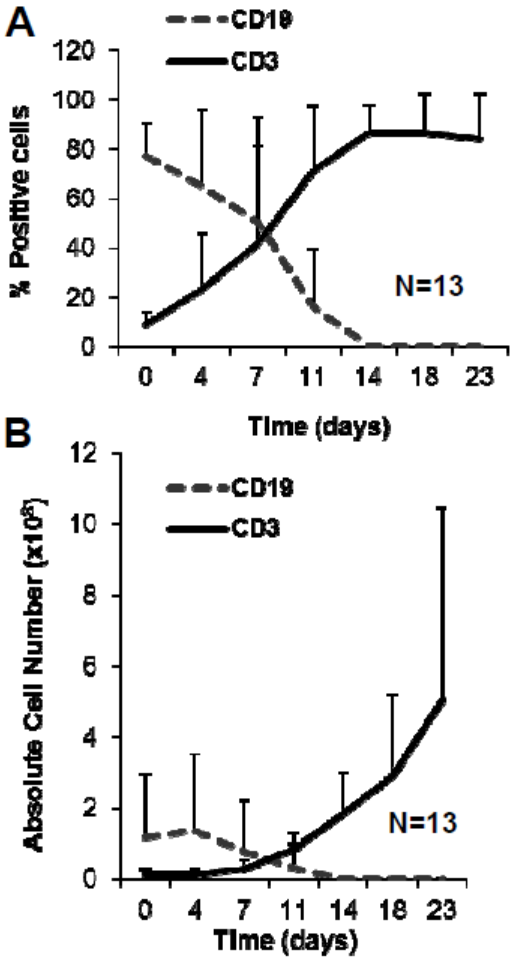


blinatumomab to expand T cells and eradicate CLL



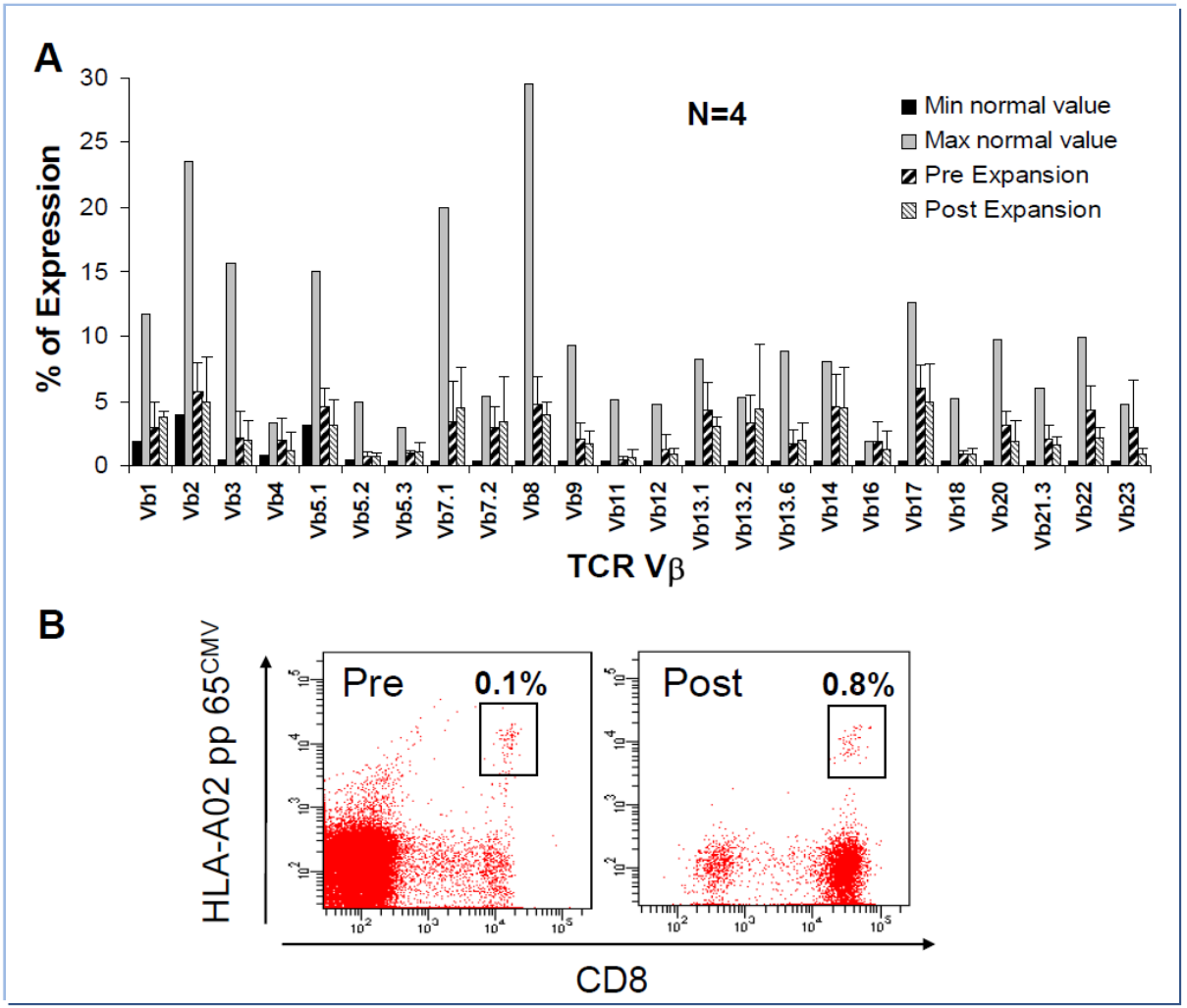
xpansion of T cells from CLL patients using blinatumomal and rhIL-2





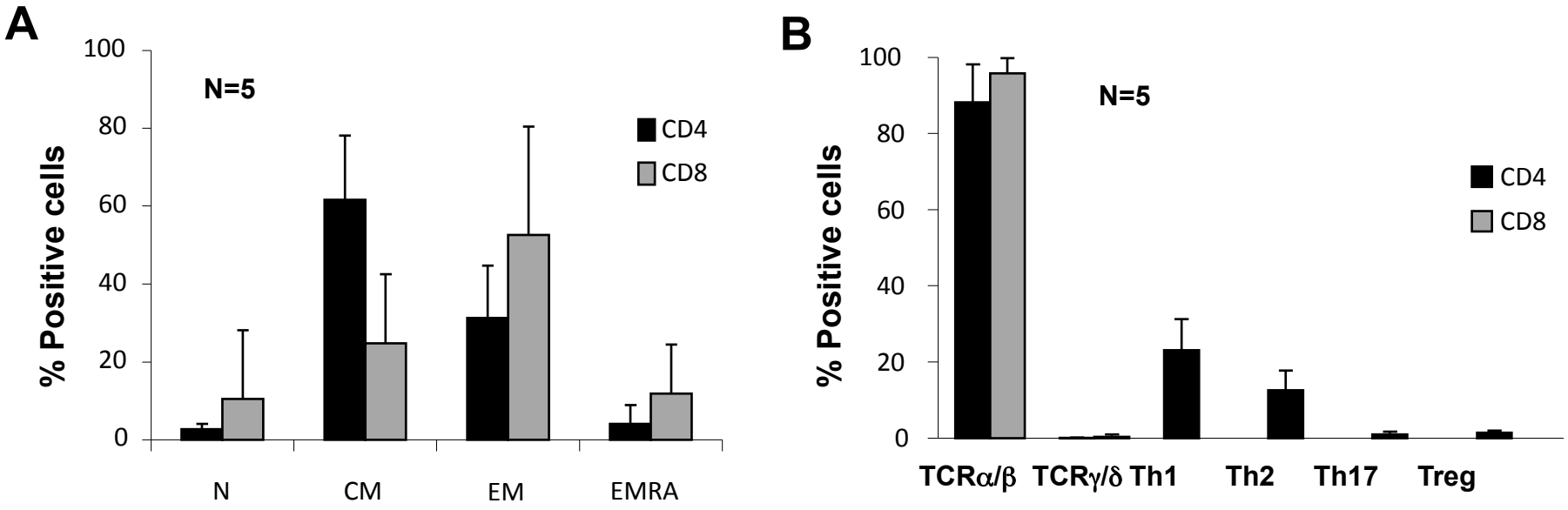
Golay J et al, The Journal of Immunology, 2014, 193: 4739–4747.

linatumomab Expanded T cells (BET) are polyclonal and contain virus specific T cell clones



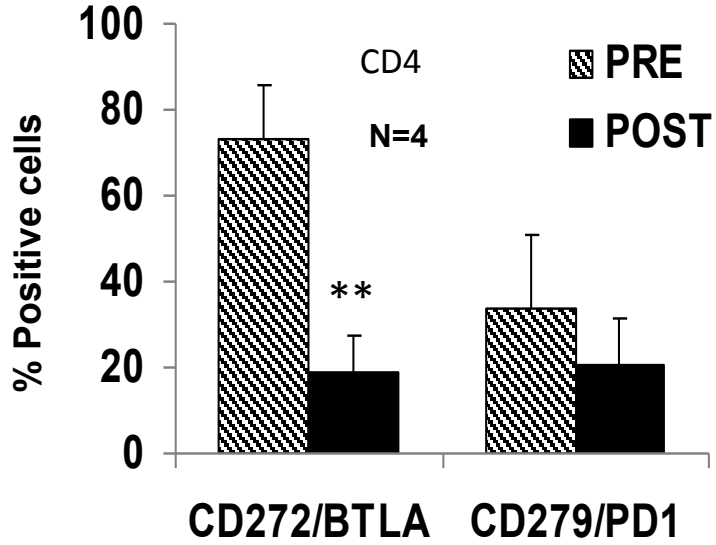
olay J et al, The Journal of Immunology, 2014, 193: 4739–4747.

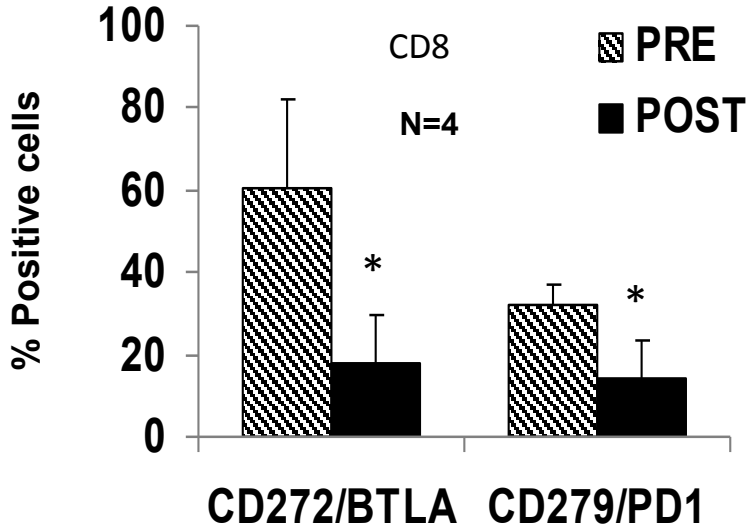
BET are mostly αβ-T cells with memory and effector memory and Th1 phenotype



Golay J et al, The Journal of Immunology, 2014, 193: 4739–4747.

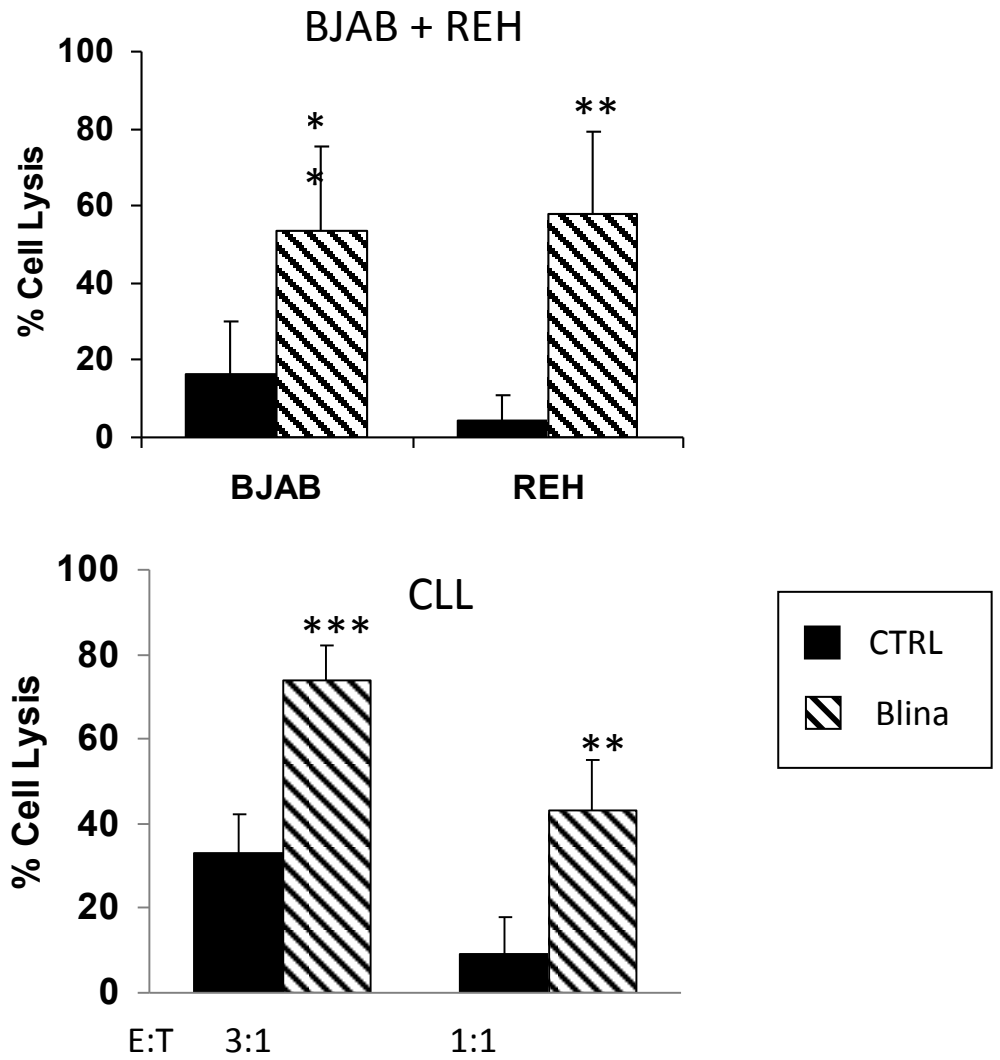
T have down-modulated inhibitory molecules CD272/BTLA and CD279/PD-1 normally overexpressed on CLL T cells





Golay J et al, The Journal of Immunology, 2014, 193: 4739–4747.

BET are cytotoxic against B lymphoma cell lines and CLL in presence of blinatumomab in vitro



Golay J et al, The Journal of Immunology, 2014, 193: 4739–4747.

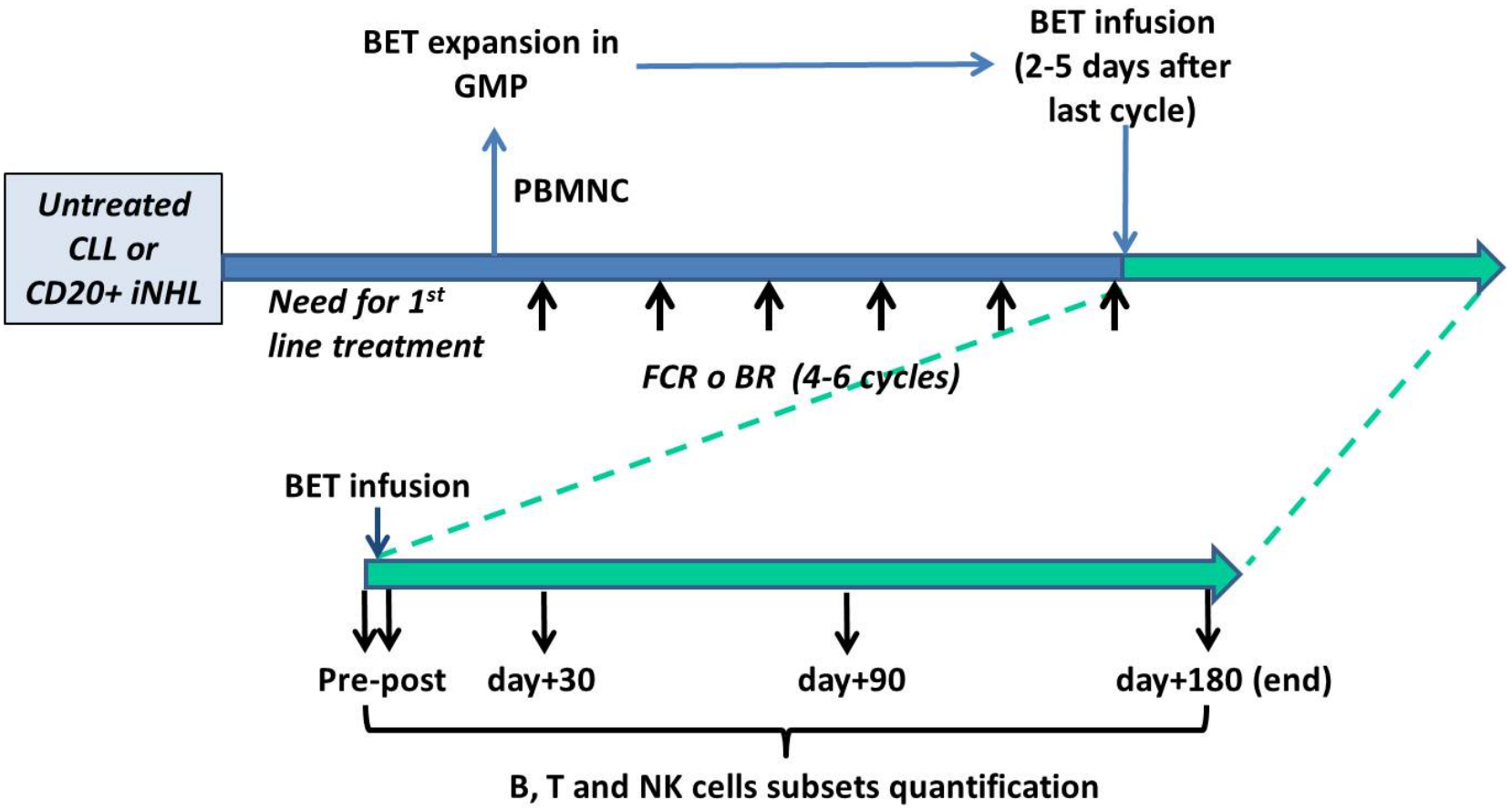
Immune Reconstitution with Blinatumomab Expanded T-cells (BET) After First-line eatment with Fludarabine-Cyclophosphamide-Rituximab or Bendamustine-Rituximab 20+ Indolent Non-Hodgkin Lymphomas/Chronic Lymphocytic Leukemia: a Phase I Stu

IMP Identifiers:	Blinatumomab Expanded T-cells (BET)
Protocol Number:	FROM-BET.1 2017-02
EudraCT Number:	2017-003030-87
Protocol Version (Date):	V 1.0; 16 – July--2017
Sponsor:	Ospedale Papa Giovanni XXIII di Bergamo
Study Design	Phase I open-label, single center study
Patient population	adult patients with indolent non-Hodgkin lymphomas (iNHL) or CLL

Planned study timelines

- Duration of enrolment: 30 months
- Expected FPI: February 2018
- Expected LPO: August 2020
- Expected LPLV: August 2020
- Duration of whole study (from FPI to LPLV): 36 months

Immune Reconstitution with Blinatumomab Expanded T-cells (BET) After First-line Treatment with Fludarabine-Cyclophosphamide-Rituximab or Bendamustine-Rituximab in CD20+ Indolent Non-Hodgkin Lymphomas/Chronic Lymphocytic Leukemia: a Phase I Study

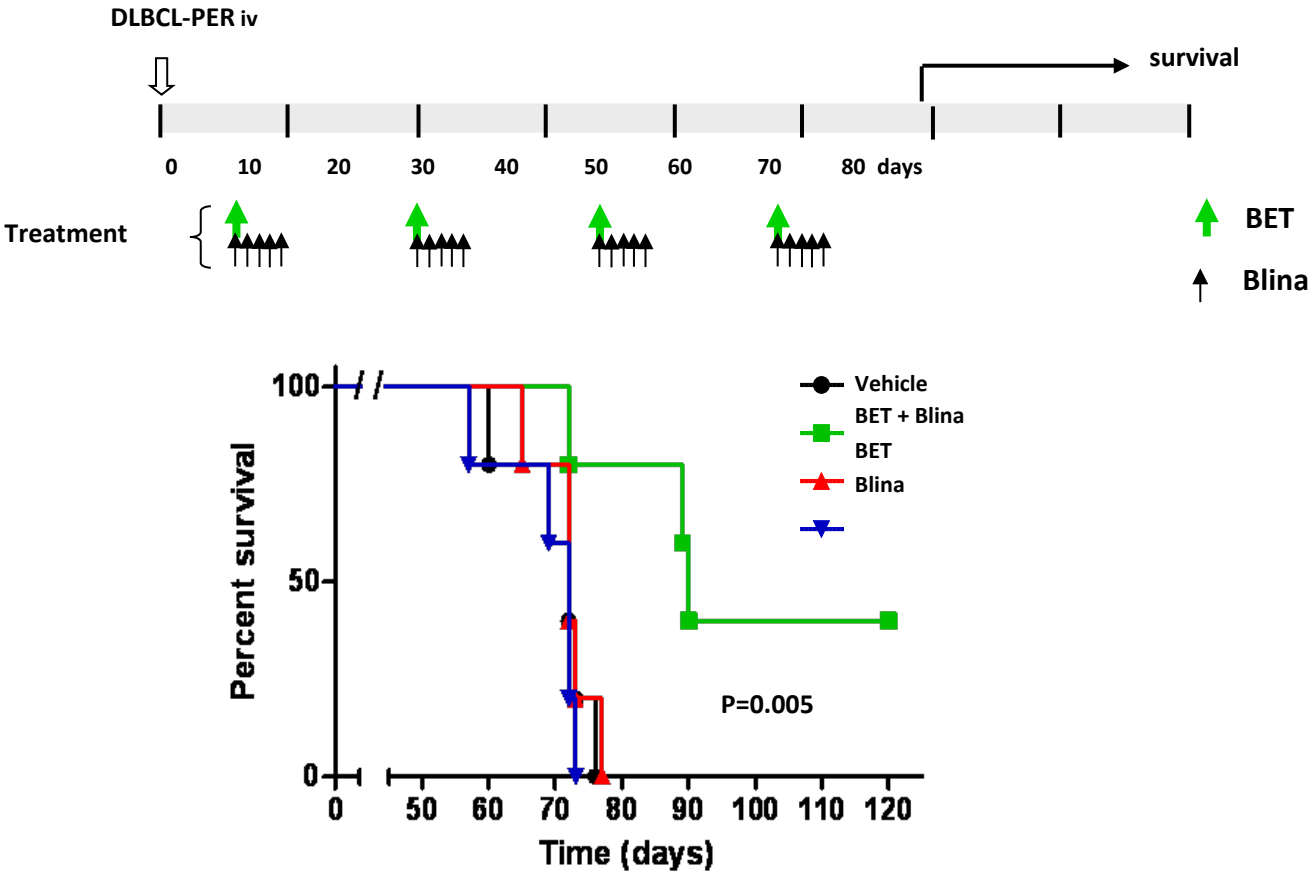


Primary endpoint

ssessment of Dose Limiting Toxicities

– DLTs, defined as any grade 3 or 4 events that are considered by the investigator to be at least possibly related to therapy) observed during 14 days after BET infusion: four escalating dose coho will be evaluated and monitored for DLTs (and safety) in order to define MTD.

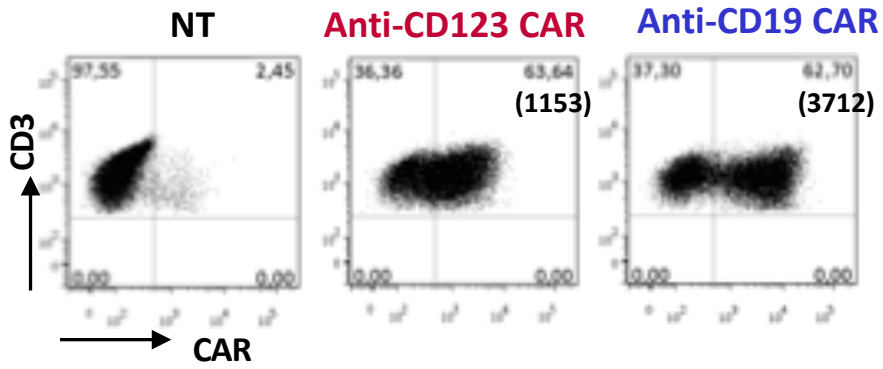
Combined Treatment with BET and Blinatumomab



Golay J et al, The Journal of Immunology, 2014, 193: 4739–4747

A non-viral CART cell approach using an improved SB platform: results

Over 60% (up to 90%) of stable CAR expression in CD3⁺ CIK cells



gnani CF, et al. Oncotarget 2016;7:51581–97.
le courtesy of Prof Andrea Biondi