Neoplasias Hematológicas tratadas com imunoterapia

Breno Moreno de Gusmão

Hospital Israelita Albert Einstein

BP, a Beneficência Portuguesa de São Paulo

bgusmao@hotmail.com

Hematologia ⟷ Imunologia

Doenças Hemato - Benignas

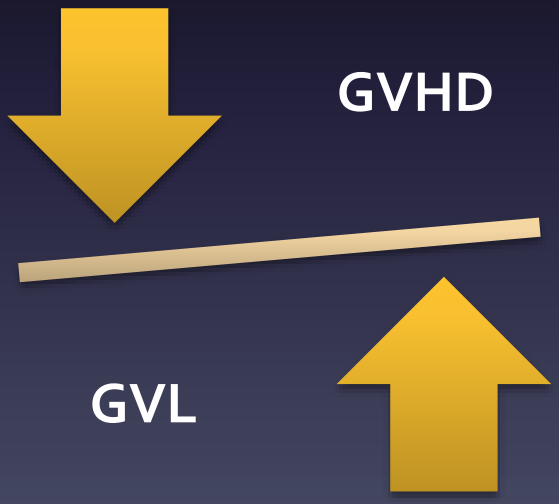
- PTI
- AHAI
- Sínd. Linforoliferativos benignos

Medicina Transfusional

- Politranfusão
- PTT
- Outras Doenças - Plasmerese

Transplantes de Cel Tronco

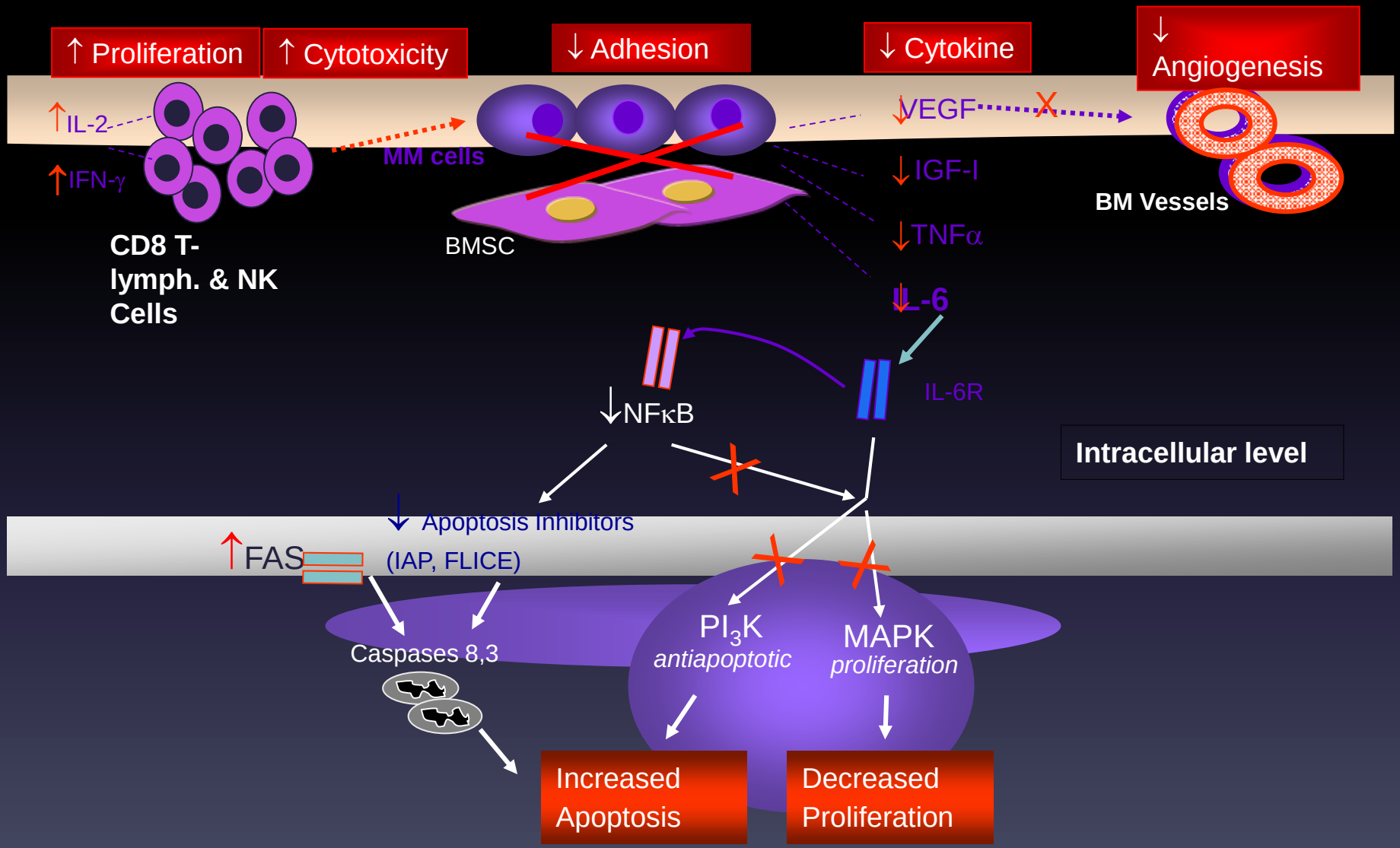
- 1968 – E. Donnal Thomas
- Modelo de imunoterapia
- Diferentes fontes e tipo de transplantes
  - Medula , SP, cordão , Dual
  - Alogênico
    - Aparentado
    - Não aparentado
    - Cordão umbilical
    - Haploidêntico



Imunoterapia Neoplasias Malignas

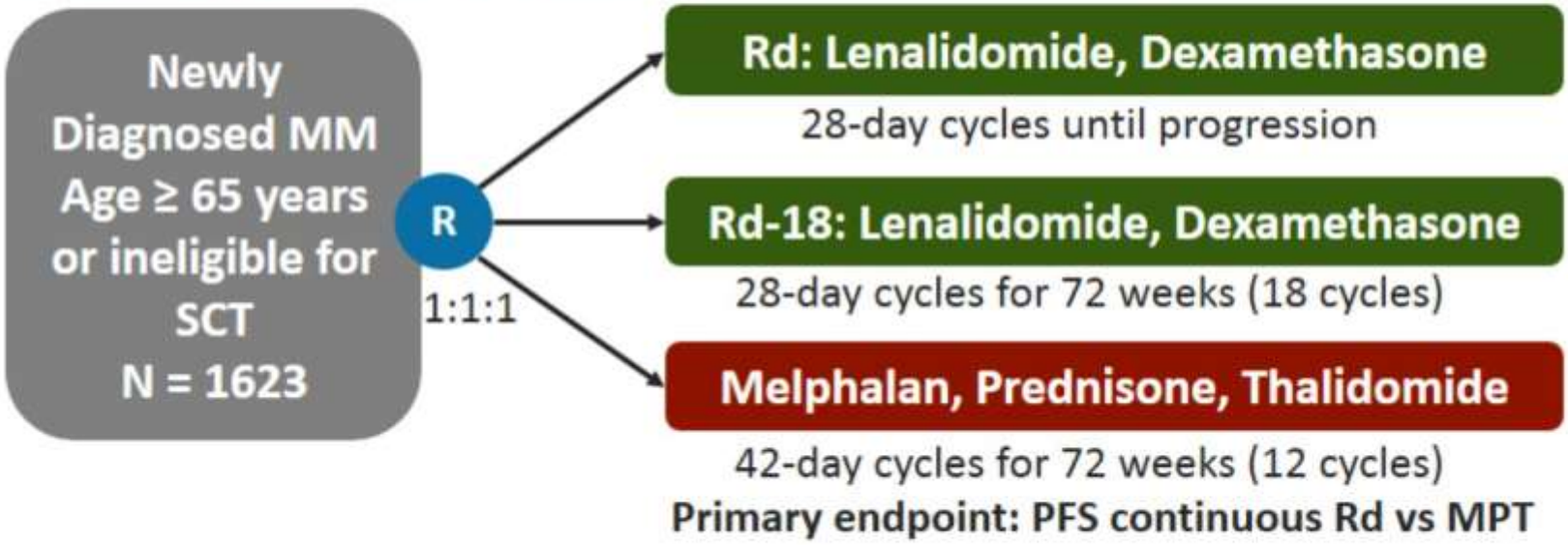
- Neoplasias Mieloides
  - SMD
  - LMA
- Neoplasias Linfoides
  - Linfomas
  - LLA
- Discrasias de Cel Plasmocitarias
  - Mieloma multiplo
  - Amiloidose

Lenalidomide: Mechanism of Action



San Miguel J. Hematol J. 2003;4 Suppl 3:201-7.

FIRST Trial
Continuous Rd vs Rd-18 vs MPT



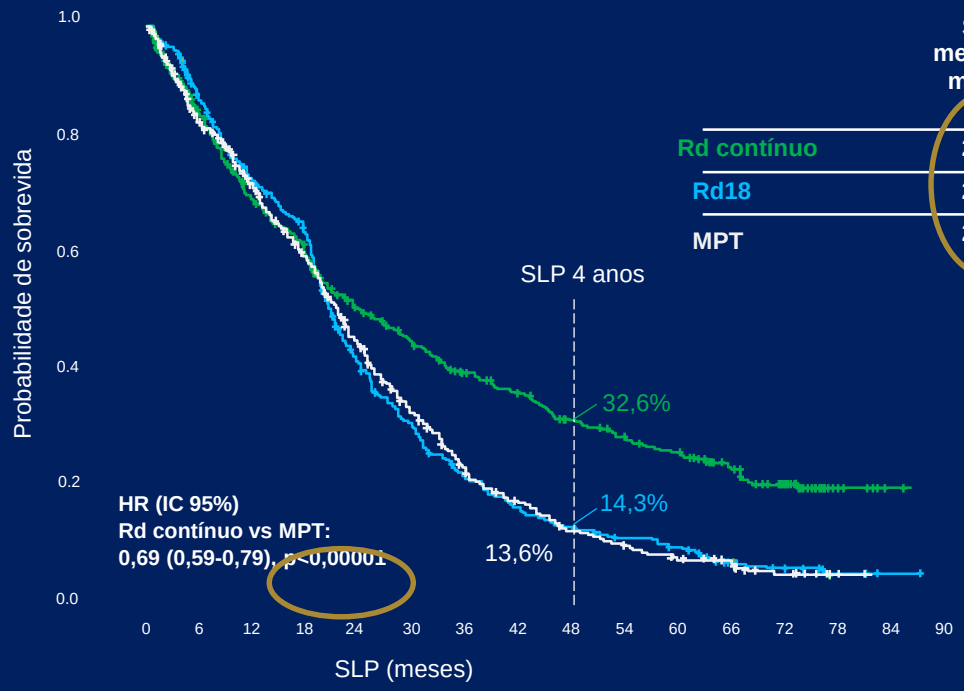
	Rd	Rd-18	MPT	HR; *P* value (Rd vs MPT)
Median PFS, mo	26	21	22	0.69; .00031
3-y OS, %	70	66	62	
High-risk, %	41	40	47	
4-y OS, %	59	56	51	0.78; .02
ORR, %	75	73	62	

Median follow-up: 37 mo

Benboubker L, et al. *N Engl J Med*. 2014;371:906-917; Avet-Loiseau H, et al. *Blood*. 2015;126. Abstract 730.

ESTUDO FIRST: Sobrevida livre de progressão

SLP FAVORÁVEL PARA PACIENTE COM TRATAMENTO CONTÍNUO



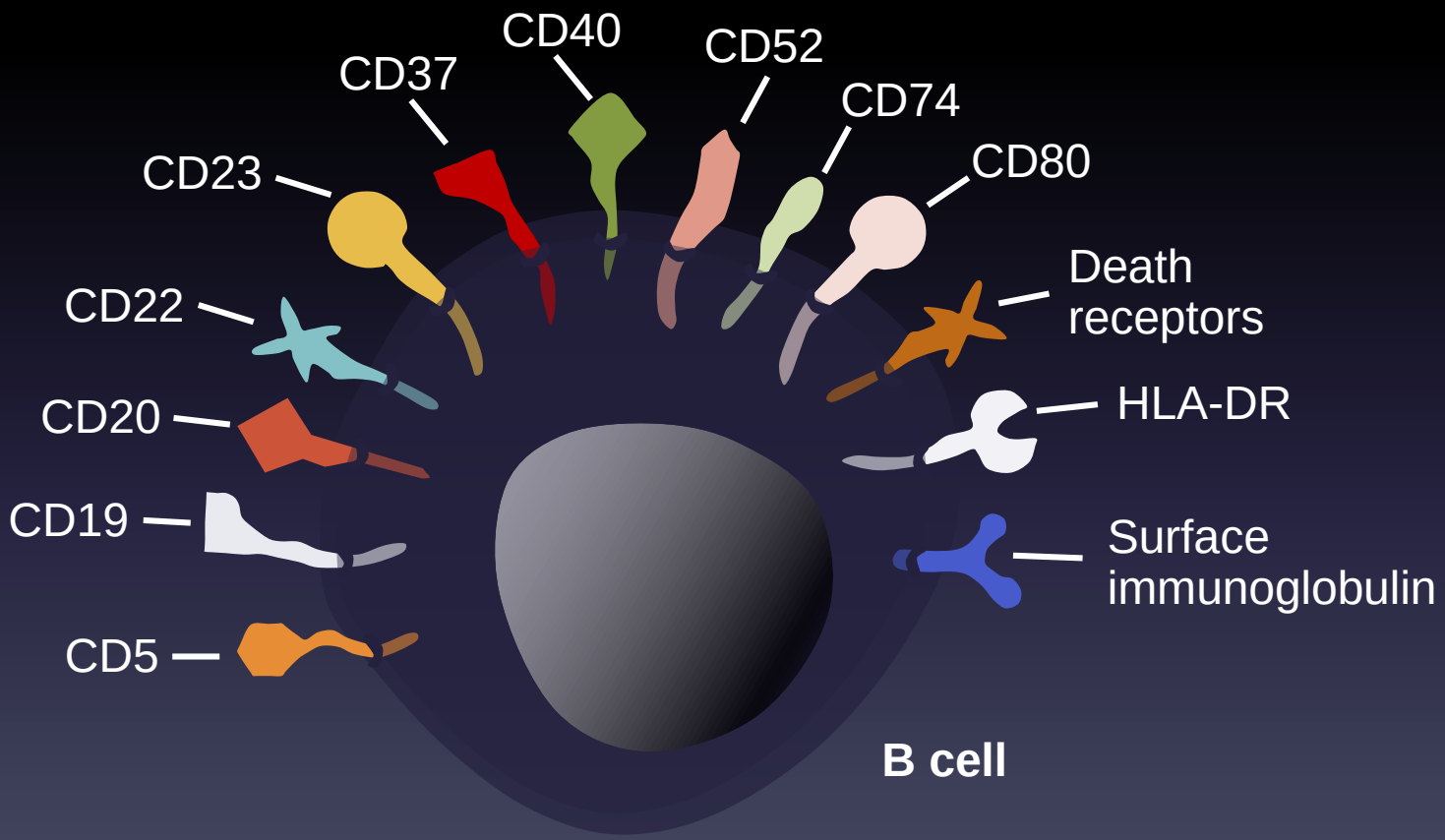
	SLP mediana, meses	SLP 4 anos, %
Rd contínuo	26,0	32,6
Rd18	21,0	14,3
MPT	21,9	13,6

N:1623

Bahlis N, et al. EHA abstr P277, 2015.

LLC e Linfomas

Potential Antibody Targets for B-Cell Lymphomas



Cheson BD, et al. N Engl J Med. 2008;359;613-626.

Maturação das células B normais e expressão do CD20

IMUNOTERAPIA - LLC

Landmark Phase 3 Trials: CLL8: FC vs FCR

First-line therapy (n = 817)

- Fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 days 1-3
- +/- rituximab 375 mg/m^2 cycle 1 then 500 mg/m^2 cycles 2-6

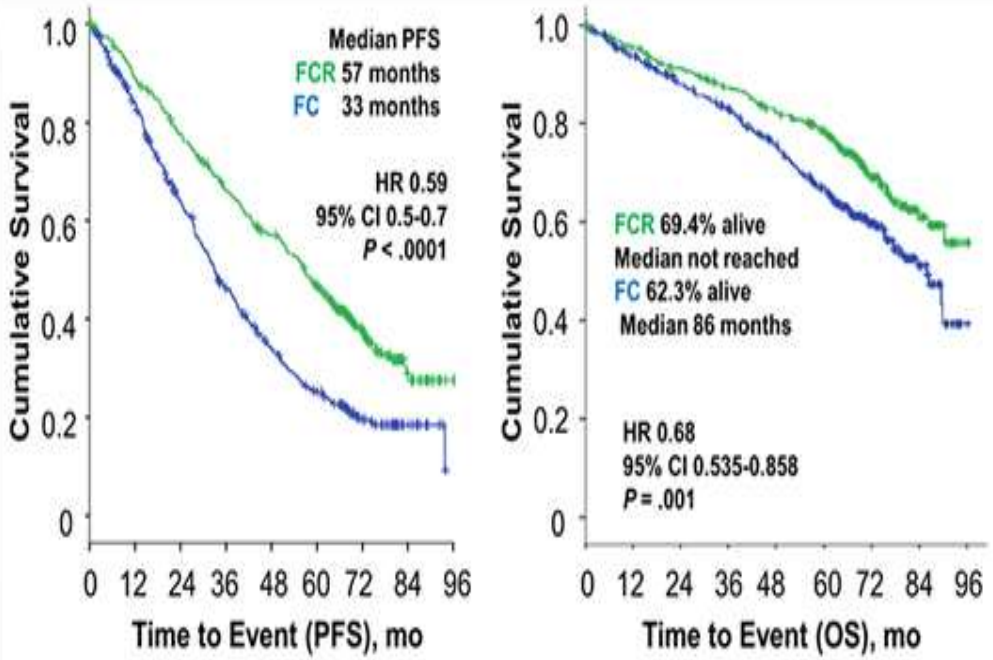
Clinical characteristics:

- Median age 61 years (71% age < 65 years)

	FC	FCR	*P* Value
ORR	88%	95%	< .01
CR	22%	44%	< .01
Grade 3/4 AE	63%	77%	< .0001
Grade 3/4 infect	22%	26%	.18

llek M, et al. *Lancet*. 2010;376:1164-1174.[48]

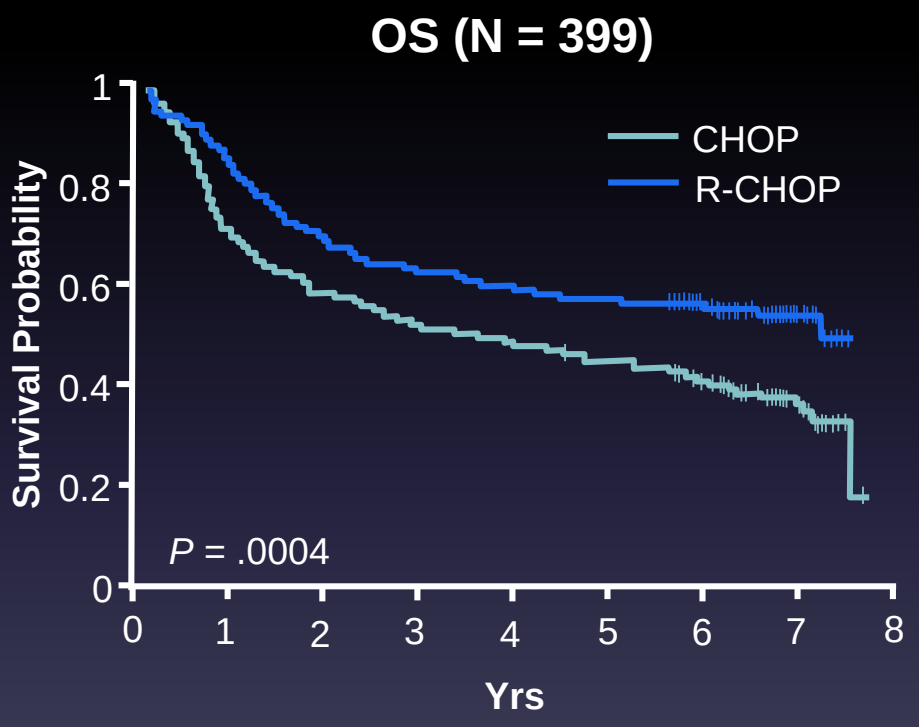
Update PFS CLL8 Trial: F/U 5.9 years



Despite indolent and recurrent nature of CLL, efficient first-line treatment is important

Fisher K, et al. *Blood*. 2012;120: Abstract 435.[49]

CHOP ± Rituximab in DLBCL: 7-Yr Survival Results (GELA LNH-98.5 Study)



Parameter, %	Low Risk	High Risk
Age, < 70 vs ≥ 70 yrs	58.0	49.0
LDH, NI vs > NI	69.0	45.0 *
Stage, I/II vs III/IV	67.0	50.0
Bone marrow, yes vs no	60.0	34.5 *
Tumor size, < 10 vs ≥ 10 cm	60.0	36.5
β_2-microglobulin, NI vs > NI	64.5	39.0 *
Serum albumin, ≥ 35 vs < 35 g/L	60.0	40.0

*P < .05 (multivariate analysis).

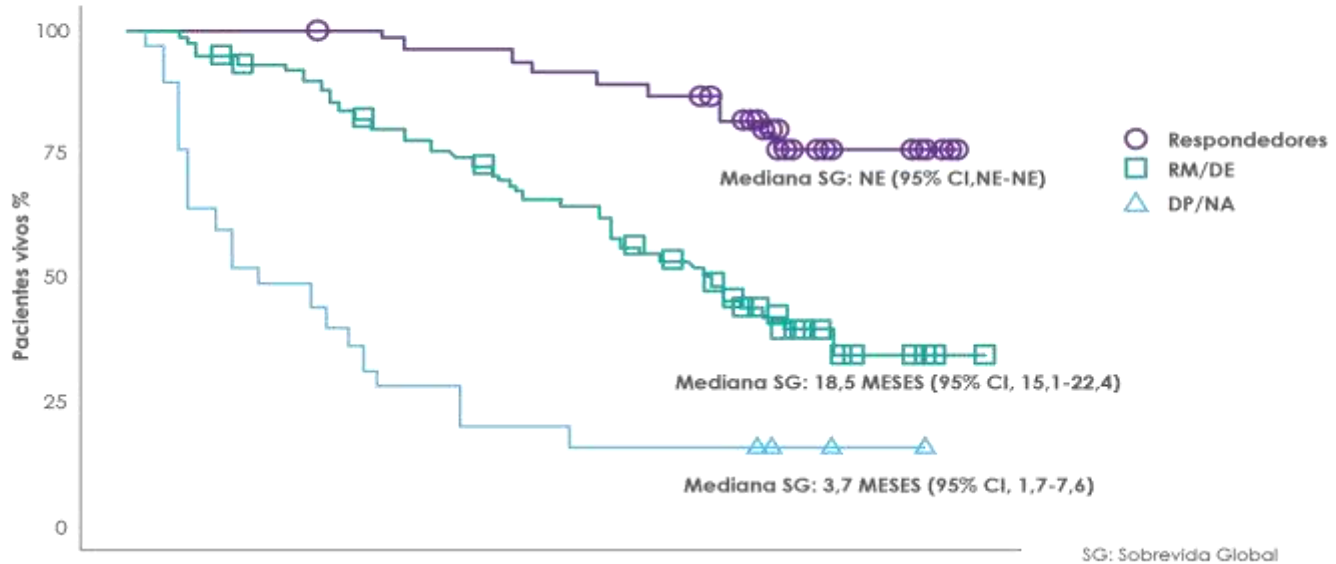
Coiffier B, et al. ASCO 2007. Abstract 8009.

Mieloma Múltiplo

First Randomized Trial in MM: 1962

- A controlled trial of urethane treatment in multiple myeloma.
- Randomized 83 patients with treated or untreated multiple myeloma to receive *urethane* or a placebo consisting of a cherry- and cola-flavoured syrup.
- No difference was seen in objective improvement or in survival in the two treatment groups. In fact, the urethane-treated patients died earlier

DARATUMUMAB em monoterapia: SG em respondedores e não respondedores

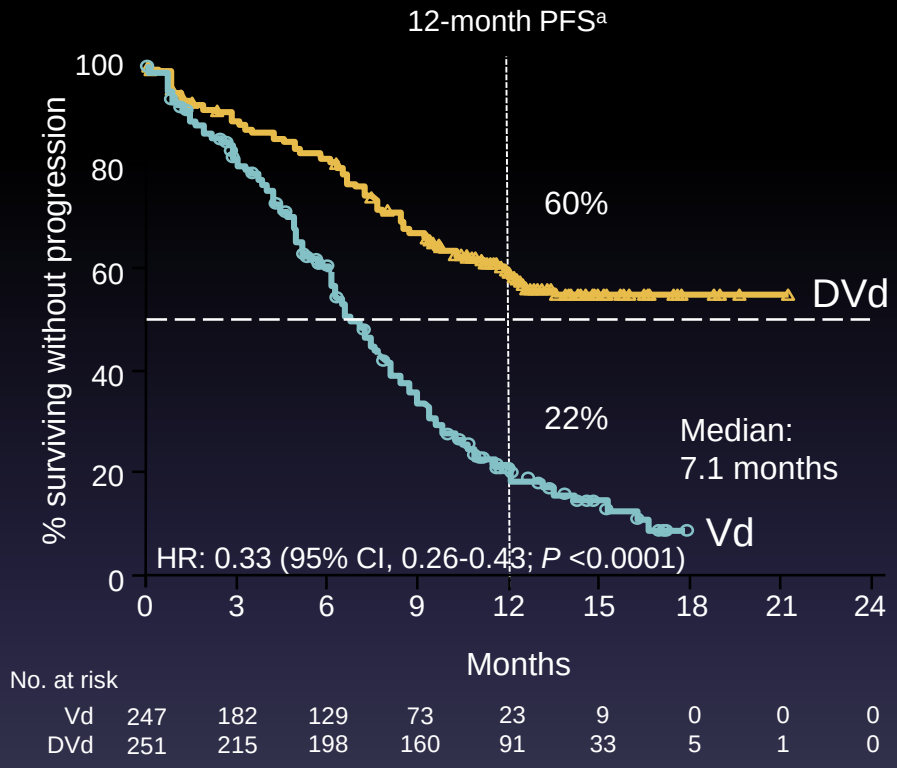


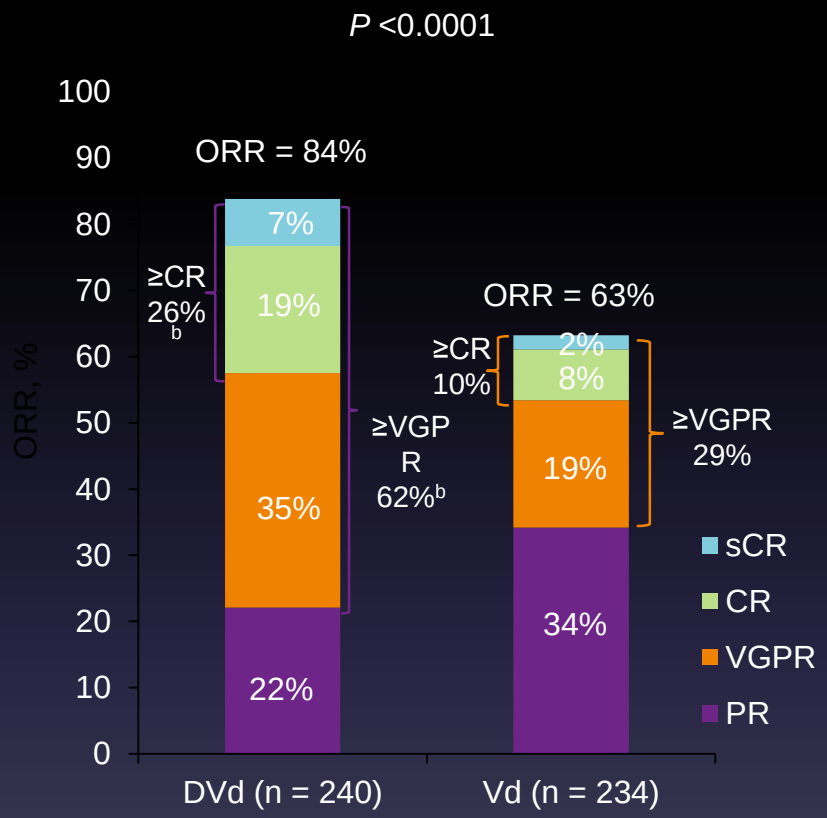
Adaptado de Usmani et al, Blood 2016.

Mediana de acompanhamento: 20.7 meses[1]

Adaptado de Usmani SZ et al. Blood. 2016.

CASTOR STUDY : Updated Efficacy - ASH 2016



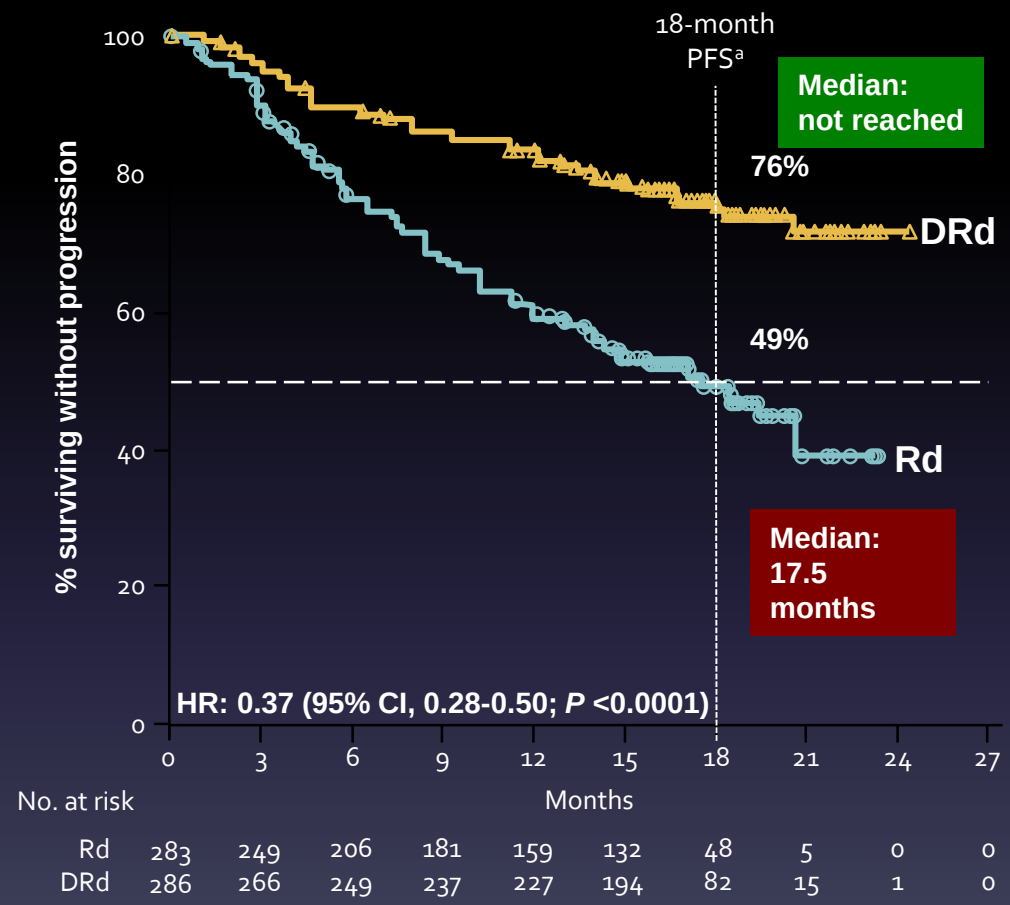


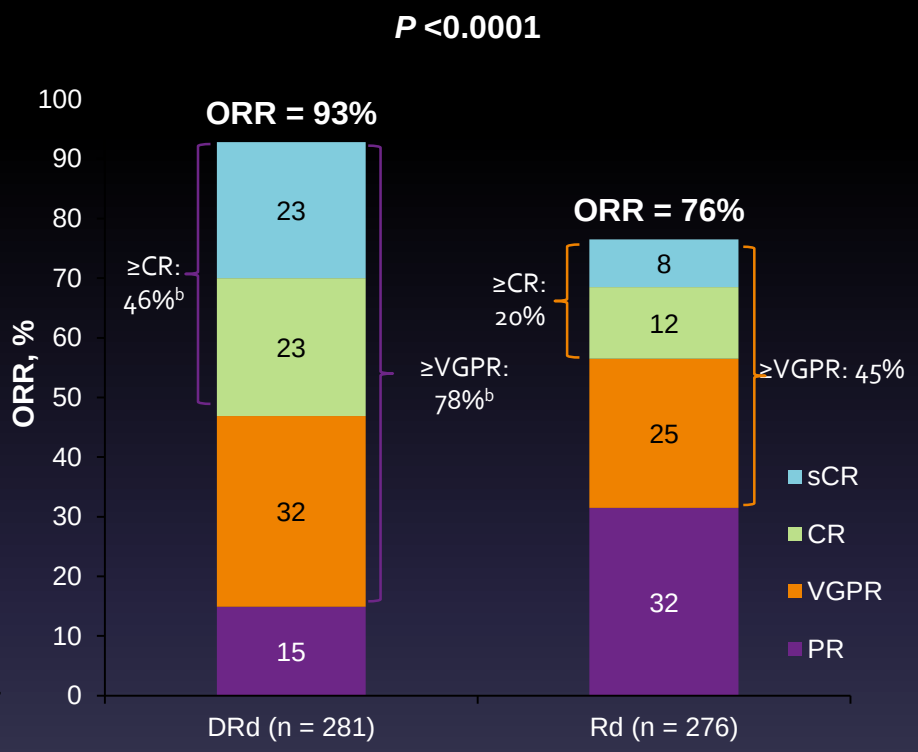
- Median (range) follow-up: 13.0 (0-21.3) months
- An additional 7% of patients receiving DVd achieved ≥CR with longer follow-up

Responses continue to deepen in the DVd group with longer follow-up

ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DVd versus Vd.

POLLUX STUDY : RD +/- DARA . Updated Efficacy ASH 2016



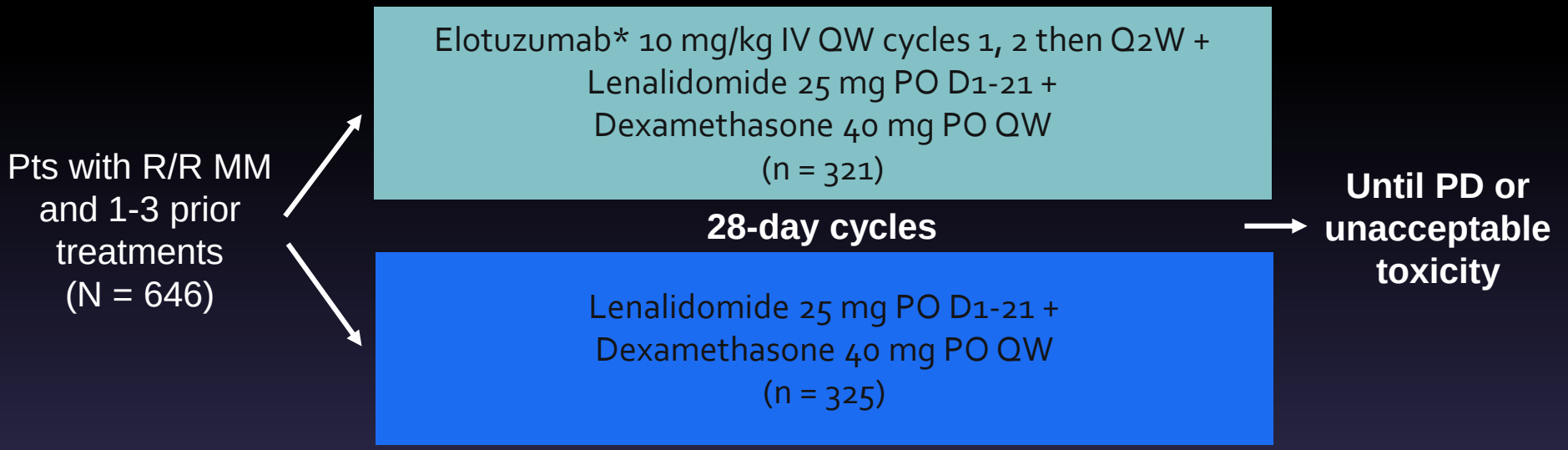


Responses continue to deepen in the DRd group with longer follow-up

HR, hazard ratio; CI, confidence interval; sCR, stringent complete response; PR, partial response; ITT, intent-to-treat.
Note: PFS = ITT population; ORR = response-evaluable population.
[a]Kaplan-Meier estimate.
[b]*P* <0.0001 for DRd vs Rd.

ELOTUZUMAB - ELOQUENT-2 Study

Randomized, open-label, multicenter phase III trial



**Prophylactic medication administered prior to elotuzumab to mitigate infusion -related reactions.*

- Primary endpoints: PFS, ORR
- Secondary endpoints: OS, safety, DoR, health-related QoL
  - Threshold for interim OS significance: $P = 0.014$

Dimopoulos MA, et al. ASH 2015. Abstract 28.

ELOQUENT-2: Efficacy

Outcome	Elotuzumab + Len/Dex (n = 321)	Len/Dex (n = 325)	HR (95% CI)
PFS			
▪ Median, mos	19.4	14.9	0.73 (0.60-0.89; P = .0014)
▪ 1 yr, %	68	57	
▪ 2 yrs, %	41	28	
▪ 3 yrs, %	26	18	
Median time to next treatment, mos	33	21	0.62 (0.50-0.77)
ORR, %	79	66	
Interim OS, mos	43.7	39.6	0.77 (0.61-0.97; P = .0257)

- PFS benefit seen with elotuzumab in all predefined subgroups

Dimopoulos MA, et al. ASH 2015. Abstract 28.

Indatuximab Ravtansine (BT062) in Combination with Low-Dose Dexamethasone and Lenalidomide or Pomalidomide: Clinical Activity in Patients with Relapsed / Refractory Multiple Myeloma

- BT062 is an antibody-drug conjugate comprising a CD138-binding chimerized antibody and the cytotoxic maytansinoid, DM4. It is designed to target and kill CD138-positive cancer cells
- To evaluate the safety and activity of BT062 (on days 1, 8, and 15 in a 4-week cycle) used in combination with dex (20-40 mg on days 1, 8, 15, and 22) and Len (25 mg, daily on days 1-21) or Pom (4 mg, daily on days 1-21) in patients with relapsed/refractory MM
- 47 PTS BT062/LEN/DEX : ORR of 77% and DOR of 21.0 months.
- 17 pts BT062/POM/DEX, all had prior exposure to both Len and Bort and progressed on or within 60 days of their last therapy. ORR was 79%, with 4 VGPR and 7 PR . Median PFS has not been reached after 7.5 months median follow up, with 7 patients still on treatment

Kevin R. Kelly et al , ASH 2016 - Abstract 4486

Pembrolizumab/Pomalidomide/Dexamethasone for R/R MM:

Response, %	Full Efficacy Population (N = 45)	Refractory to 2 Classes (n = 32)	High-Risk Cytogenetics (n = 27)
ORR	65	68	56
Clinical benefit	72	69	60
Best response			
▪ sCR	7	3	7
▪ CR	2	3	4
▪ VGPR	20	18	4
▪ PR	36	44	41
▪ MR	7	3	4
▪ SD	23	22	31
▪ PD	5	4	7
sCR + CR + VGPR, %	29	24	15

Badros AZ, et al. ASH 2016. Abstract 490.

Pembrolizumab treatment in RRMM

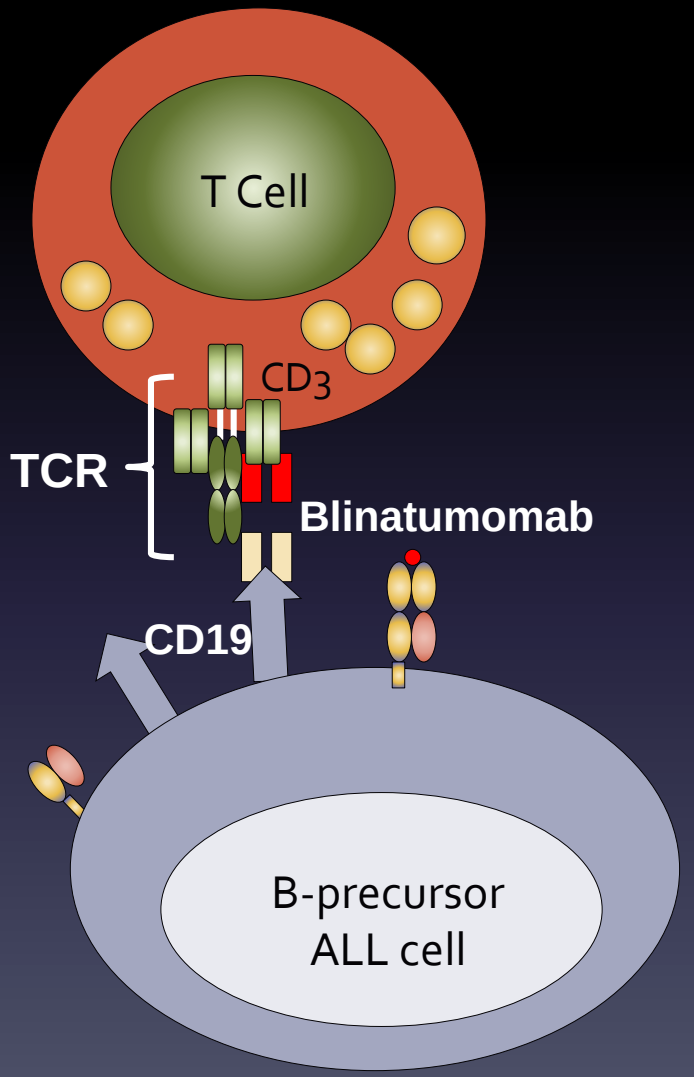
	KEYNOTE 23 (phase I)[1] **Pembro – Len - Dex**	**Phase I / II [2]** **Pembro – Pom – Dex**
Study design	Pembro 200mg/ 2qw LEN 25mg 1-21 Dex 40mg weekly	Pembro 200mg/ 2qw Pom 4mg 1-21 Dex 40mg weekly
Patient population	> 2 prior lines PI & IMID exprosure	> 2 prior lines - RRMM PI & IMID exprosure
ORR	Efficacy Population (n=50) 44% Len – refract = 35% Median PFS 7.2m	Total (n=38) ORR 66% Double Refractory 65 % PFS 14m

1. Ocio et al, ASCO 2017 2. Bardros et al , ASH 2016 oral presentation

LLA

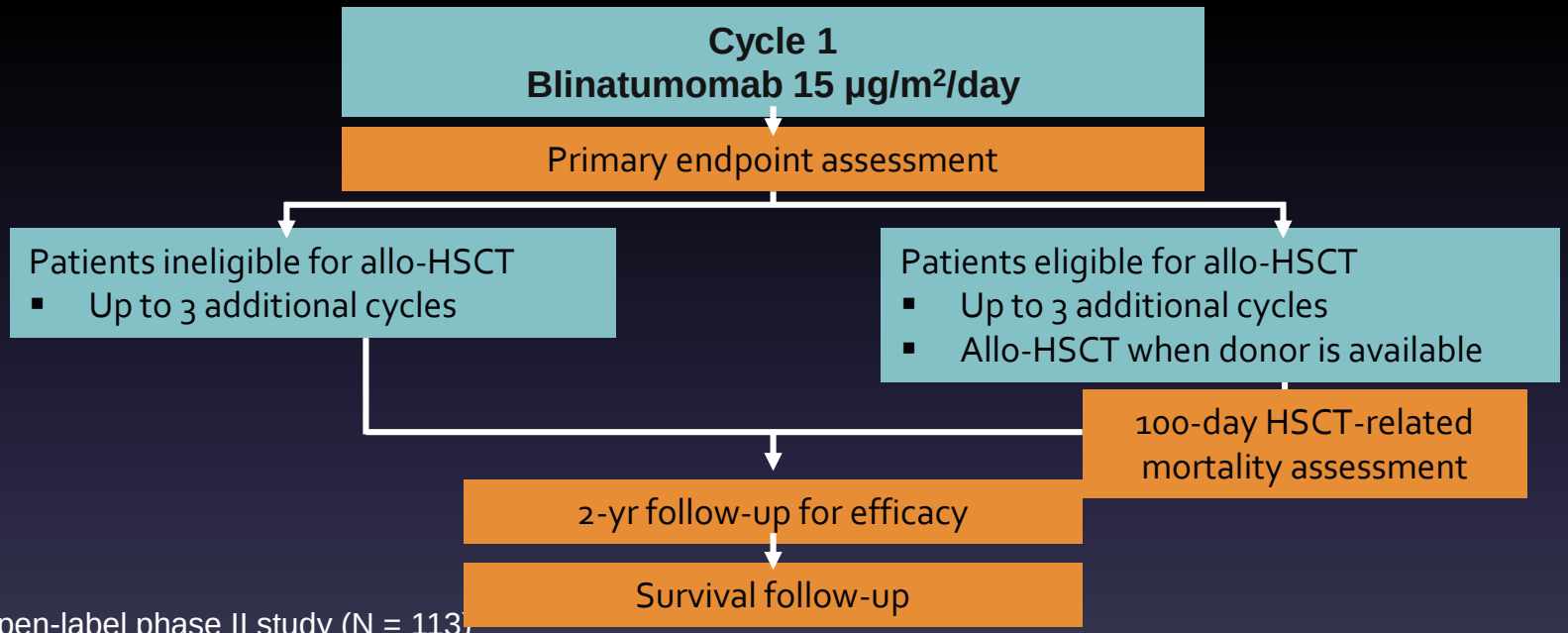
Blinatumomab: Bispecific T-Cell Engager Antibody MOA

- Blinatumomab[1]
  - Blinatumomab: bispecific T-cell engager antibody construct that directs cytotoxic T cells to CD19-positive cells, resulting in serial lysis[2]
  - CD19: highly specific B-cell marker expressed throughout B-cell development and in >90% of B-cell lineage cancers[3]
  - Blinatumomab was approved in December 2014 by the FDA to treat pts with Ph- precursor B-cell ALL



1. Gökbuget N, et al. ASH 2014. Abstract 379.
2. Bargou R, et al. Science. 2008;321:974-977.
3. Raponi S, et al. Leuk Lymphoma. 2011:52;1098-1107.

BLAST: Blinatumomab in MRD+ Patients With ALL in Hematologic CR



Open-label phase II study (N = 113)

- Blinatumomab was given by continuous IV infusion, 15 µg/m²/day x 28 days per cycle, for 4 wks on/2 wks off (one cycle) for a maximum of up to 4 cycles
  - All eligible patients received HSCT after the first cycle
  - Primary endpoint: complete MRD response after 1 cycle (MRD- with no PCR amp)

Gökbuget N, et al. ASH 2014. Abstract 379

BLAST: MRD Response Within Cycle 1

MRD Response	Primary Endpoint Full Analysis Set (N = 113)			Primary Endpoint Efficacy Analysis Set (N = 103)		
	n	%	95% CI	n	%	95% CI
Patients with evaluable MRD	112	99		102	99	
Complete MRD response after cycle 1 (Primary endpoint)	88	78	69-85	82	80	71-87
MRD response after cycle 1 (exploratory endpoint)	96	85	77-91	88	85	77-92

- 2 patients who achieved an MRD response in cycle 1 achieved a complete MRD response after continued treatment in cycle 2
- Responses occurred in all subgroups including older pts and those with high MRD level

Gökbuget N, et al. ASH 2014. Abstract 379.

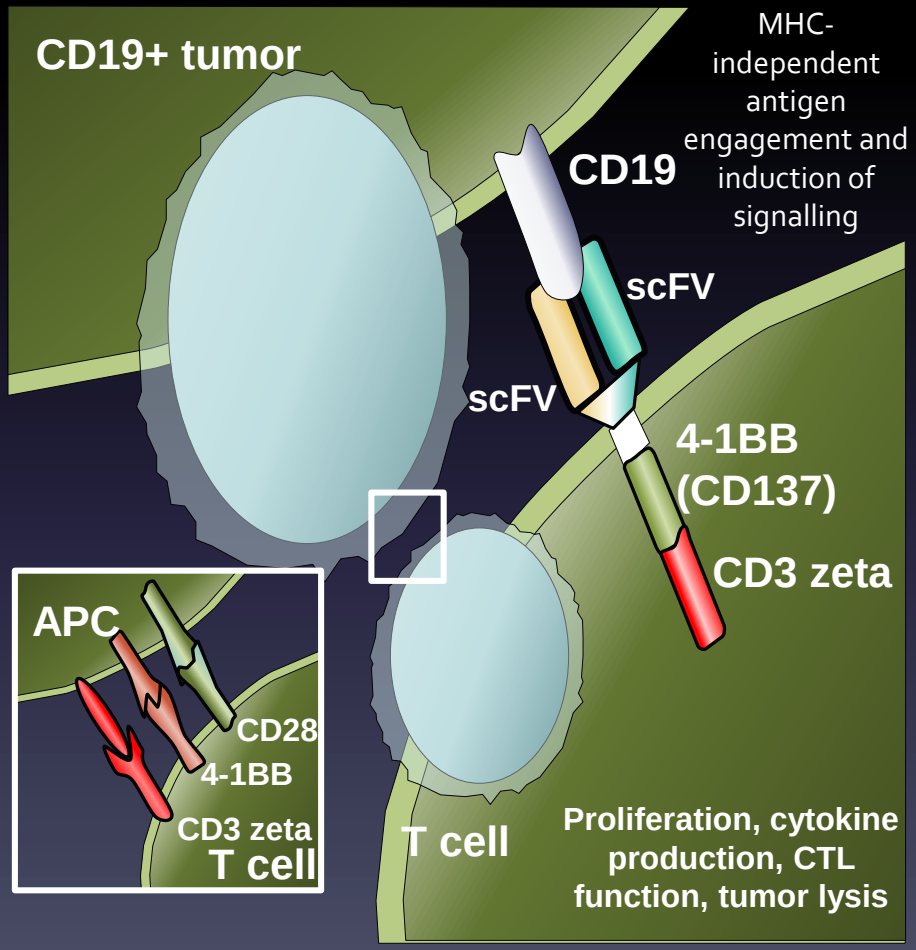
BLAST: Blinatumomab in MRD+ Pts With ALL in Hematologic CR: Conclusions

- Blinatumomab induced complete MRD response in 80% of patients with ALL who achieved hematologic CR but had persistent or recurrent MRD
  - Complete MRD response rate after 1 cycle: 78%
- Treatment interruptions due to treatment-related AEs in 28% of pts
- Primarily neurologic events, influenzalike symptoms
  - Most neurologic AEs grade 2 or less
- Further study required to assess effect of MRD response rate on clinical outcomes

Gökbuget N, et al. ASH 2014. Abstract 379.

Chimeric Antigen Receptors: MOA

- Chimeric antigen receptors[1]
  - Genetically engineered receptors that combine anti-CD19 single chain variable fragment of an antibody with intracellular signaling domains of T cells
  - With the use of lentiviral-vector technology, CTL019 T cells express a CAR with CD3 zeta and 4-1BB (CD137) signaling domains[2]



1. Grupp S, et al. ASH 2014. Abstract 380.
2. Maude SL, et al. N Engl J Med. 2014; 371:1507-1517.

CAR T-Cell Therapy (CTL019) in Relapsed/Refractory ALL in Pediatric Pts

- Phase I/IIa study in pediatric pts (N = 39) with relapsed/refractory ALL in ≥ second relapse
  - Previous allogeneic SCT: 69%
- Infusion of ex vivo–produced CAR T cells (CTL019 cells) back into pt to induce CD19-directed antitumor response
- Median follow-up: 6 mos (range: 1.5-31.0)

Grupp S, et al. ASH 2014. Abstract 380.

CTL019 in Relapsed/Refractory ALL: Results

- CTL019 induced CR in 92% of pts
- CR rates high regardless of disease burden at time of CTL019 infusion
  - > 50% blasts: 82%; > 5% blasts: 88%; < 0.01% to 5% blasts: 100%
- 10 pts (26%) relapsed after CR at 1 mo, 5 (13%) with tumors CD19+, 5 (13%) with tumors CD19(-)
- CTL019 therapy feasible post allogeneic SCT
  - No graft-vs-host disease noted
  - 3 pts (8%) proceeded to SCT
  - High levels of proliferating CTL019 cells detected up to 12 mos after infusion

Grupp S, et al. ASH 2014. Abstract 380.

Obrigado pela atenção

Breno Moreno de Gusmão

Hospital Israelita Albert Einstein

BP, a Beneficência Portuguesa de São Paulo

bgusmao@hotmail.com