¿Avances en LLA?

Ensayos clínicos con blinatumomab, inotuzumab y CAR-T cells

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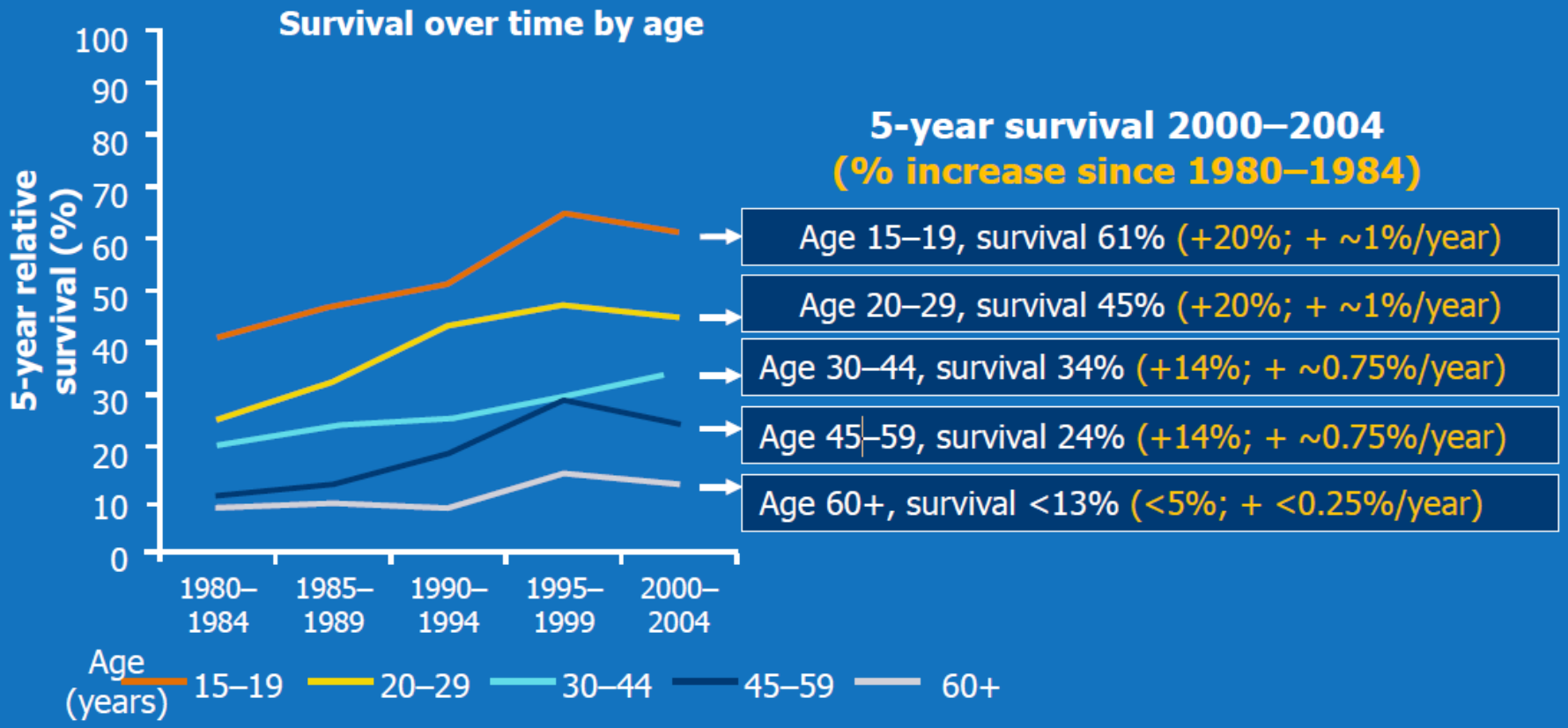
¿Avances en LLA?
Guía de la presentación

- Antecedentes: nuevos tratamientos necesarios
- Ensayos Blinatumomab
- Ensayos Inotuzumab
- Ensayos CAR-T cells
- Conclusiones

Supervivencia en LLA del adulto



Since 1980, there has been no significant improvement in survival rates in patients >60 years of age

Pulte D, et al. Blood 2009;113:1408–11

RC y SG en LLA del adulto

Referencia	Año	N	Edad, mediana	RC, %	SG
CALBG 9111	1988	198	35	85	50%, 3 años
SWOG 8417/8419	2001	353	32	62	35%, 8 años
NILG 08/96	2001	121	35	84	48%, 3 años
JALSG 93	2002	263	31	78	30%, 6 años
Sweden	2002	153	42	86	28%, 5 años
GIMEMA 02/86	2002	767	28	82	27%, 9 años
MDACC	2004	288	40	92	38%, 5 años
EORTC ALL3	2004	340	33	74	36%, 6 años
LALA 94	2004	922	33	84	36%, 5 años
GOELAL 02	2004	198	33	86	41%, 6 años
PETHEMA ALL-93	2005	222	27	82	34%, 5 años
GMALL 07	2007	713	34	89	54%, 5 años
MRC-ECOG	2008	1646	NR	90	39%, 5 años

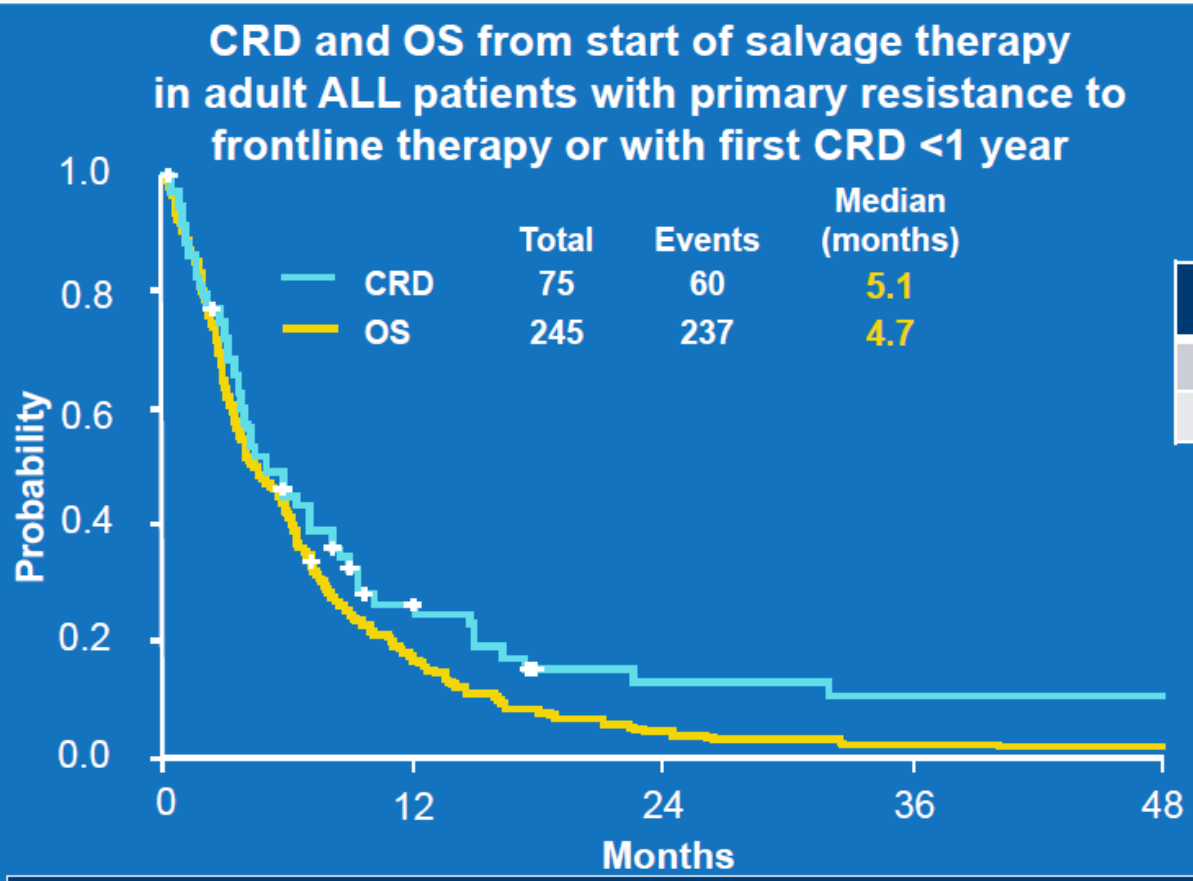
Bassan R, et al. J Clin Oncol 2011;29:532–43

Tratamiento de rescate Quimioterapia (Adultos)

Referencia	Año	Tipo LLA	Esquema	N	RC (%)	SG (mediana)
Schiller, et al	1993	LLA	IFOSFAMIDA + VP-16 + MTZ	11	73	7,7 m
Rosen, et al	2000	LLA-B, LLA Ph +	HiDAC + MTZ	31	23	4 m
Weiss, et al	2002	LLA	HiDAC + IDA	29	38	6 m
Reman, et al	2004	LLA-B	AMSA + IDAC-VP-16	40	40	5,4 m
Camera, et al	2004	LLA-B, LLA Ph +	IDA + IDAC + PDN	135	55	6,4 m
Specchia, et al	2005	LA-B, LLA-T, LLA Ph+	FLAG-IDA	23	39	4,5 m
Yavuz, et al	2006	LLA-B, LLA Ph +	FLAG-IDA	22	42	3 m
Candoni, et al	2006	LLA-B, LLA-T, LLA Ph+	DNR lip + Ara-C	25	80	39% a 1 a
Giebel, et al	2006	LLA-B, LLA-T, LLA Ph+	FLAM	50	50	12% a 2 a
Tedeshi, et al	2007	LLA	HiDAC + IDA	25	44	8 m
Faderl, et al	2011	LLA-B, LLA-T, LLA Ph+	Hyper-VAD ampliado	90	47	6,3 m

VP-16: etopósido; HIDAC: dosis altas de Ara-C; MTZ: mitoxantrone; IDA: idarubicina; AMSA: amsacrine; IDAC: dosis intermedias de Ara-C; PDN: prednisona; FLAG-IDA: fludarabina, Ara-C, G-CSF, idarubicina; DNR lip: daunorubicina liposómoca; FLAM: fludarabina, Ara-C, mitoxantrone; m: meses; a: años

Los resultados son muy malos en pacientes con resistencia primaria o una corta RC



Replased/Refractory	N = 245
Primary refractory disease	68
Duration of CR < 12 months	177

- **Median OS of 4.7 months overall**
- **Only 30% of patients achieved CR, which was generally of limited duration**

CRD, duration of complete remission

Kantarjian HM, et al. Cancer 2010;116:5568–74

Nuevos fármacos en la LLA

ANÁLOGOS DE NUCLEÓSIDO DE PURINAS	
Clofarabina	LLA (todas)
Nelarabina	LLA - T
Forodesina	LLA - T
ALCALOIDES DE LA VINCA	
Vincristina liposomal	LLA (todas)
INHIBIDORES DE KINASAS	
Inhibidores de ABL 1 Kinasa	
Dasatinib, Nilotinib, Imatinib, Ponatinib	*BCR-ABL1 +; BCR-ABL1 + like*
Inhibidores de Aurosa Kinasa	
MLN8237	*BCR-ABL1 +;*
Inhibidores de JAK	
Ruxolitinib, TG101348, CYT387	LLA con mutación JAK, *BCR-ABL1 + like*
Inhibidores de tirosin kinasa	
Lestaurtinib, Midostaurina, Sorafenib, …	Reordenamiento *MLL +*

Dr. Carlos Grande, 2014, Madrid

Nuevos fármacos en la LLA

OTROS INHIBIDORES DE SEÑAL	
Inhibidores de proteosoma	LLA (todas)
Inhibidores de m-TOR	LLA (todas)
Inhibidores de gamma-secretasa	LLA - T
Inhibidores de Bcl-2	LLA (todas)
Antagonistas de CXCR4	LLA (todas)
Inhibidores de farnesiltranferasa	LLA (todas)
Inhibidores de angiogénesis	LLA (todas)
TERAPIA EPIGENÉTICA	
Inhibidores de DNA metiltransferasa	
Azacitidina, Decitabina	LLA (todas)
Inhibidores de histonas metiltranferasa	
EPZ-5676	Reordenamiento *MLL* +
Inhibidores de deacetilasas de histonas	
Vorinostat, Panobinostat, Depsipétido	LLA (todas)

Dr. Carlos Grande, 2014, Madrid

Nuevos fármacos en la LLA

INMUNOTERAPIA	
Anticuerpos monoclonales	
Blinatumomab	
SAR3419	
DT2219ARL	
Rituximab	
Epratuzumab, Inot	
Alemtuzumab	
Terapia celular	
Células Natural Killer	Mismatch KIR donante/receptor
Células T con receptor antiCD19 quimérico	LLA CD19 +

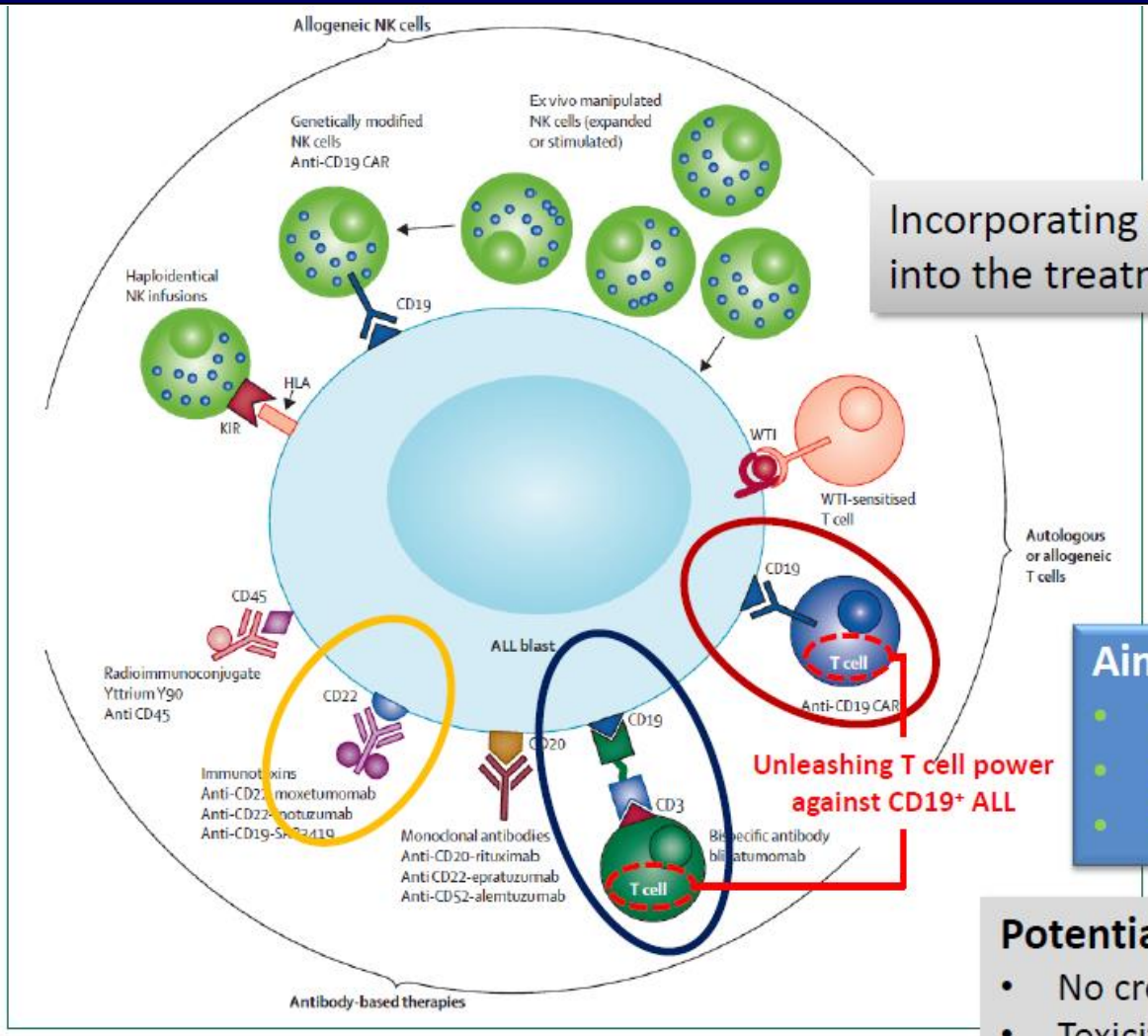
Blinatumomab

Inotuzumab ozogamicina

CAR T Cells anti CD19

Dr. Carlos Grande, 2014, Madrid

Inmunoterapia en LLA



Incorporating **targeted immunotherapy** into the treatment of ALL

Inotuzumab
Blinatumomab
CAR T cells

Aim to enable
- More CRs
- Better CRs (MRD-)
- More HSCTs

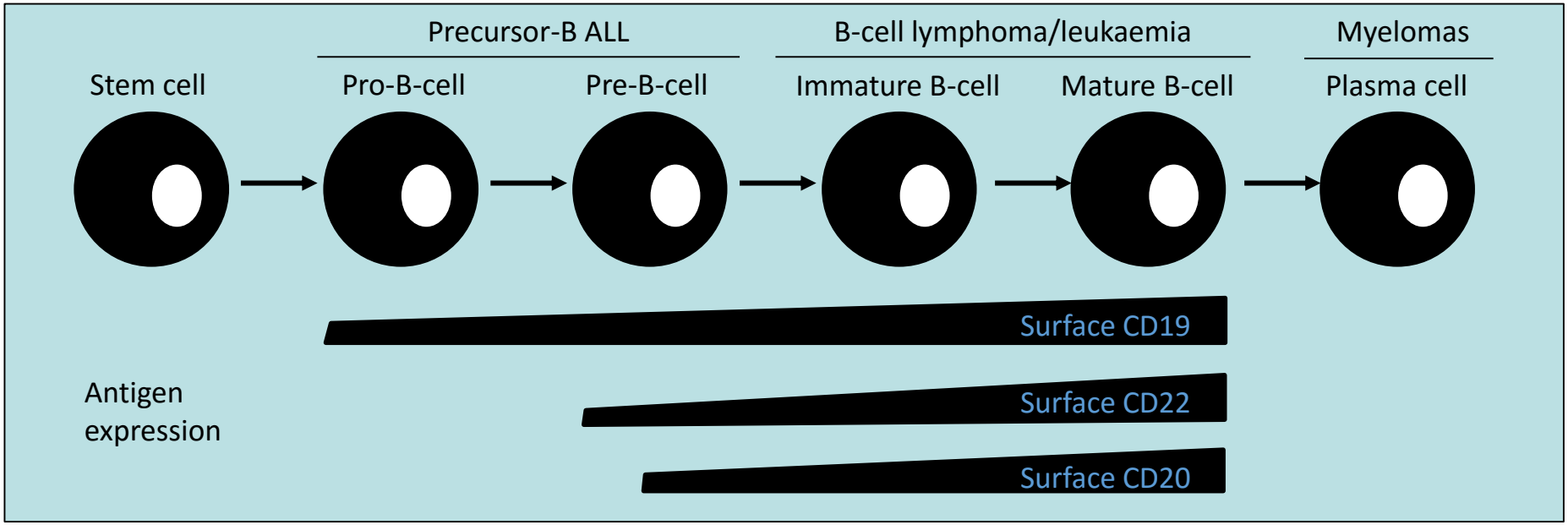
Potential advantages (over CT)
- No cross-resistance/synergism
- Toxicity profile (BM and GI tract)

Bhojwani D & Pui CH, Lancet Oncol 2013;14:e205–17; CT, chemotherapy

Antigen expression depends on stage of development

Examples of surface antigen expression during B-cell maturation

- CD19: surface expression from pro-B-cell stage ('pan-B-cell antigen')[1,2]
- CD22: although may be present in the cytoplasm at pro-B-cell stage, surface expression is seen from pre-B-cell stage[1,3]
- CD20: surface expression seen after expression of CD22[1,3]

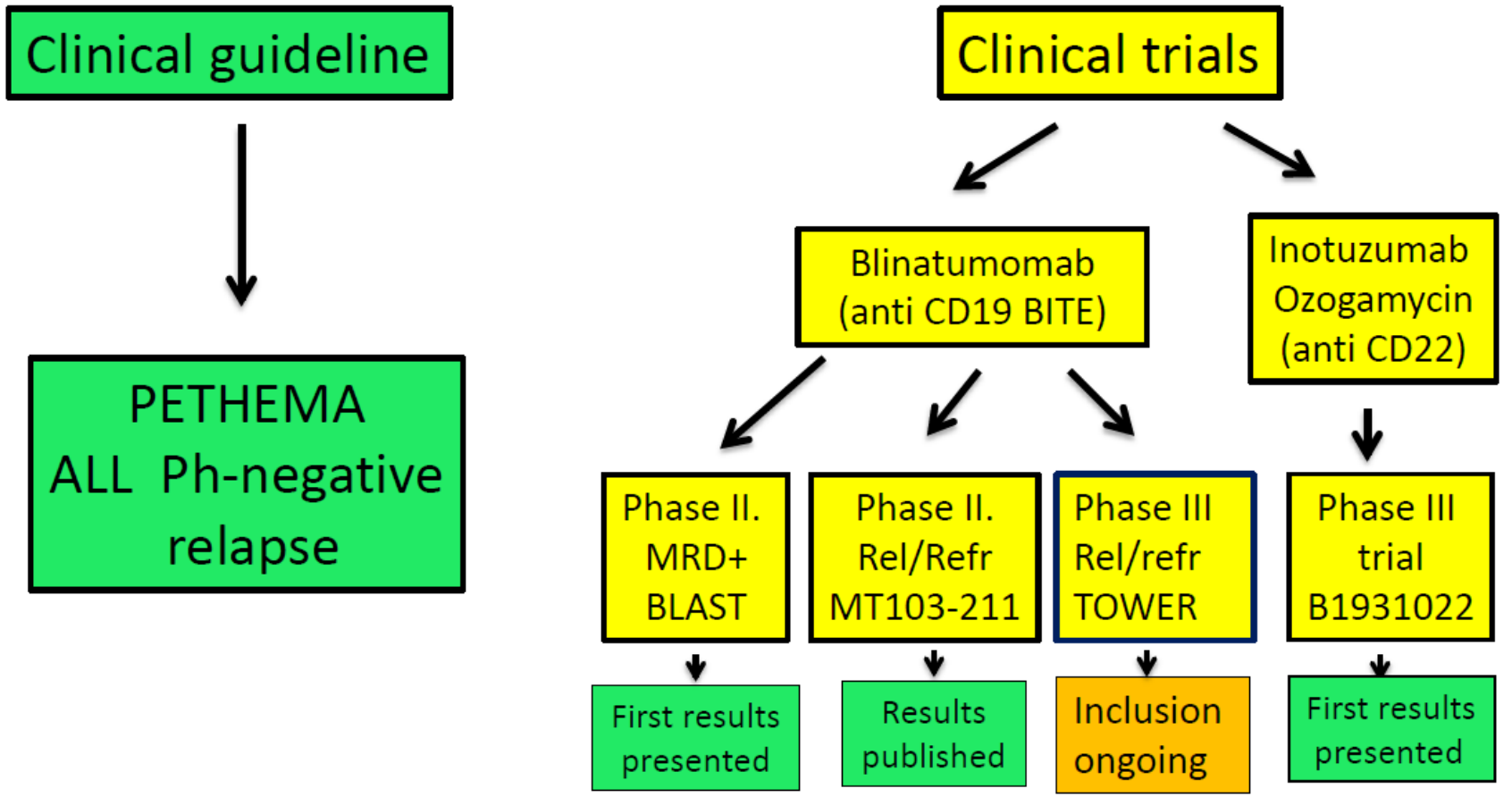


1. Bene MC. Immunol Lett 2005;98:9–21;
2. Wang K, et al. Exp Hematol Oncol 2012;1:36;
3. Hoelzer D. Hematology Am Soc Hematol Edu Program 2011:243–9

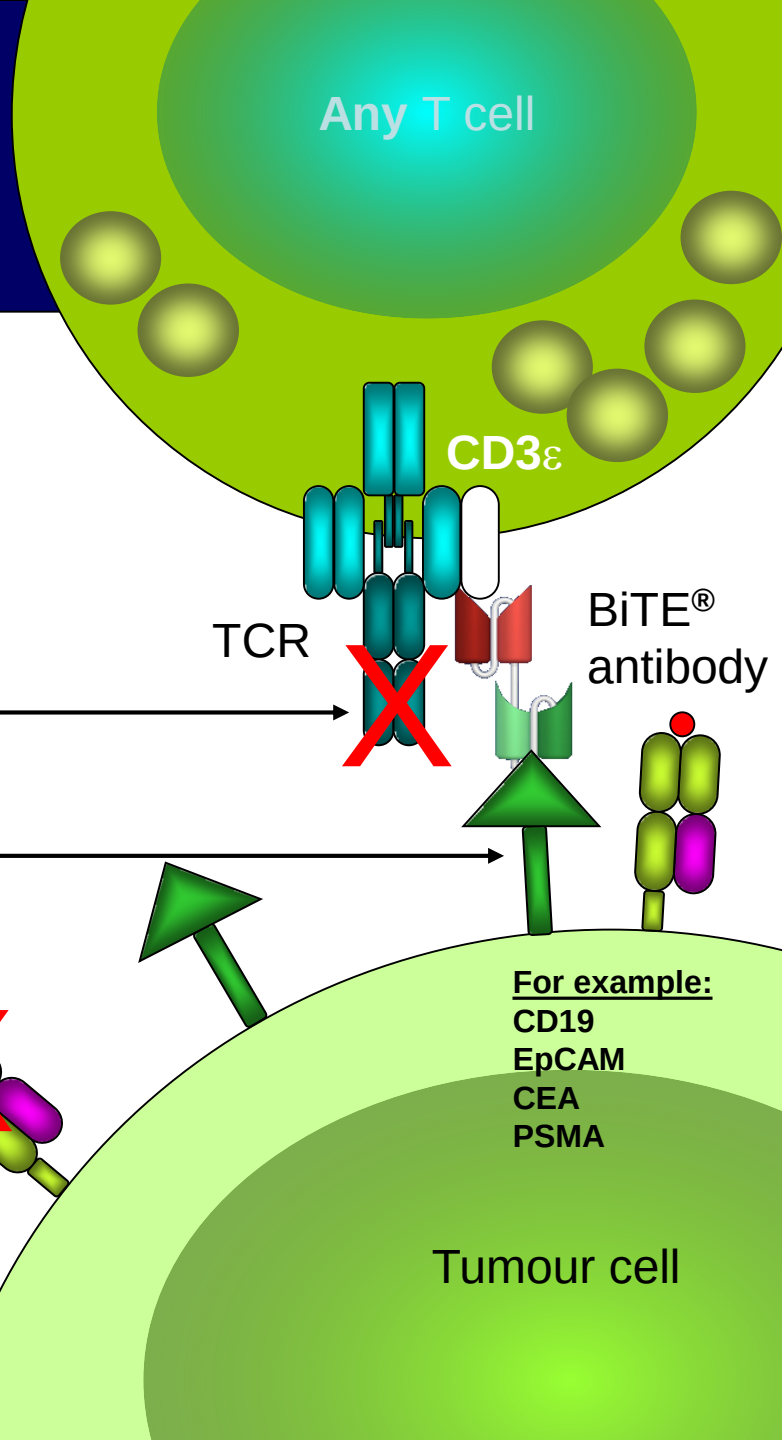
Antígenos B en LLA: dianas terapéuticas

Surface antigen	ALL subtype	Expression in Lymphoid blasts	Monoclonal antibody
CD20	Mature B B precursor	86-100% 30-40%	Rituximab , Ofatumumab, Obinutuzumab
CD22	Mature B B precursor	~100% 93-98%	Epratuzumab Inotuzumab ozogamycin Moxetumomab pasudotox
CD19	Mature B B precursor	95-<100% 95-<100%	Blinatumomab (anti CD19/CD3) Anti CD19 CAR T-cells
CD52	B precursor	70%	Alemtuzumanb

Tratamiento de rescate
PETHEMA



BiTE® antibody constructs may circumvent frequent escape mechanisms

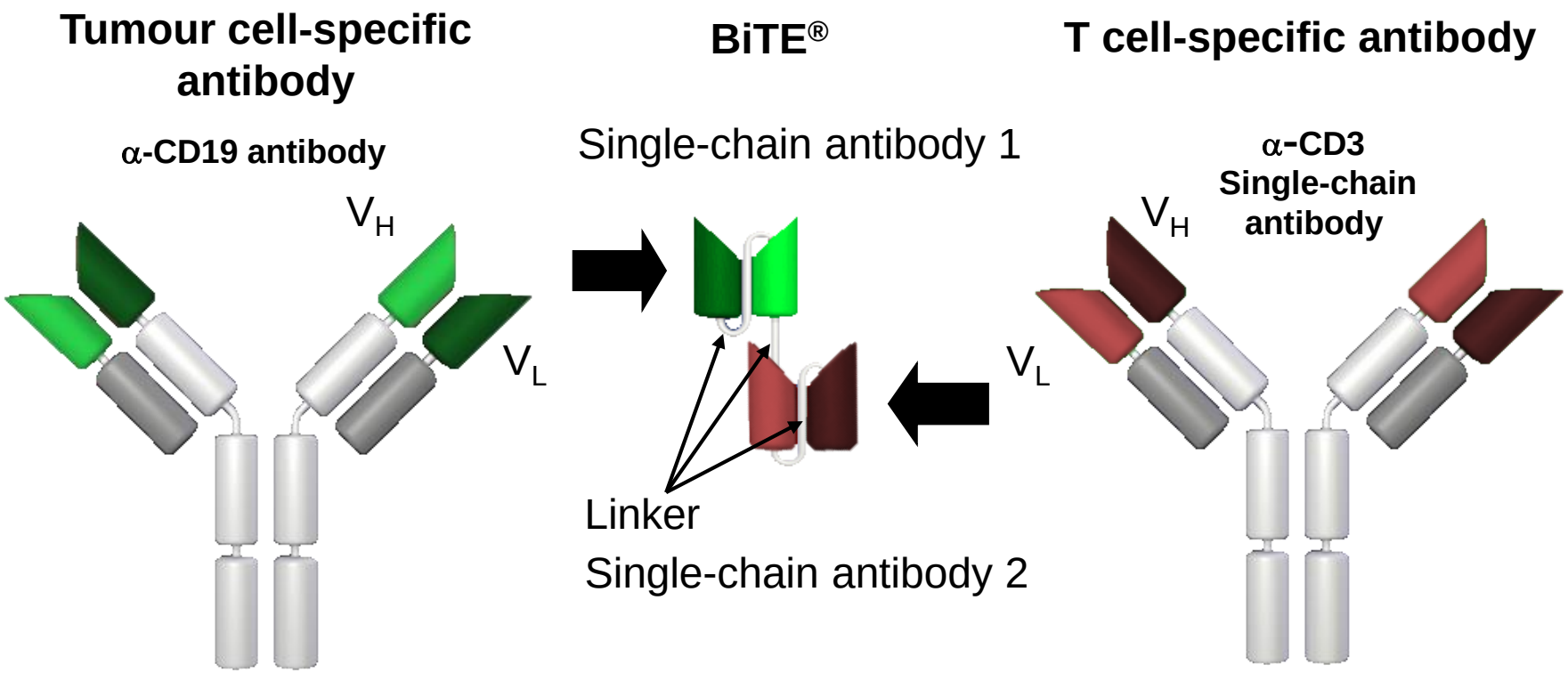


TCR, T-cell receptor complex

Adapted from Baeuerle PA & Reinhardt C. Cancer Res 2009;69:4941–4944

Engineering a BiTE® antibody: blinatumomab

BiTE® = **Bi**specific **T** cell **E**ngager

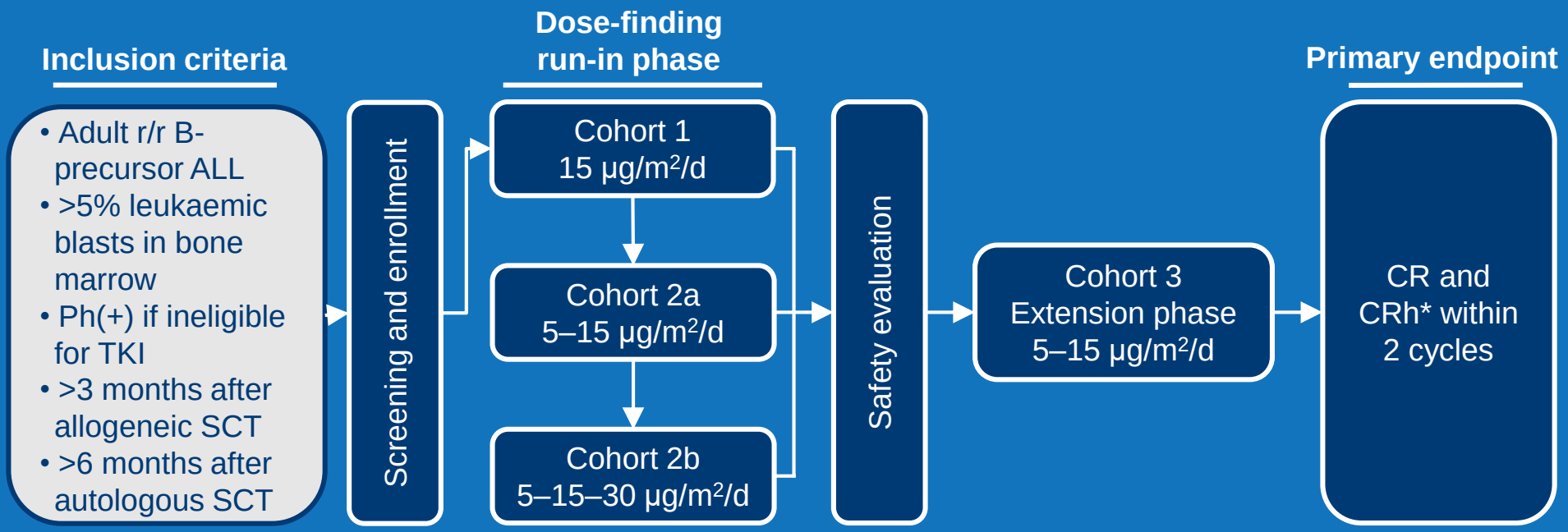


Nagorsen D, Baeuerle PA. Exp Cell Res. 2011;317:1255–60

Resultados con blinatumomab en LLA del adulto

Study Group Reference	Study population/ status	N Pts.	Age (yrs.)	CR rate	MRD resp.	RFS/DFS (median)	OS (median)/ SCT rate
Topp et al / GMALL JCO 2011; 29: 2493	MRD+ Pilot	21	47	-	80%	61% at 2.5 yr	
Gokbuget et al/ International ASH 2015 (#680)	MRD+ Confirmatory	110	45	-	80%	23.6 (R) 5.7 (NR)	38.9 (R) 12.5 (NR) 72% allo
Topp et al / GMALL JCO 2014; 32:4134-40	Rel./Refr. Pilot	36	32	69% CR+CRi	88%	7.6 mo.*	9.8 mo**/ 52% allo
Topp et al / International Lancet Oncol 2015; 16: 57-66	Rel./Refr. Confirmatory	189	39	43% CR+CRi	82%	5.9 mo. DFS	11.4 mo. 40% allo
Kantarjian et al / MDACC EHA 2015 (#115)	Rel/Refr. Elderly Confirmatory	36	70	56% CR+CRu	80%	7.4 mo	5.5.mo
Martinelli et al ASH 2015 (#679)	Rel./Refr. Ph+	45	55	36%	88%		7.1 mo/ 69% allo

Open-label, multicentre, exploratory, phase II study (study 206)



Blinatumomab cIV, 4 weeks on/2 weeks off, for up to 5 cycles

Consolidation after CR/CRh* within the first 2 cycles:

- 3 more cycles of blinatumomab *or*
- Allogeneic SCT

Topp MS et al. J Clin Oncol 2014;32:4134–40

Dose evaluation

Cohort	Dose	Number of AEs
1 (n=7)	15 µg/m^2/d	260
2a (n=5)	**5–15 µg/m^2/d**	**110**
2b (n=6)	5–15–30 µg/m^2/d	145

- The lowest incidence of AEs, regardless of causality, was in Cohort 2a
- Selected dose/schedule for the extension phase (Cohort 3): **5 µg/m^2/d in Week 1, then 15 µg/m^2/d thereafter**

AEs, adverse events

Topp MS et al. J Clin Oncol 2014;32:4134–40

Key response data

Haematological remission rates within 2 cycles of treatment

Response	Total N=36 n (%)
CR/CRh	25 (69)
CR	15 (42)
CRh	10 (28)
Partial remission*	2 (6)
Hypocellular bone marrow	3 (8)
Refractory	4 (11)
Not evaluable†	2 (6)

- Of those achieving CR/CRh
  - 13/25 (52%) went on to receive an allogeneic SCT
  - 22/25 (88%) achieved molecular remission (MRD-) across all cycles

*Bone marrow blasts ≤25% and platelets <50,000/µL and/or neutrophils <500/µL;
†Due to lacking bone marrow assessment

Topp MS et al. J Clin Oncol 2014;32:4134–40

Most common AEs in all patients

AEs	Treatment-emergent AEs regardless of causality	
	All grades (n=36), %	Grade ≥3 (n=36), %
Pyrexia	81	6
Fatigue	50	0
Headache	47	0
Tremor	36	8
Leukopenia*	19	14

- Most AEs were transient, occurring in the first few days of Cycle 1
- Some AEs were consistent with local polyclonal T-cell activation

*Grade ≥3 leukopenia is defined as a lymphocyte count of <0.5–<0.2 x 10^9 /L or white blood cell count of <2.0–1.0 x 10^9/L

Topp MS, et al. Oral presentation at ASH, December 8–11 2012, Atlanta, Georgia. Abstract 670; Topp MS et al. J Clin Oncol 2014;32:4134–40

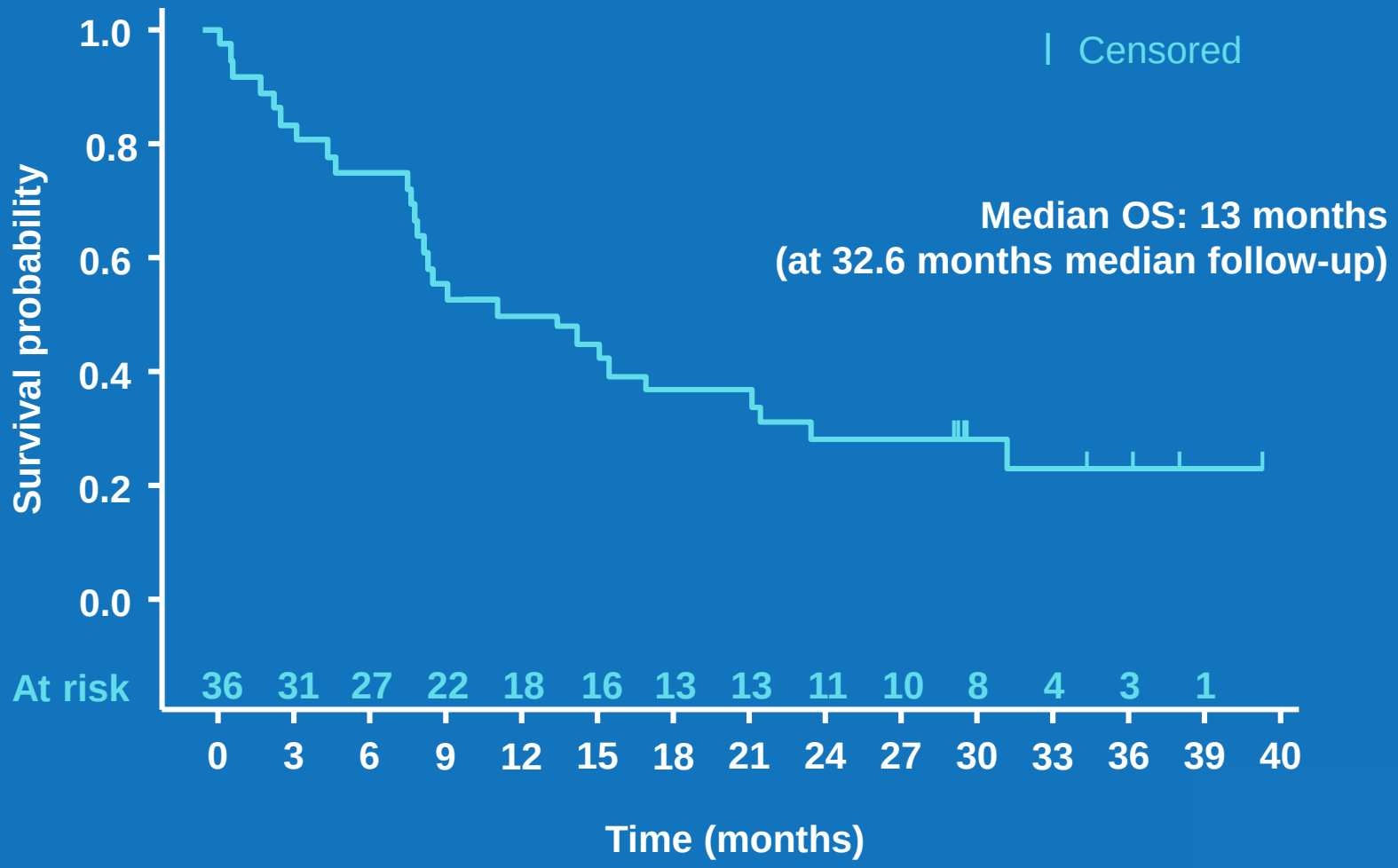
Medically important safety events

AEs	n	Comments
CRS		
Required treatment discontinuation or interruption	2	Patients had high tumour burden (≥50% blasts) and no cytoreductive pre-phase dexamethasone
Neurological events		
Required treatment interruption	6	All patients restarted on blinatumomab at 5 µg/m^2/d
Encephalopathy	3	Two patients had recurring events and permanently stopped treatment
Seizures	3	Patients were given anticonvulsant medication; all patients continued blinatumomab
Infection		
Fungal encephalitis	1	Fatal → mandatory fungal prophylaxis medication given to patients with allograft relapse

- **Prevention and mitigation of CRS:** initial blinatumomab dose of 5 µg/m^2/d and administration of pre-phase dexamethasone 10 mg/m^2 (up to 5 days) and/or cyclophosphamide 200 mg/m^2 (up to 3 days) in cases of ≥50% blasts in bone marrow was permitted

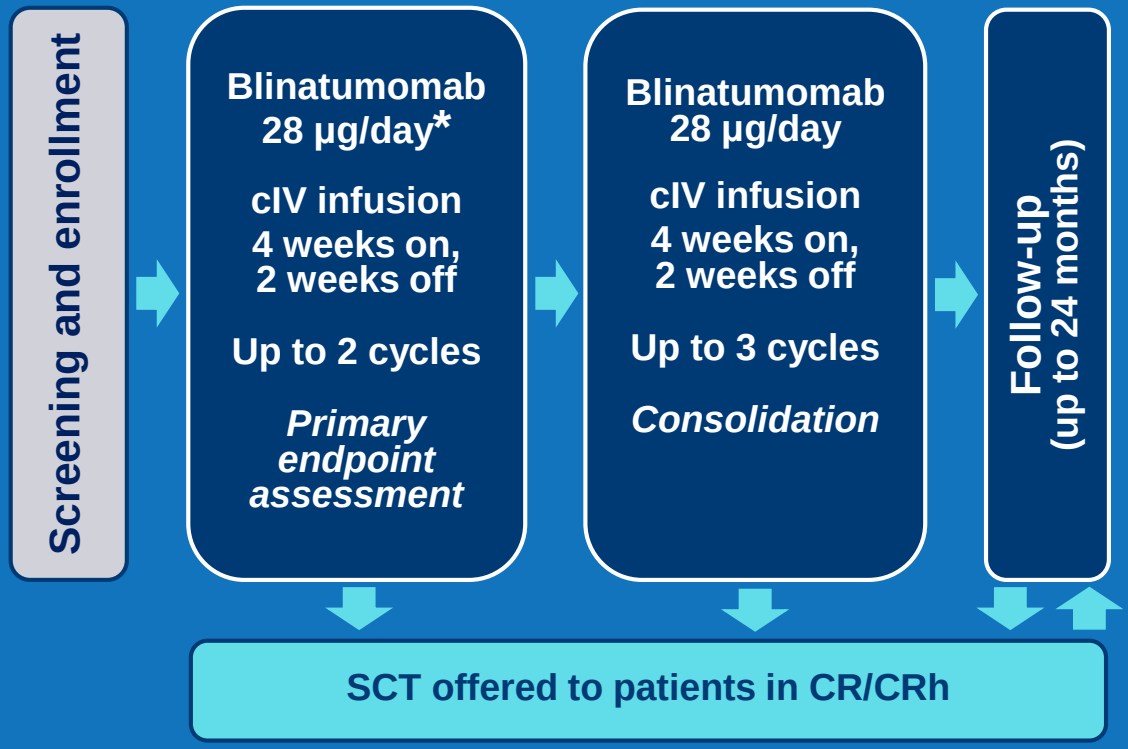
CRS, cytokine release syndrome
Topp MS et al. J Clin Oncol 2014;32:4134–40

Long-term follow-up
Overall survival (all patients)



Zugmaier G et al. Poster presentation at ASH, San Francisco, CA;
December 6–9 2014, Abstract 2287

Confirmatory open-label, single-arm, multicentre, phase II study (study 211)



*9 µg/day in cycle 1 (days 1 to 7)

Study endpoints

Primary
- CR/CRh during the first 2 cycles

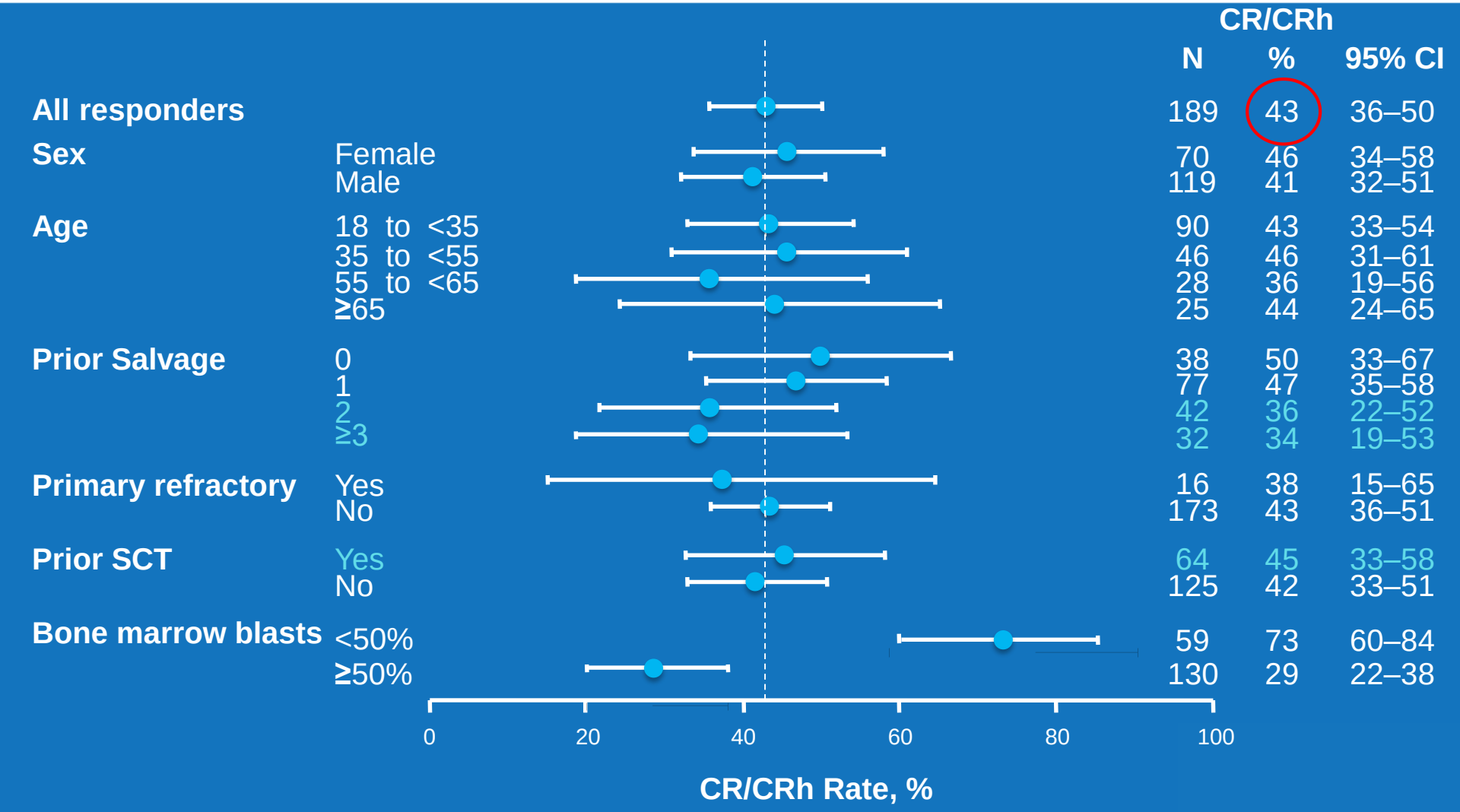
Secondary included
- CR, CRh
- RFS
- OS
- AlloSCT realisation
- 100-day mortality after alloSCT
- Incidence of AEs

Exploratory included
- MRD response by PCR during the first 2 cycles

- All patients: Dexamethasone (20 mg) within 1 h before treatment initiation in each cycle and before the dose step in cycle 1
- >50% blasts/>15.00 WBC: Pre-phase dexamethasone 10–24 mg/m^2/day (for up to 5 days) to minimise the risk of severe CRS

Topp MS, et al. Lancet Oncol 2015;16:57–66 and supplementary appendix

Subgroup analyses of CR/CRh



Topp MS, et al. Lancet Oncol 2015;16:57–66;
Topp MS et al. EHA 2014, Abstract S722 and oral presentation

Overall results of MRD evaluation

CR/CRh within 2 cycles and MRD data, n	73†
Patients with MRD response*, n (%)	60 (82)
MRD response in cycle 1	59
MRD response in cycle 2	1

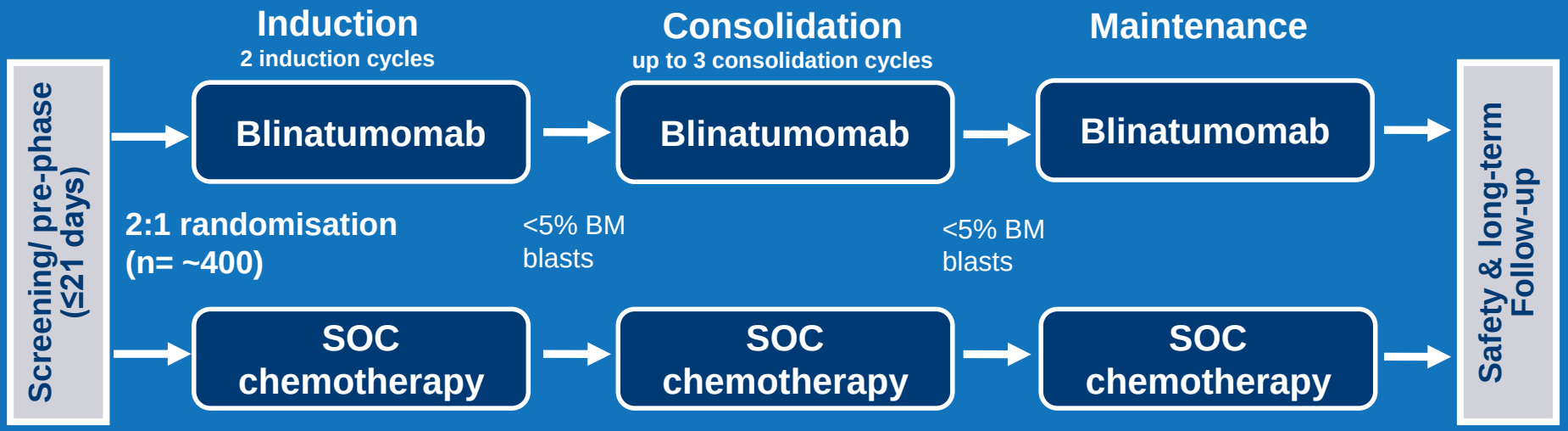
†Missing diagnostic and/or follow-up sample in 8/81 responders (10%)
*MRD $<10^{-4}$ by PCR

Survival by MRD response

	Median (months) (95% CI)	
	Relapse-free survival	Overall survival
CR\CRh:	6.7 (5.1, 8.9)	11.5 (8.5, NE)
CR\CRh MRD+	2.3 (1.2, NE)	6.7 (2.0, NE)
CR\CRh MRD-	6.9 (5.5, 10.1)	11.5 (8.5, NE)

Topp MS, et al. Lancet Oncol 2015;16:57–66

Phase III, randomized, open-label study of blinatumomab vs. standard of care chemotherapy in adults with r/r B-ALL (TOWER study)

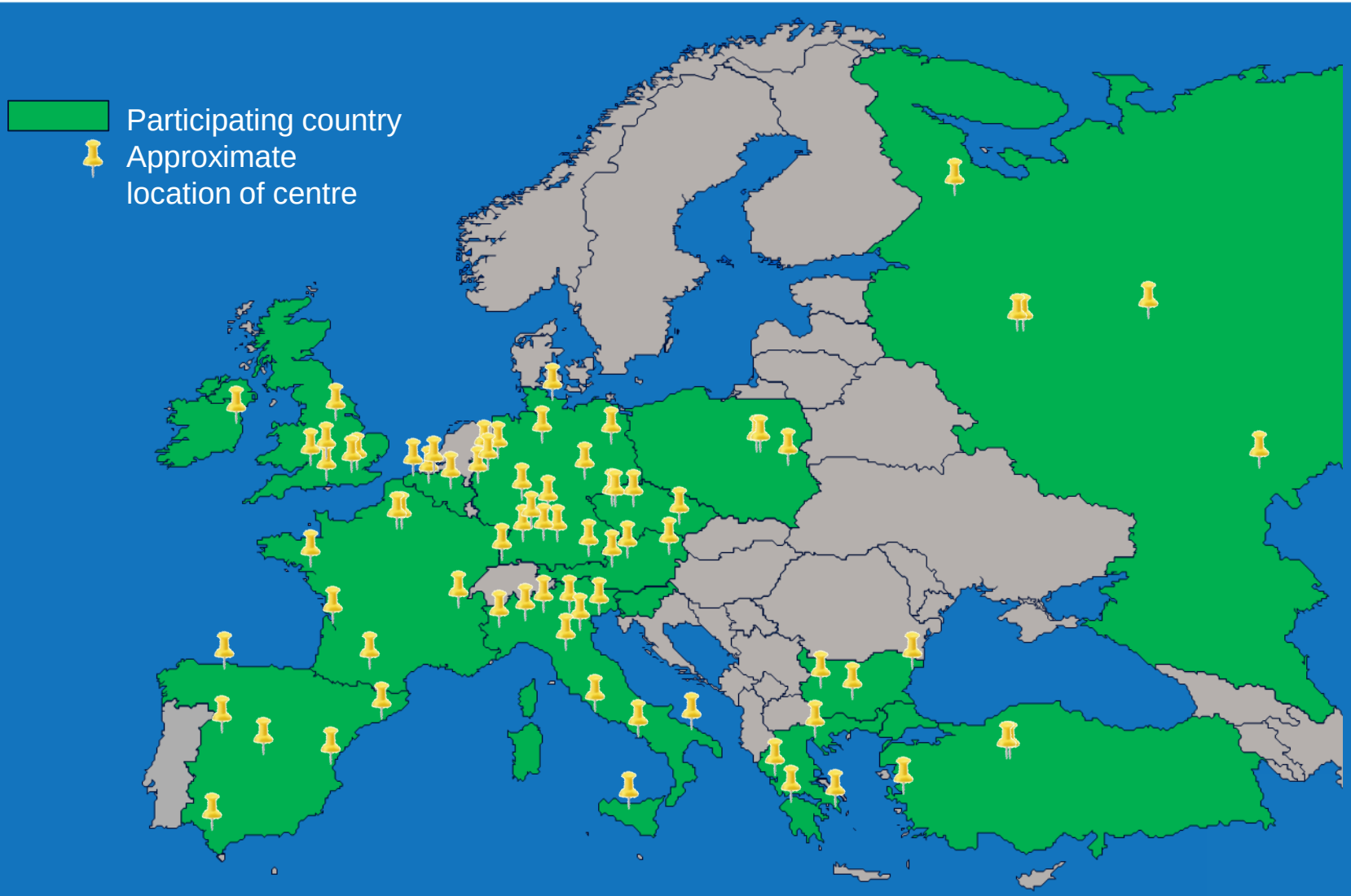


Primary endpoint	• Overall survival	
Key secondary endpoints	• CR and CR/CRh/CRi within 12 weeks • Duration of CR/CRh/CRi • MRD remission (<10^{-4} by PCR or flow cytometry)	• Rate of alloSCT ± blinatumomab • Event Free Survival (EFS) • Safety

Key inclusion criteria	• Ph- B-ALL with any of:
	  • Refractory to primary induction therapy or salvage therapy
	  • If Salvage 1: CR1 duration <12 months
	  • ≥2nd salvage
	  • Relapse at any time after alloSCT
		• >5% blasts in the bone marrow
		• ECOG PS ≤2
		• Age ≥18 years

http://clinicaltrials.gov/ct2/show/NCT02013167

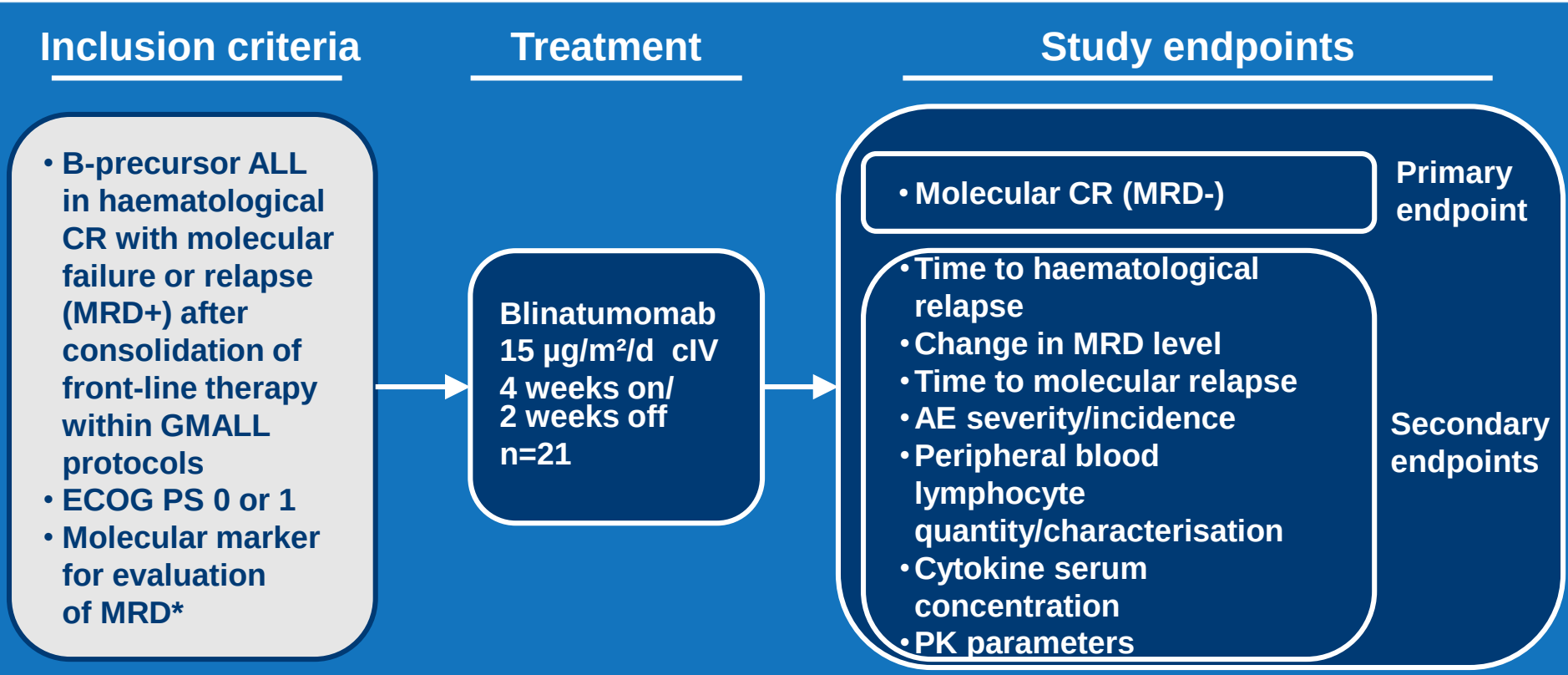
TOWER study: participating centres in Europe/Russia



Resultados: TOWER
(EHA 2016, Topp, et al)

- N = 405 patients: blina (n=271) or SOC (n=134)
- CR higher for blina vs SOC, including CR (39% vs 19%; p<.001) and CR/CRh/CRi (46% vs 28%, p=.001).
- Median OS was 7.8 months for blina and 4.0 months for SOC (p=.011)

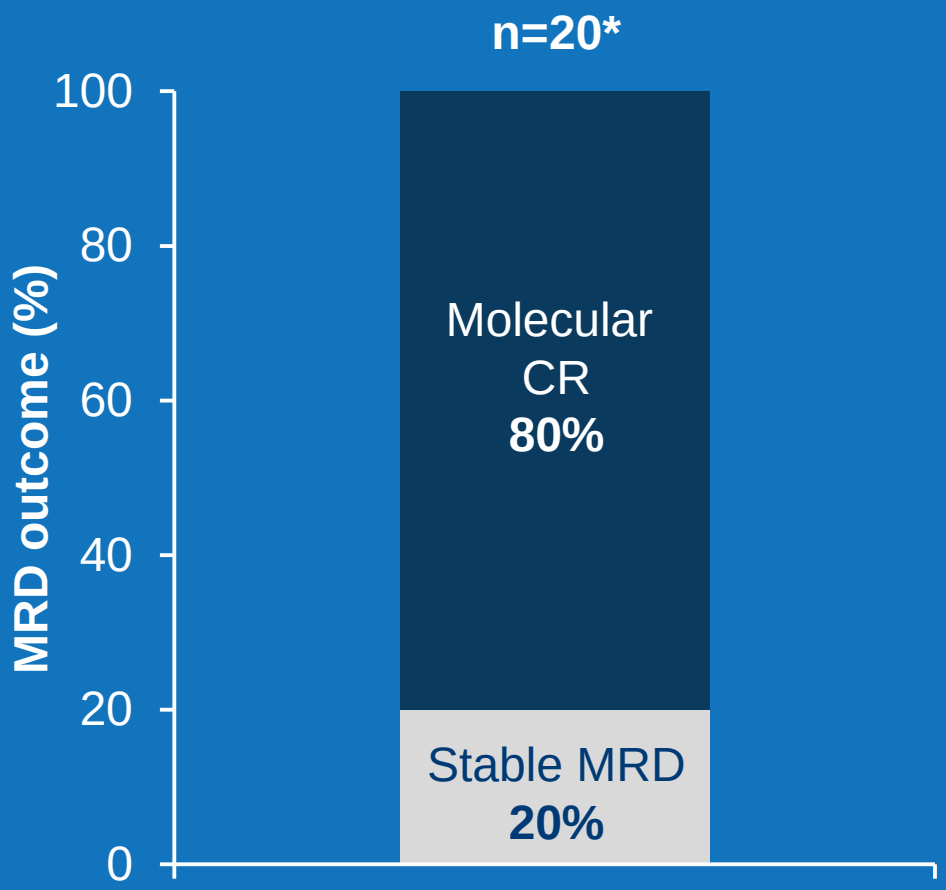
Phase II study of blinatumomab in patients with MRD+ B-precursor ALL



- Patients achieving molecular CR could proceed to allogeneic SCT or receive 3 blinatumomab consolidation cycles

*Assessed by qPCR central lab by Ig/TCR rearrangement, BCR-ABL, or t(4;11)
ECOG PS, ECOG performance status; GMALL, German Multicenter Study Group for adult ALL
Topp MS, et al. J Clin Oncol 2011;29:2493–98

MRD responses



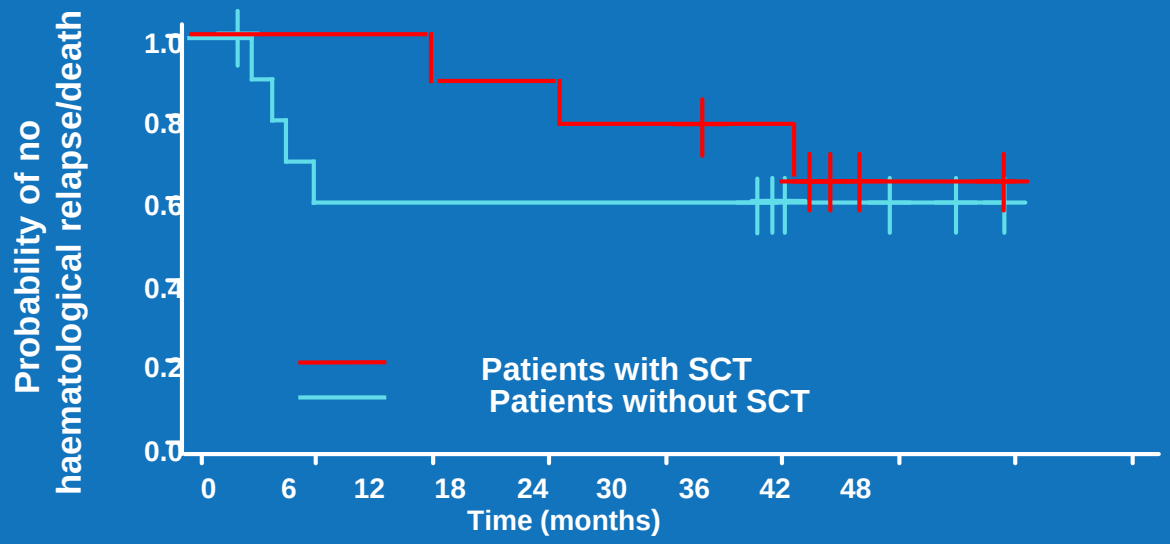
- Responses were rapid
  - All responses occurred within the first cycle of treatment
- Majority of AEs were transient
  - Lymphopenia most common grade 3/4 AE (seen in 33%)
  - No CRS observed

*1 patient not evaluable: <1 treatment cycle and lack of response assessment

Topp MS, et al. J Clin Oncol 2011;29:2493–98

RFS and duration of MRD response

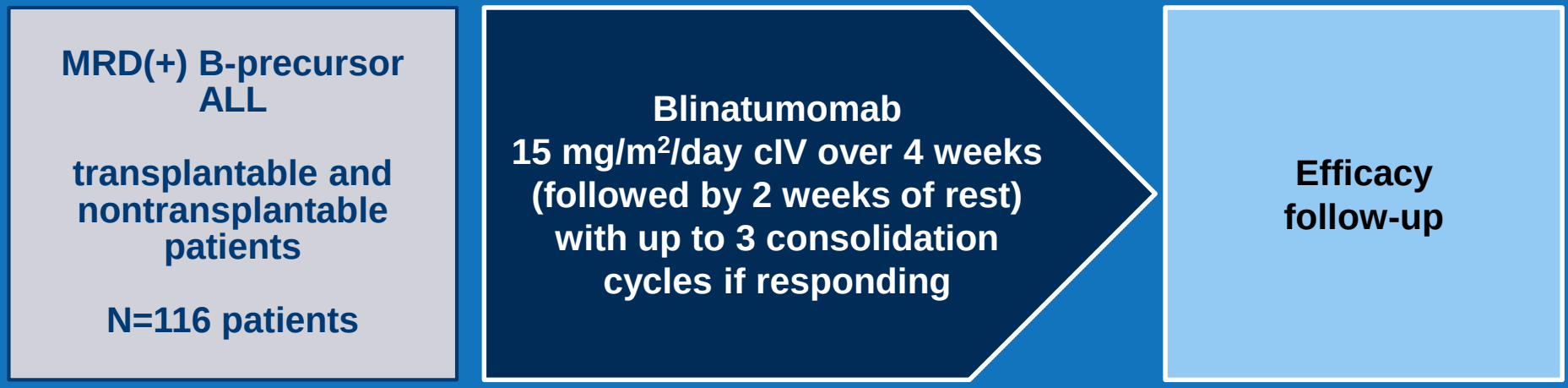
Haematological RFS



- With SCT (n=9): median follow-up = 32.9 months
- Without SCT (n=11): median follow-up = 30.8 months

Topp MS, et al. Blood 2012;120:5185–87

Confirmatory phase II study of blinatumomab in adults with MRD+ B-precursor ALL (BLAST)



Primary endpoint	• Complete MRD response rate after 1 cycle	
Secondary endpoints	• Incidence and severity of AEs • Hematological RFS rate at 18 months • Overall survival	• Time to haematological relapse • Duration of complete MRD response

Gökbuget N et al. Oral presentation at ASH, San Francisco, CA; December 6–9 2014, Abstract 379

Complete MRD response within 1 cycle

	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	
Primary endpoint **Complete MRD response after Cycle 1**	**88**	**78**	**69–85**	**82**	**80**	**71–87**
Exploratory endpoint MRD response after Cycle 1	96	85	77–91	82	85	77–92

- 2 patients achieving reduction of MRD to below the quantifiable limit during Cycle 1 achieved a complete MRD response after continued treatment in Cycle 2

Gökbuget N et al. Oral presentation at ASH, San Francisco, CA; December 6–9 2014, Abstract 379

Blinatumomab
Indicaciones

- FDA, EMA:
  - Tratamiento de la LLA de precursores B Ph - refractaria o en recaída
- AEMPS (España):
  - Programa de uso expandido
  - Programa de «uso compasivo»

Blinatumomab
«Uso compasivo»

1. Sujeto con LLA de precursores B y cualquiera de las características siguientes *(al menos una de las 3 opciones siguientes debe ser Sí):*

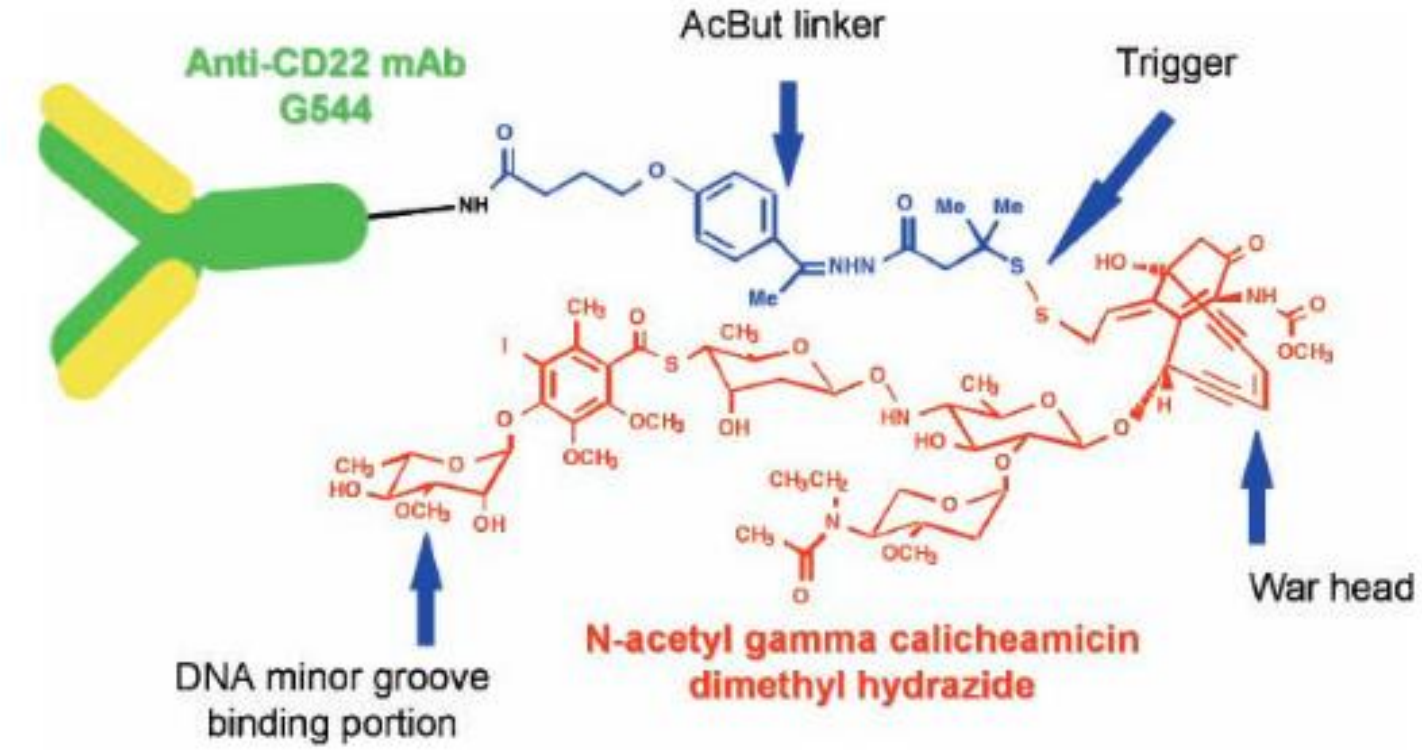
   1.1. Adultos en remisión hematológica completa definida como <5% de blastos en la médula ósea tras quimioterapia intensiva y presencia de enfermedad residual mínima a un nivel ≥10^{-4} por PCR o 10^{-3} por citometría de flujo (de acuerdo con la práctica clínica en España).

   1.2. Adultos con LLA Ph+ refractaria o en recaída tras el tratamiento con ≥2 TKI.

   1.3. Sujetos pediátricos o adolescentes (edad < 18 años) en segunda o posterior recaída medular o en cualquier recaída medular tras un TPH alogénico o refractarios a otros tratamientos.

2. Consentimiento informado escrito firmado por el paciente o representante

Inotuzumab ozogamicina: mecanismo de acción



DiJoseph et al. Hematology Meeting Reports 2008;5(6):74-77

Ensayo fase II: Inotuzumab ozogamicina en monoterapia

Original Article

Results of Inotuzumab Ozogamicin, a CD22 Monoclonal Antibody, in Refractory and Relapsed Acute Lymphocytic Leukemia

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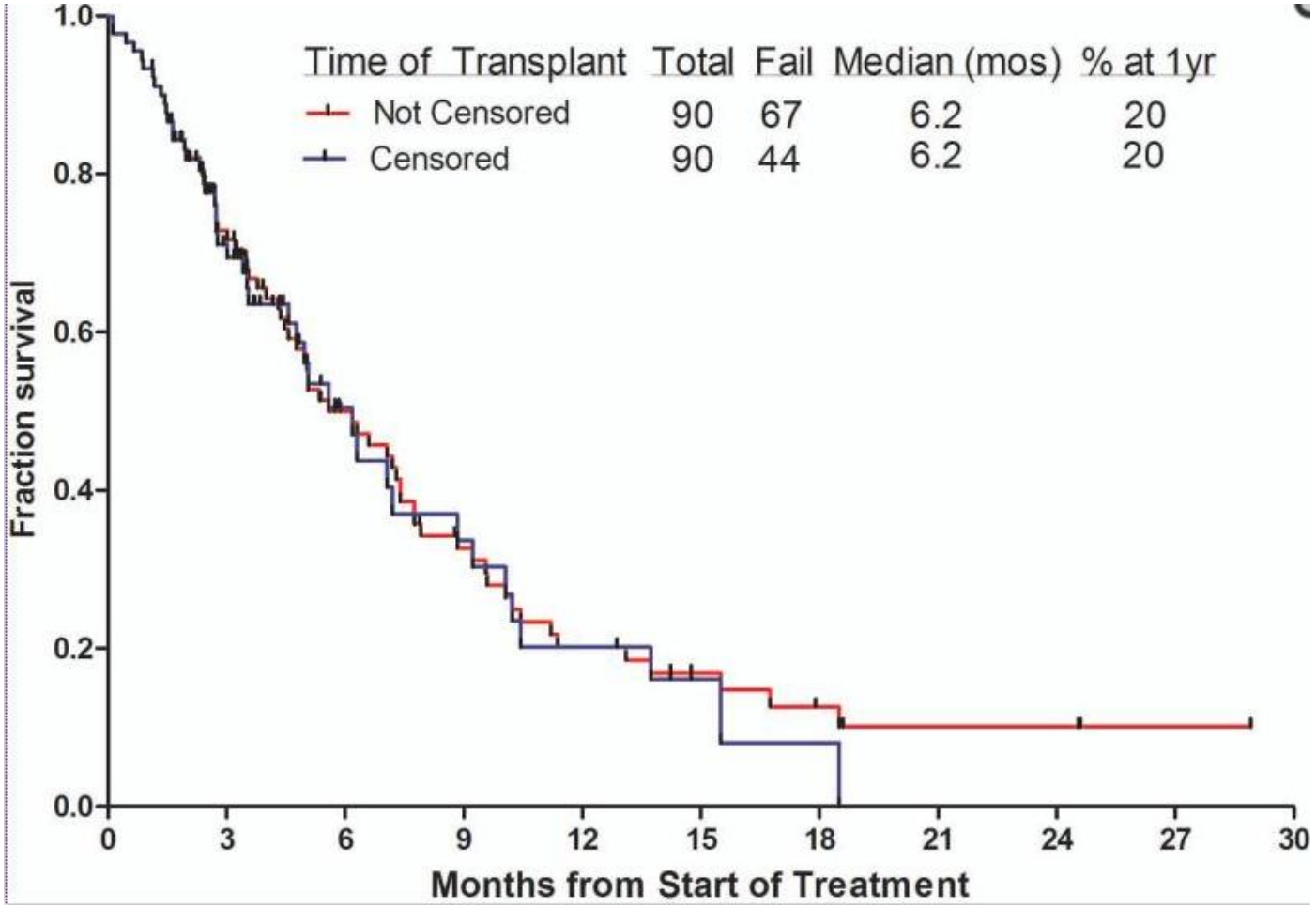
- N=90
- RC: 58% (72% con EMR neg)

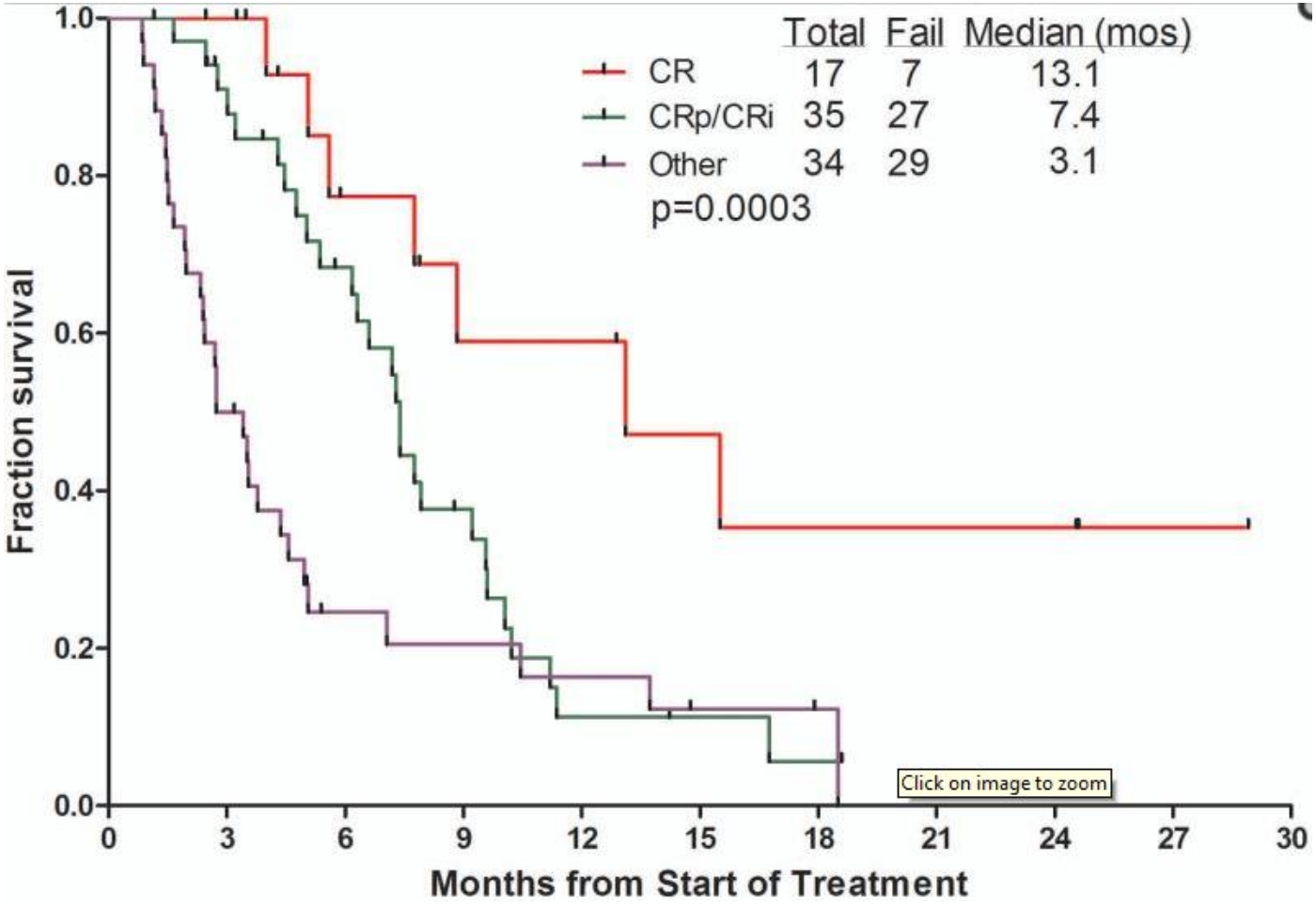
Cancer. 2013 Aug 1;119(15):2728-36

SG con Ino



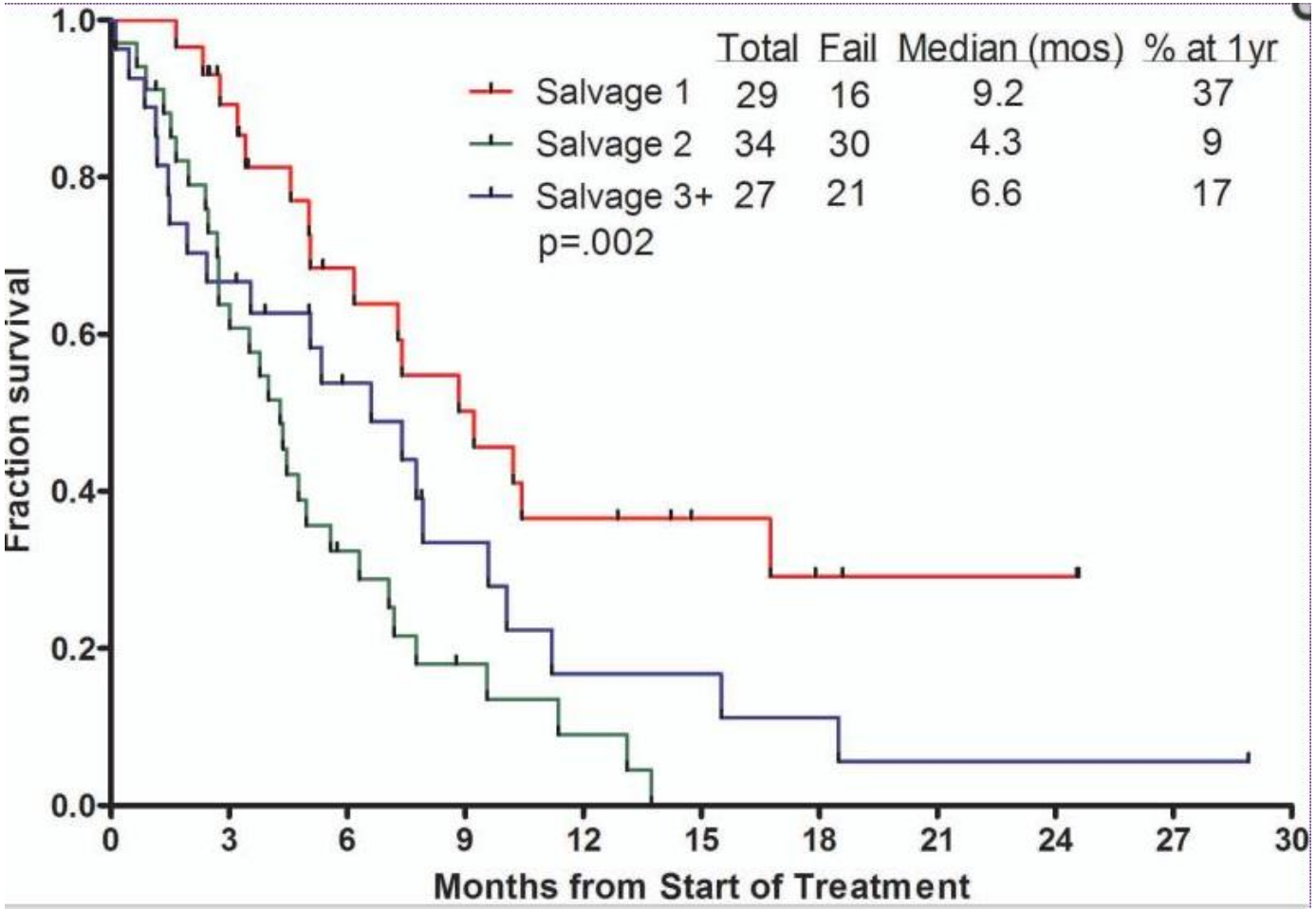
Cancer. 2013 Aug 1;119(15):2728-36

SG según respuesta



Cancer. 2013 Aug 1;119(15):2728-36

SG según línea



Cancer. 2013 Aug 1;119(15):2728-36

Inotuzumab ozogamycin.Phase III trial B1931022

Primary endpoints:
- CR/CRi
- Overall survival

Secondary endpoints
- Duration of remission (DOR)
- MRD-neg in CR/CRi (<0.01%, by central flow)
- HSCT rate

Primary ITT analysis for efficacy (218/326 pts)

Outcome	InO (n=109)	SOC (n=109)	1-sided P value
CR/CRi, % (95%CI)	80.7 (72-88)	33.3 (24-44)	<0.0001
S1	87.7	31.3	<0.0001
S2	66.7	37.9	0.0104
Median DOR, mo	4.6 (3.9-5.4)	3.1 (1.4-4.9)	0.0169
MRD <0.01% in CR/Cri, %	78.4 (68.87)	28.1 (14-47)	<0.0001
Allo HSCT, n	48	20	

Safety issues in InO arm vs SOC (259 pts)

Event	InO (n=139)	SOC (n= 120)
Grade ≥3 cytopenias	Similar frequency	
Grade ≥3 hepatobiliary	9%	3%
VOD	15 pts (10 after HSCT)	1 pt
Grade ≥3 VOD	13	1

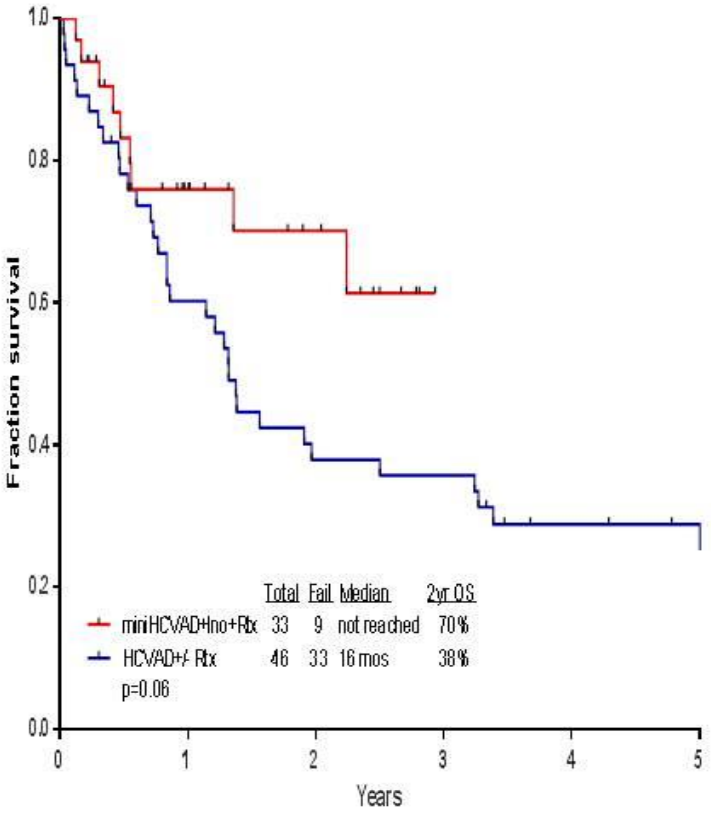
DeAngelo D
EHA 2015

Inotuzumab ozogamicina con quimioterapia

Table1. Patient characteristics and outcome

Parameter	Category	N (%)/Median [Range]
Follow-up (mos)		15 [2-35]
Age (yrs)		69 [60-79]
Performance Status (ECOG)	0-1	29 (88)
WBC		3.5 [0. 6- 111.0]
Karyotype	Diploid	9 (33)
	Miscellaneous	18 (55)
	Insufficient metaphases/ Unknown	4 (12)
CD22		98 [72-100]
CD20	≥ 20%	23/33 (70%)
CR		24 (80)
CRp		5 (17)
No response		1 (3)
ORR		29 (97)
Cytogenetic CR	17 abnormal at start	17 (100)
Neg MRD at D21 overall	(5 not done / 3 CR at start)	 19 (79) 32 (100)
Early death		0
2-year PFS %		85
2-year OS %		70

Figure 1. Survival with mini-HCVD-INO vs HCVAD +/- Rituximab in frontline ALL



Jabbour E
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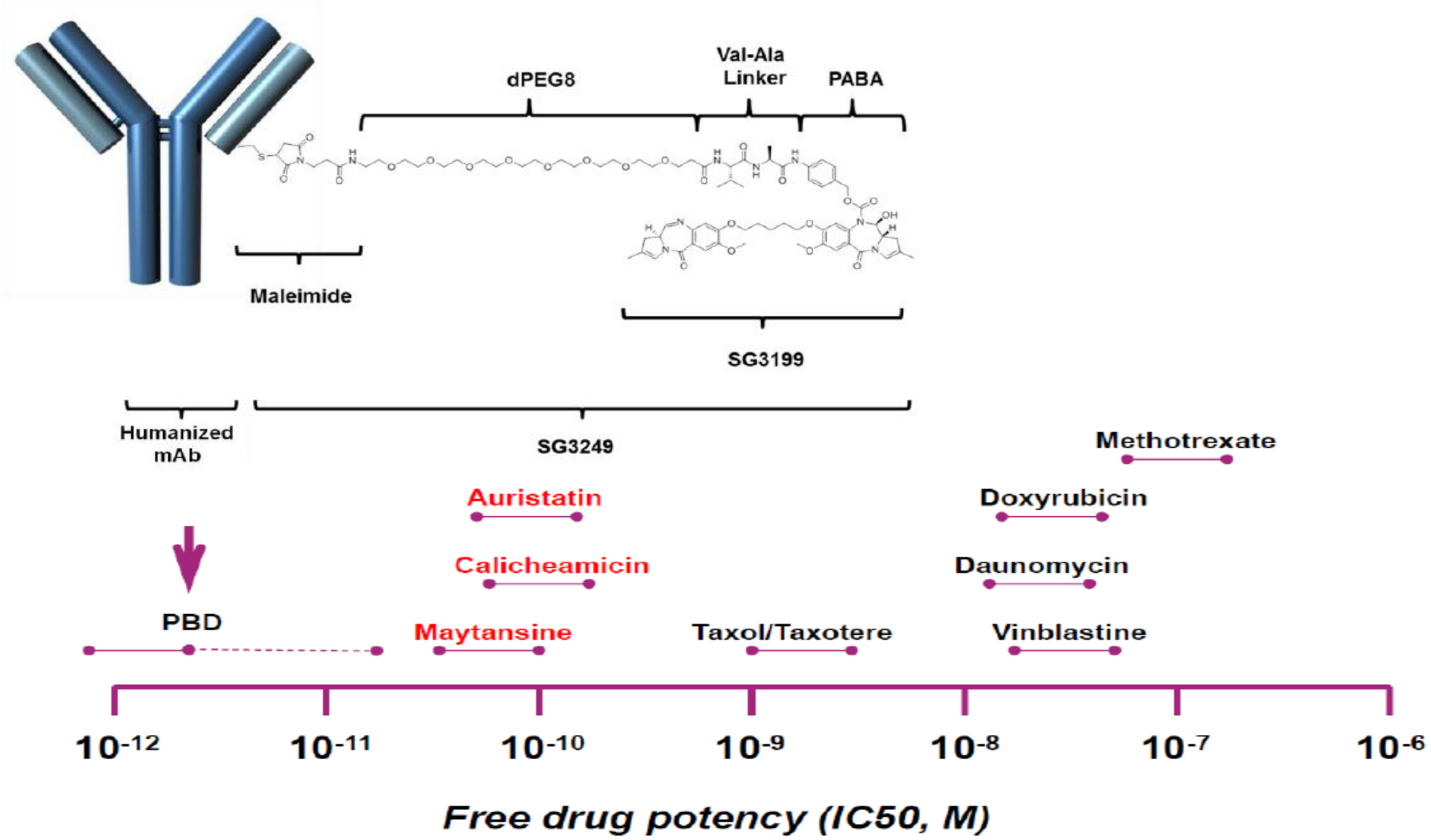
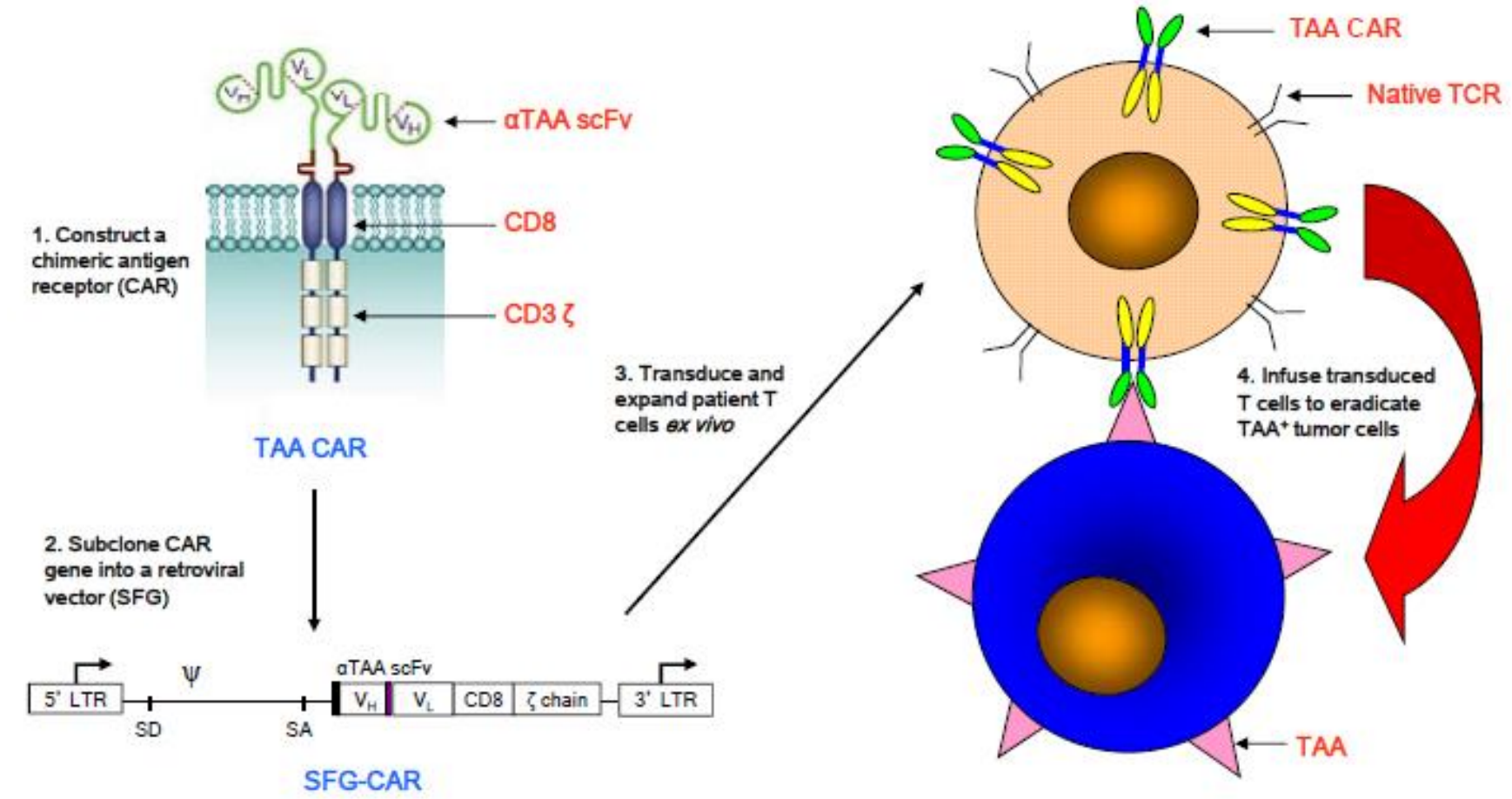
Nuevos anticuerpos conjugados: pirrolobenzodiazepina



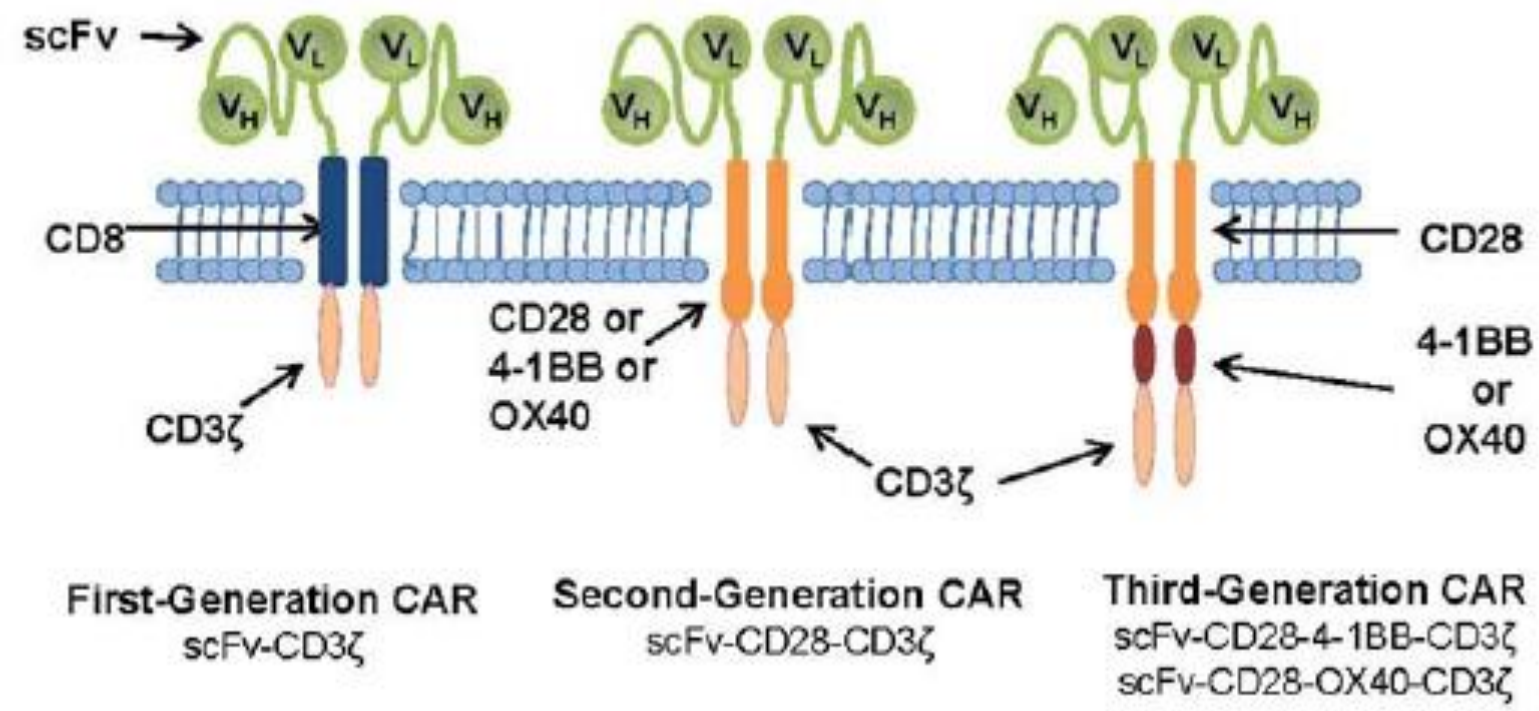
Tratamiento del cáncer con CAR-T cells



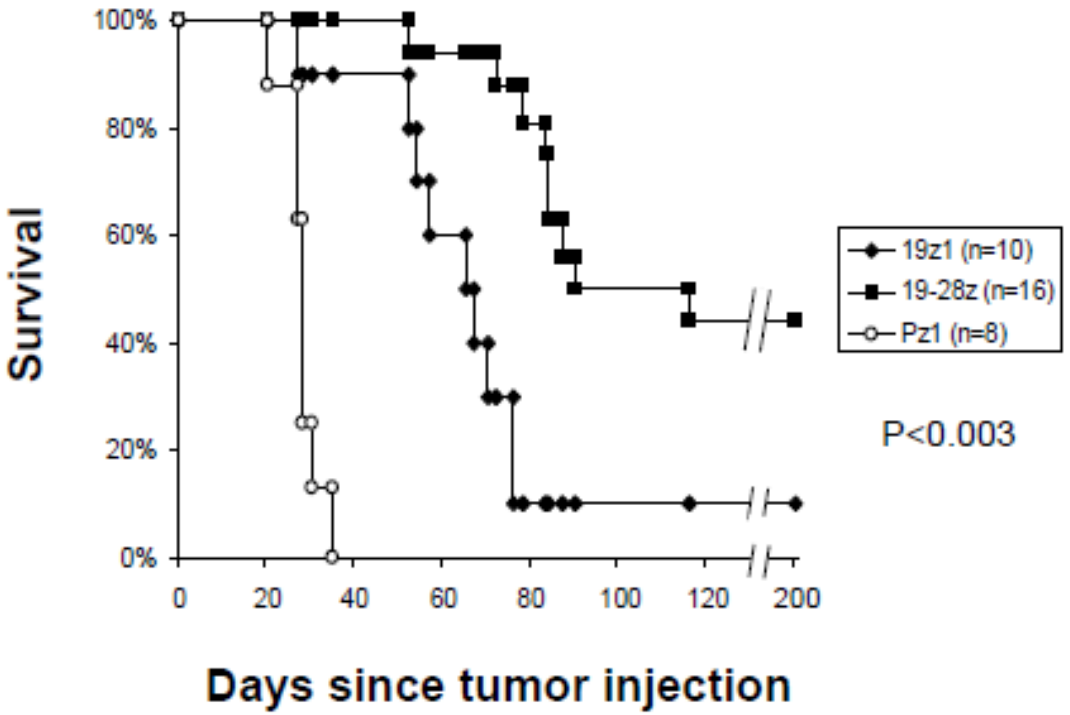
CAR-T Cells en LLA-B

- Diana terapéutica = CD19
- Se expanden después de la infusión, en respuesta al antígeno
- Pueden persistir durante meses o años
- Pueden acceder al LCR

Evolución en el diseño de CAR-T (2001-2004)

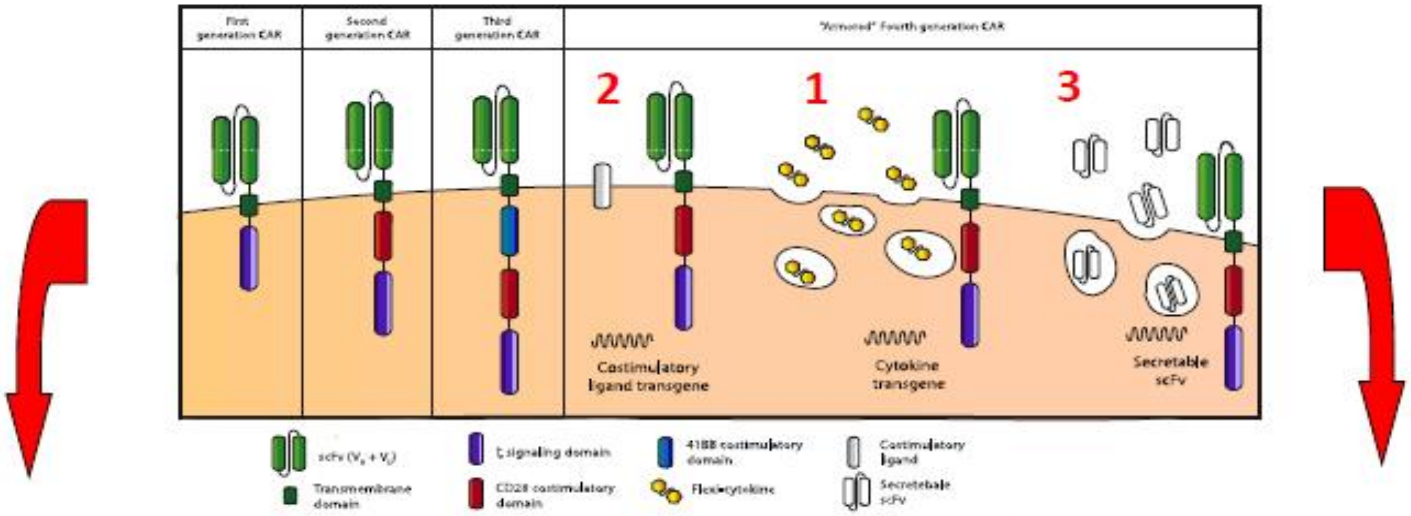


CAR-T de 2ª generación in-vivo (2006)



Brentjens et al Clin Cancer Res. 2007 Sep 15;13(18 Pt 1):5426-35

Armored CAR-T cells



A) 1928z/4-1BBL CAR T cells:
Designed to improve CAR T cell persistence in vivo and modulate the tumor microenvironment

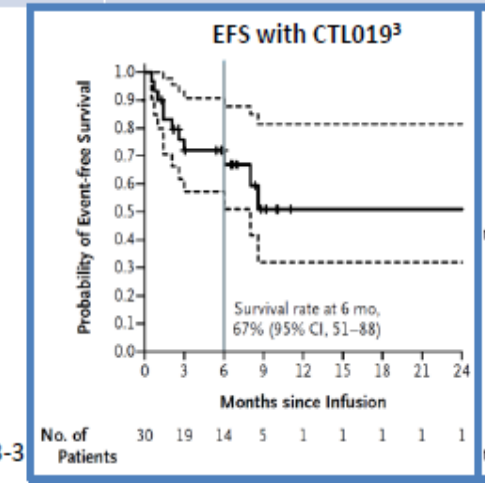
B) 1928z/IL-12 CAR T cells:
Designed to improve CAR T cell persistence in vivo as well as recruit the endogenous immune response to cancer

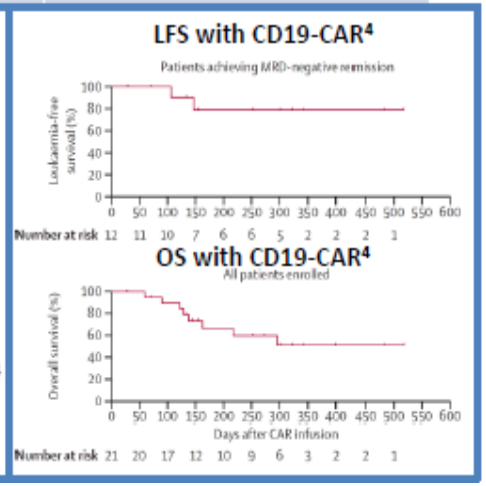
C) 1928z/CD40L CAR T cells:
Designed to improve CAR T cell persistence in vivo as well as activate AAPCs and recruit the endogenous anti-tumor immune response

CAR-T en LLA-B: publicaciones

Response after conditioning chemotherapy and CAR T-cell treatment	19-28z (MSKCC/Juno; n=28)[1]	CTL019 (CHOP/UPenn/ Novartis; n=39)[2,3]	CD19-CAR (NCI/Kite; n=20)[4]
CR/CRi (%)	89	92	67
MRD- (% of all evaluable patients)	88	(% NR)	60
AlloSCT (% of those achieving CR/CRi)	42	8	71
Clinically significant/ severe CRS (%)	(23)	27**	29
Neurotoxicity (%)*	25 (Grade 3/4)	43**	29

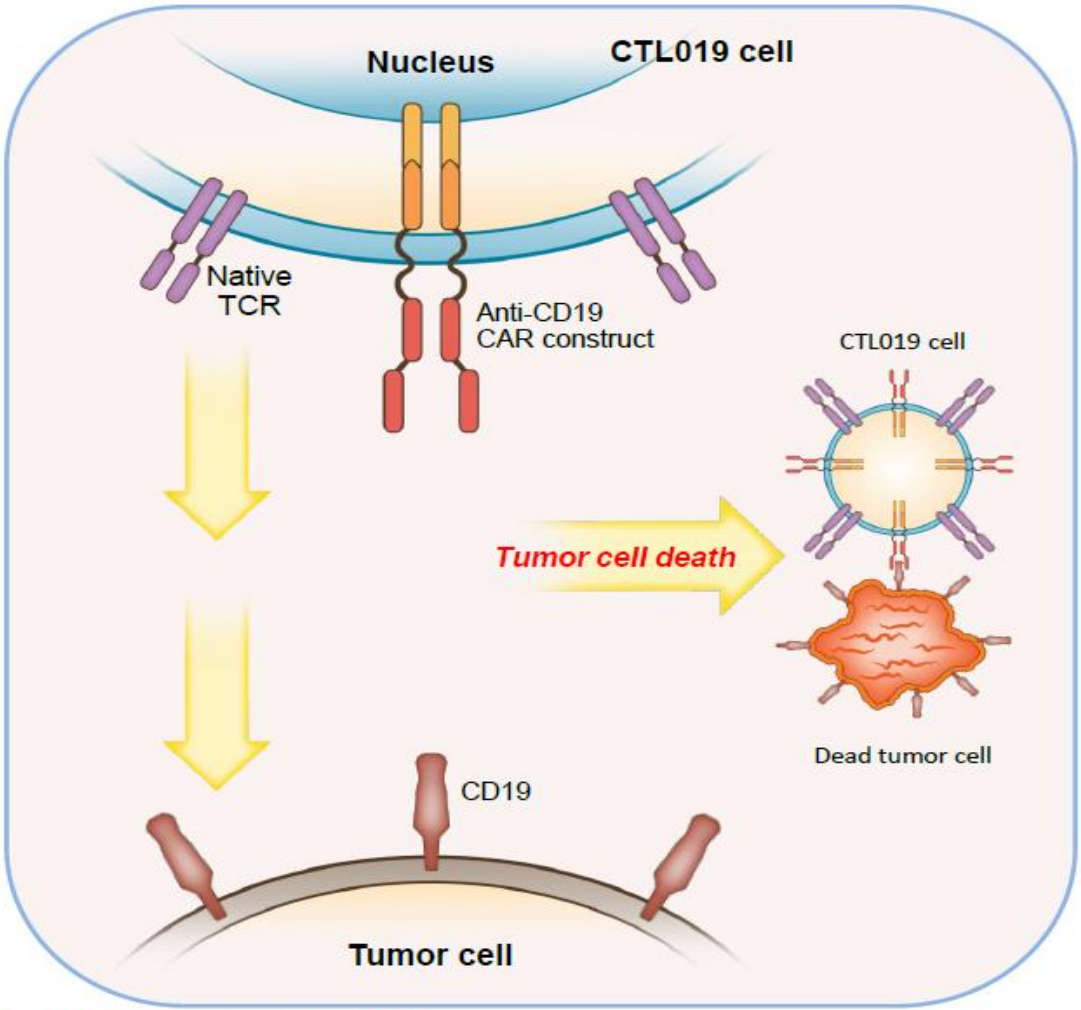
*Any grade or no details of grade; **Total n=30

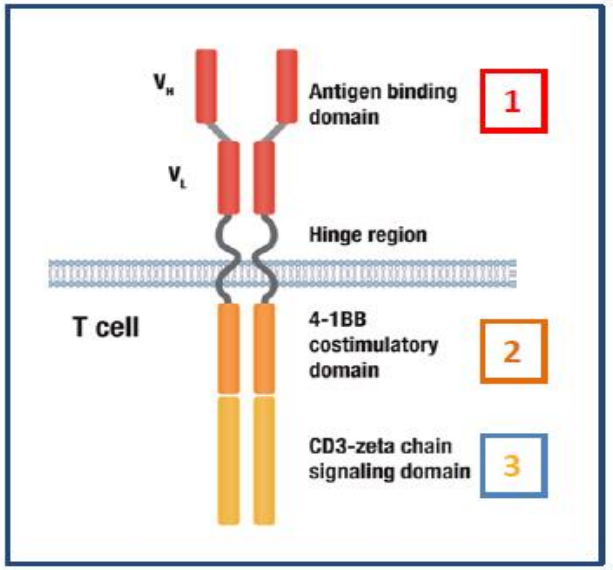




1. Park JH, et al. Oral presentation at ASH 2014. Abstract 382
2. Grupp S, et al. Oral presentation at ASH 2014. Abstract 380
3. Maude SL, et al. N Engl J Med 2014;371:1507–17
4. Lee DW, et al. Lancet 2014; doi:10.1016/S0140-6736(14)61403-3

CTL019





1. **Antigen recognition domain**
   Recognizes CD19 antigen on B cells
2. **4-1BB costimulatory domain**
   Increases T-cell activation and enhances cytolytic function of T cells
3. **CD3-zeta chain signaling domain**
   Induces T-cell activation

1. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

CTL019 in Relapsed/Refractory Pediatric ALL Response and Resistance

- 93% CR rate (55/59 pts) at 1 mo after CTL019 therapy (median follow-up: 12 mos)
  - No response in 7% of pts
  - Therapeutic response similar at both high and low disease burdens
  - 6 pts went on to SCT, 1 to DLI
- 20 pts with CR at 1 mo subsequently relapsed
  - 2/3 relapsed with CD19- blasts (antigen escape); 1/3 relapsed with CD19+ blasts (particularly those with loss of CARs before 3-6 mos)

Grupp S, et al. 2015 ASH. Abstract 681.

CTL019 in Relapsed/Refractory Pediatric ALL: Efficacy

- OS: 79% at 12 mos (95% CI: 69-91)
- RFS: 76% at 6 mos (95% CI: 65-89)
  - 55% at 12 mos (95% CI: 42-73)
  - No relapses past 1 yr
- 18 pts (33%) remain in remission beyond 1 yr
  - 13 (24%) with no further therapy

Grupp S, et al. 2015 ASH. Abstract 681.

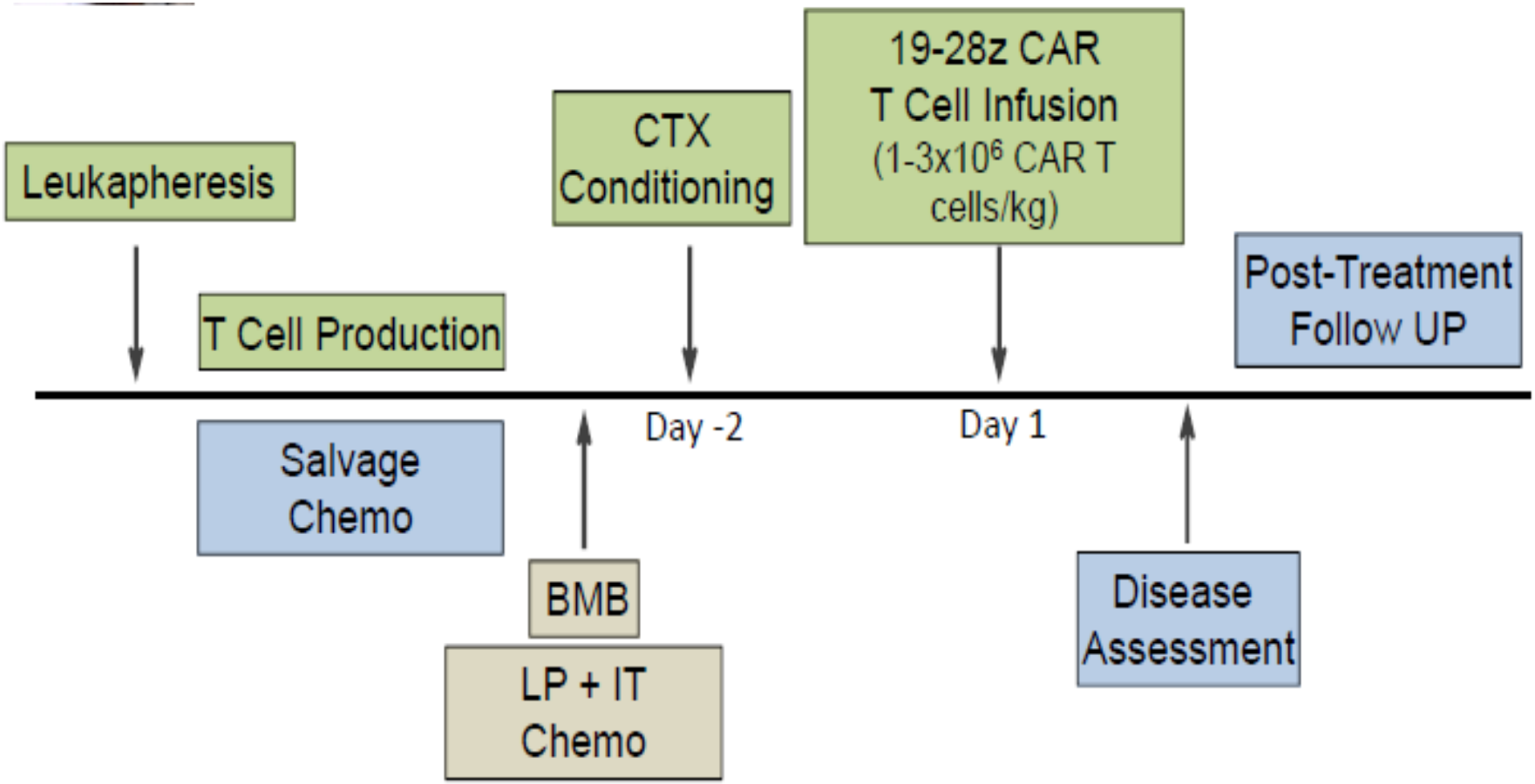
CTL019 in Relapsed/Refractory Pediatric ALL: CRS, Other AEs

- 88% of pts developed CRS, reversible with IL-6 receptor antagonist (tocilizumab)
- Severe CRS associated with elevated
  - Ferritin, suggesting macrophage activation syndrome
  - Initial disease burden (highly predictive of CRS)
  - IL-6 level (strongly associated, but not predictive of CRS)
- Analysis of cytokines showed marked increases of sgp130, IFN, and IL-1RA were highly predictive of CRS
- 100% of pts experienced B-cell aplasia (managed with IVIg)

Grupp S, et al. 2015 ASH. Abstract 681.

Update: fase I 19-28z CAR-T en adultos con LLA-B en recaída/EMR+

Park L, et al. ASH 2015



Tasas de RC

	Number of Patients N=45 (%) [95% CI]
Overall CR Rate	37/45 (82%) [68 – 92]
Morphologic disease (≥5% blasts)	18/24 (75%) [53 – 90]
Minimal disease (<5% blasts)	19/21 (91%) [70 – 99]
Overall MRD Negative CR Rate*	30/36 (83%)
Mean Time to CR (SD)	22 days (9.4)

*Assessed among those patients who achieved CR and evaluable for MRD analysis (n=36)

Supervivencia global

Pt Subgroup	Median OS, Months	6-Mo OS, Proportion of Pts (95% CI)
All	9.0	0.65 (0.47-0.78)
CR	10.6	0.71 (0.51-0.84)
MRD-negative CR	NR	0.80 (0.57-0.91)
▪ With allo HSCT	NR	0.79 (0.38-0.94)
▪ No allogeneic HSCT	10.6	0.80 (0.50-0.93)
MRD-positive CR	6.0	0.43 (0.10-0.73)

Toxicidad específica

Subgroups	Severe CRS*	Grade 3/4 Neurotoxicity	Grade 5 Toxicity
Overall (n=39)	9 (23)	11 (28)	3 (8)¶
Pre-T cell Disease Burden			
Morphologic disease (n=21)	9 (43)	8 (38)	2 (10)
MRD (n=18)	0 (0)	3 (17)	1 (6)

*Requiring vasopressors and/or mechanical ventilation for hypoxia

¶1 pt with ventricular arrhythmia (DNR); 1 pt had seizure, but unknown cause of death; and 1pt died of sepsis.

- Severity of CRS correlated with disease burden.
- CRS managed with IL-6R inhibitor (4 pts), steroid (2 pts), IL-6R inhibitor+steroid (9 pts)
- Neurological symptoms are reversible, and can occur independent of CRS

Manejo del CRS

Grade	Characteristics	Treatment
1	▪ Fever, constitutional symptoms	▪ Vigilant supportive care (treat any fever, neutropenia; monitor fluid balance) ▪ Assess for infection
2	▪ Hypotension that responds to fluids or a low-dose pressor ▪ Hypoxia that responds to < 40% O_2 ▪ Grade 2 organ toxicity	▪ If no extensive morbidities or older age: vigilant supportive care, including organ monitoring ▪ If extensive morbidities or older age: vigilant supportive care, tocilizumab ± corticosteroids
3	▪ Hypotension that requires multiple pressors or high-dose pressors ▪ Hypoxia that requires ≥ 40% O_2 ▪ Grade 3/4 organ toxicity; transaminitis	▪ Vigilant supportive care ▪ Tocilizumab ± corticosteroids
4	▪ Mechanical ventilation ▪ Grade 4 organ toxicity excluding transaminitis	▪ Vigilant supportive care ▪ Tocilizumab ± corticosteroids

CD19-CAR T Cells
Incógnitas

- Toxicidad inflamatoria puede ser grave
- Incertidumbre sobre la actividad crónica antiCD19
  - Aplasia crónica de células B
  - Agotamiento de células efectoras
- Clonas resistentes: CD19 negativos
- Eficacia a largo plazo?
- Se podrá prescindir del trasplante alogénico?

¿Soluciones?

Advance	Feature
Humanized single chain variable fragment (scFv) domains	Prevent exhaustion?
CAR T-cells from donors	- Effective in ALL pts. relapsed after HSCT without causing GVHD - Pre-emptive DLI
Addition of Fluda to Cy Lymphodepletion	Improves *in vivo* expansion of CD19 CAR T cells and clinical outcome
CAR CD4 cells alone	Better persistence?
Anti CD22 CAR T	Active in relapse after CD19 CAR T
CART123 + CART19	Active in CD19-negative relapse
Bispecific CAR-T targeting both CD19 and CD22	Preclinical data

Conclusiones

- Cambios ya reales en el manejo del paciente con LLA-B
- Y la LLA-T????
- Pero queda mucho por hacer
  - Blina en EMR o en primera línea?
  - Inotuzumab en primera línea?
  - CAR-T muy limitada experiencia

¿Avances en LLA?

Gracias