OHSU: BDMS # 20: “My” Highlights of ASH 2023

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Disclosures

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Outline

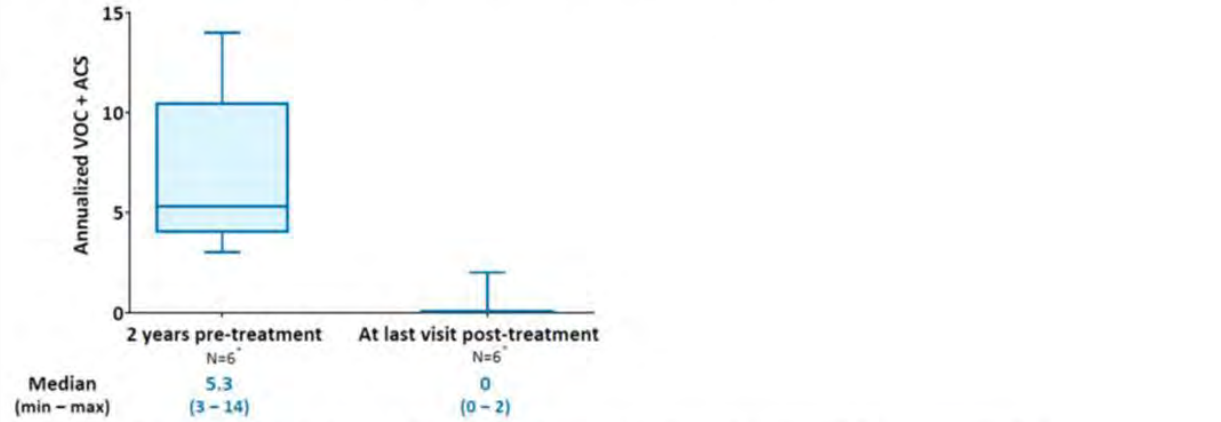
1. Disease management
2. Transplantation
3. Cell therapy

Hematologic Disease

Lentiglobin for SCD gene therapy into autoCD34+ cells after MA induction, Walters et al, 2020

Figure 1. Median Total Hb and Hb fractions at various follow-up time points in HGB-206 Group C

Figure 2. Reduction in annualized rate of VOC + ACS post-treatment



*Patients with ≥ 1 VOC/ACS in the 2 years before Informed Consent and with ~ ≥ 6 months of follow-up post-DP infusion.
One non-serious Grade 2 VOC was observed 3.5 months post-treatment. No ACS or serious VOCs were observed in Group C patients' post.

Group C:
Improve manufacture and
Plerixafor mobilization of PBSC

Gene Therapy is here to stay
ASH 2022 Abst #11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease, Walters et al

- Lovo-cel (bb1111; LentiGlobin for sickle cell disease [SCD]) gene therapy (GT) uses auto HCT of HSPC transduced with the BB305 lentiviral vector, coding for modified β-globin gene, →sickling hemoglobin (Hb), HbA^{T87Q}
- Eligiblity: SS pts, aged 12- 50, recurrent vaso-occlusive episodes
- Results- 35 pts highlighted (Gr C), med f/u 20.9 mos

Abst #11: Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease, Walters et al

Figure 1A. Total Hb and Fractions in Group C of the HGB-206 Study

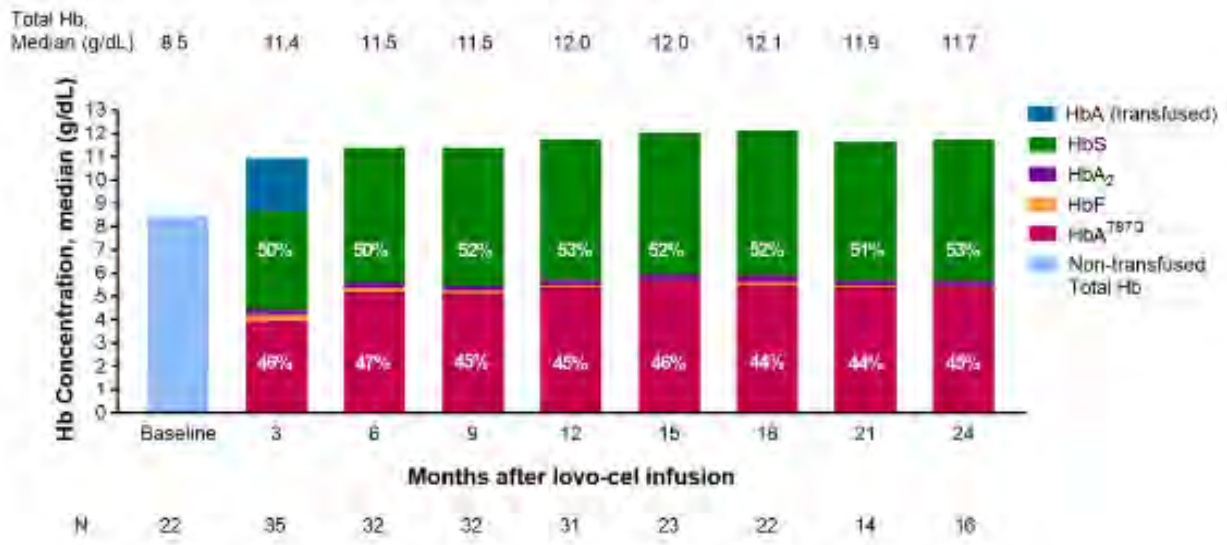
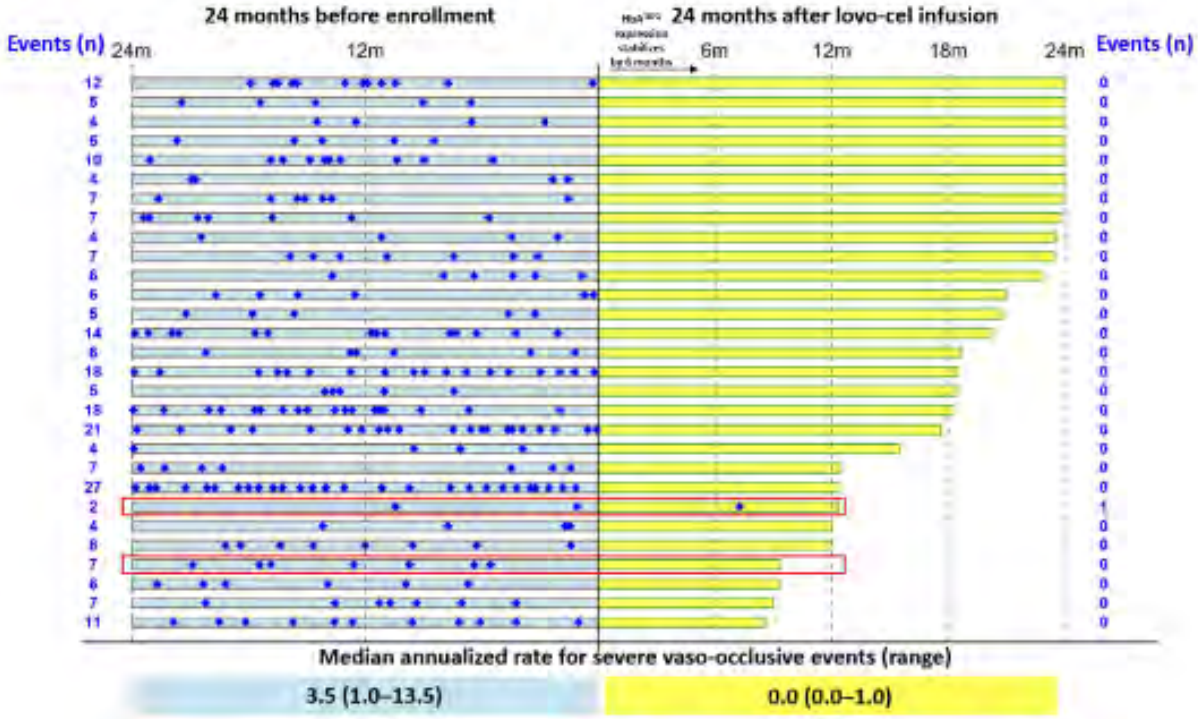


Figure 1B. Severe Vaso-Occlusive Events in Group C of the HGB-206 study



Generic name: Lovotibeglogene autotemcel

Abst. # 1052: Exagamglogene autotemcel for severe SSD, Frangoul et al

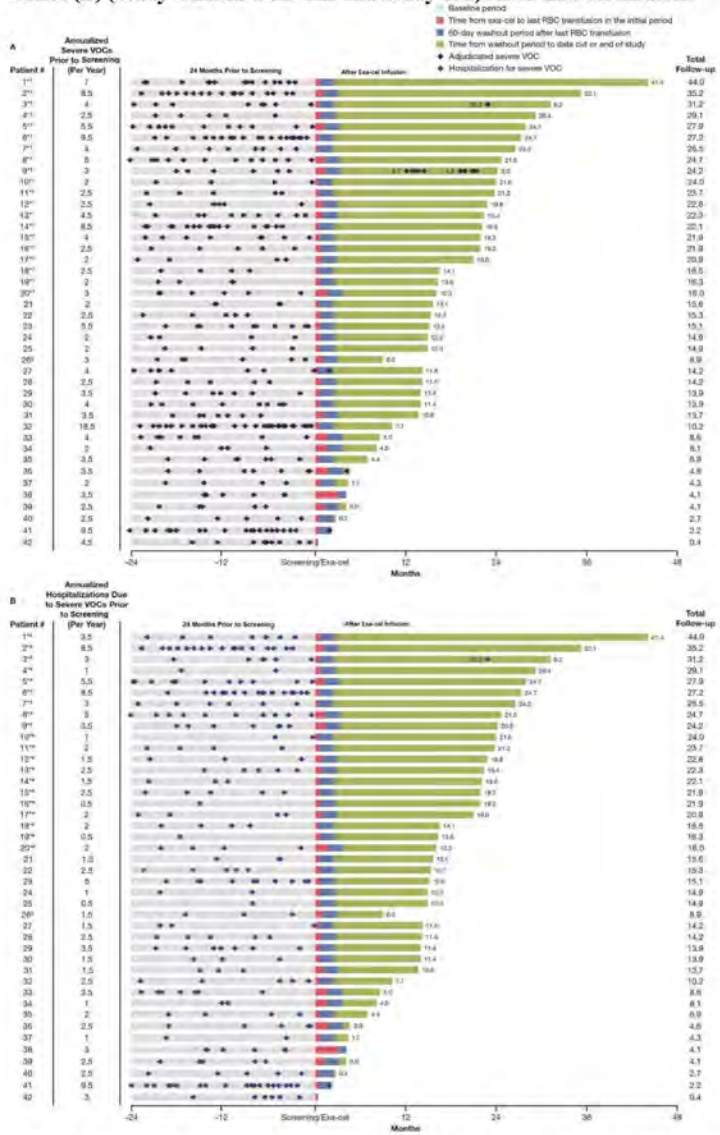
CLIMB SCD-121 trial

Non-viral cell therapy designed to reactivate HGB F via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ HSPCs at the erythroid-specific enhancer region of BCL11A gene in pts with severe SSD

N = 42, med age 21.
19/20 evaluable free of VOC ≥ 12 mos; 29/30 evaluable free of VOC ≥ 9 mos; 100% of subjects did not require hospitalizations.

Parallel study: # 1053, Locatelli et al:
CLIMB THAL-111→met 1° & 2° endpoints, with exa-cel treatment resulting in early and sustained increases in Hb and HbF leading to transfusion independence in >90% of pts with TDT and improved QOL.

Figure. Duration of Period Free From Vaso-Occlusive Crises (A) and Hospitalizations for Vaso-Occlusive Crises (B) (Study CLIMB SCD-121 and Study 131) After Exa-cel Infusion

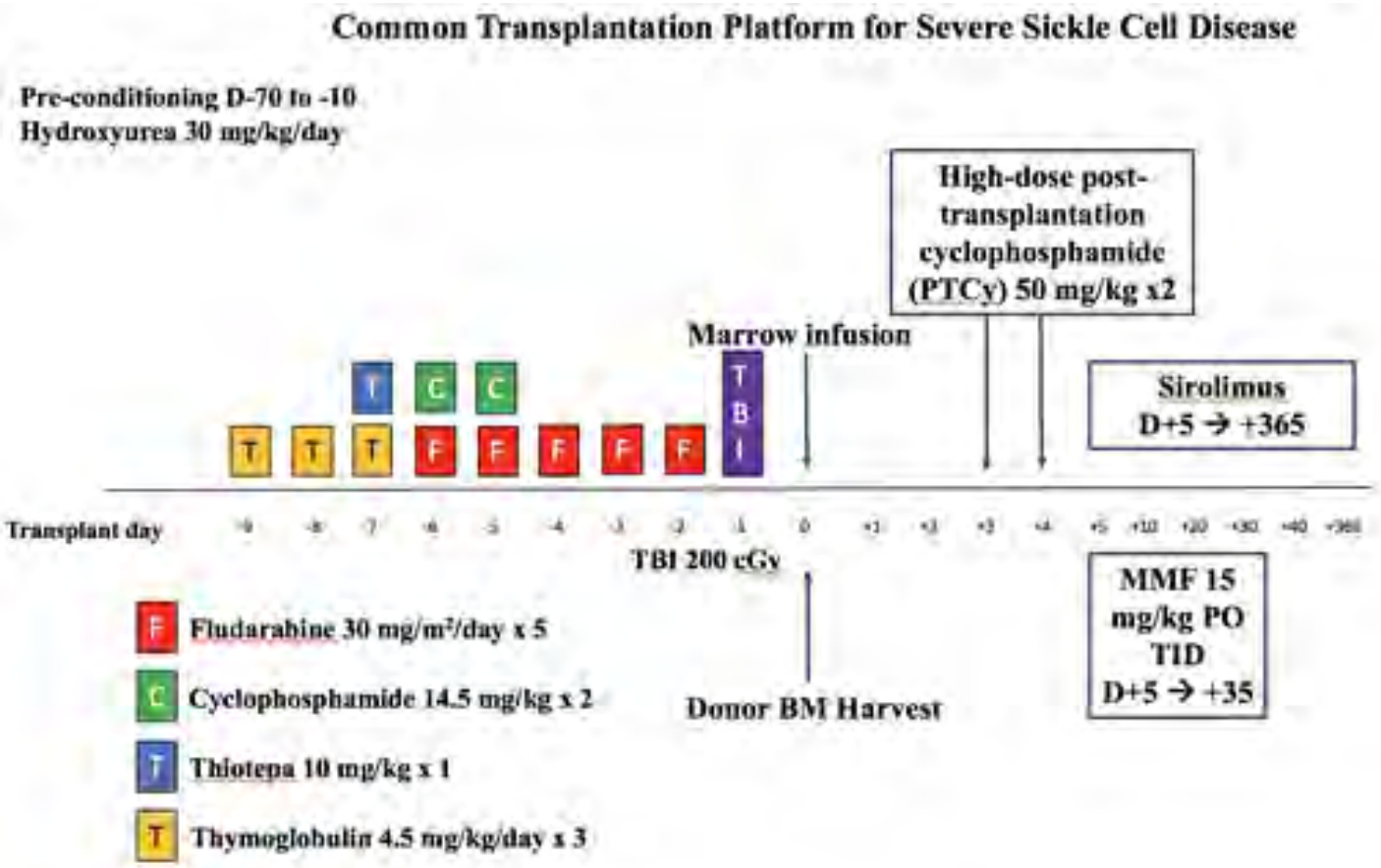


All VOCs were adjudicated by the Independent Endpoint Adjudication Committee. *Participant was evaluable for the primary endpoint (VF12) and first key secondary endpoint (HF12); †Participant achieved VF12; ‡Participant did not achieve VF12; §Death from respiratory failure due to COVID-19 infection; ‖Participant achieved HF12

Pros and Cons of gene therapy

Gene Addition	Mechanism	Pros	Cons
Lentiviral vector gene addition	Lentiviral vector encoding of either a human γ-globin gene or a normal or modified β-globin gene designed for anti-sickling activity Lentiviral vector encoding a short hairpin RNA molecule for posttranscriptional silencing of BCL11A	Stable integration into the host genome for long-term expression No immunogenicity Transduce non-dividing HSCs with high efficiency Can accommodate large transgenes	Semi-random integration leading to potential off-target effects or insertional mutagenesis
Gene Editing	**Mechanism**	**Pros**	**Cons**
Nuclease editing (CRISPR/Cas9, ZFN)	NHEJ: HbF induction via disruption of BCL11A erythroid enhancer HbF induction via disruption of BCL11A binding at the gamma globin promoter	Non-integrating Tools are transient High editing efficiency In use in multiple clinical trials	Requires DSB (genotoxicity) Potential off-target editing Induce a p53 response
	HDR: Direct correction of the sickle mutation	Non-integrating Tools are transient High editing efficiency Direct conversion	Requires DSB (genotoxicity) Potential off-target editing Induce a p53 response Requires donor template Lower editing efficiency
Base editing	Direct conversion of the sickle mutation to create Makassar mutation HbF induction by disruption of non-coding regions (BCL11A, gamma globin promoter) or generation of de novo activators (gamma globin promoter)	No DSB Limited insertion/deletions Single or multiplex genome engineering	Potential off-target editing, unwanted bystander editing, or spurious deamination

Abst. LBA-4: Reduced Intensity Haploidentical Bone Marrow Transplantation in Adults with Severe Sickle Cell Disease: BMT CTN 1507, Kassim et al



Abst. LBA-4: Reduced Intensity Haploidentical Bone Marrow Transplantation in Adults with Severe Sickle Cell Disease: BMT CTN 1507, Kassim et al

- Eligibility: adv. SCD pts; age 15-45; HLA haploID 1st degree donor; BM only
- Primary objective: EFS at 2 yrs
- **N = 54**; 42 → allo HCT as planned.. Med age 22.8 yrs. VOC 3%; Chest syndrome 17%; CVA 17%
- Results:
  - EFS 88%; 2 yr OS 95% post HCT; 3 graft failures
  - aGVHD II-IV 26%; GR III/IV 5%; severe cGVHD 7%
  - 3 deaths in yr 1: organ failure-lung; CNS hemmorhage & ARDS.
- Conclusion: Haploidentical BMT with PTCy - suitable and tolerable curative therapy for adults with SCD & severe end-organ toxicity
  - N.B.: Included stroke and pulmonary hypertension- typically excluded from myeloablative gene therapy and gene editing trials

BMT CTN 1507

Comparison of the two curative therapies for adults with severe SCD.

Variables	**Haploidentical BMT with Post-Transplant Cyclophosphamide**	**Current Gene Therapy Approaches**
Curative	Yes	Yet to be validated
Intensity of regimen	Non-myeloablative	Myeloablative
Eligibility	Most adults with organ dysfunction	Limited to children with no organ dysfunction
Donor availability	>90% will have eligible related haploidentical donors	None needed (autologous)
Stem cell procurement	Single bone marrow harvest or peripheral stem cell mobilization of eligible family donor	Requires multiple apheresis cycles
Requirements	Requires only a FACT-accredited facility	Requires both GMP and FACT accredited facilities

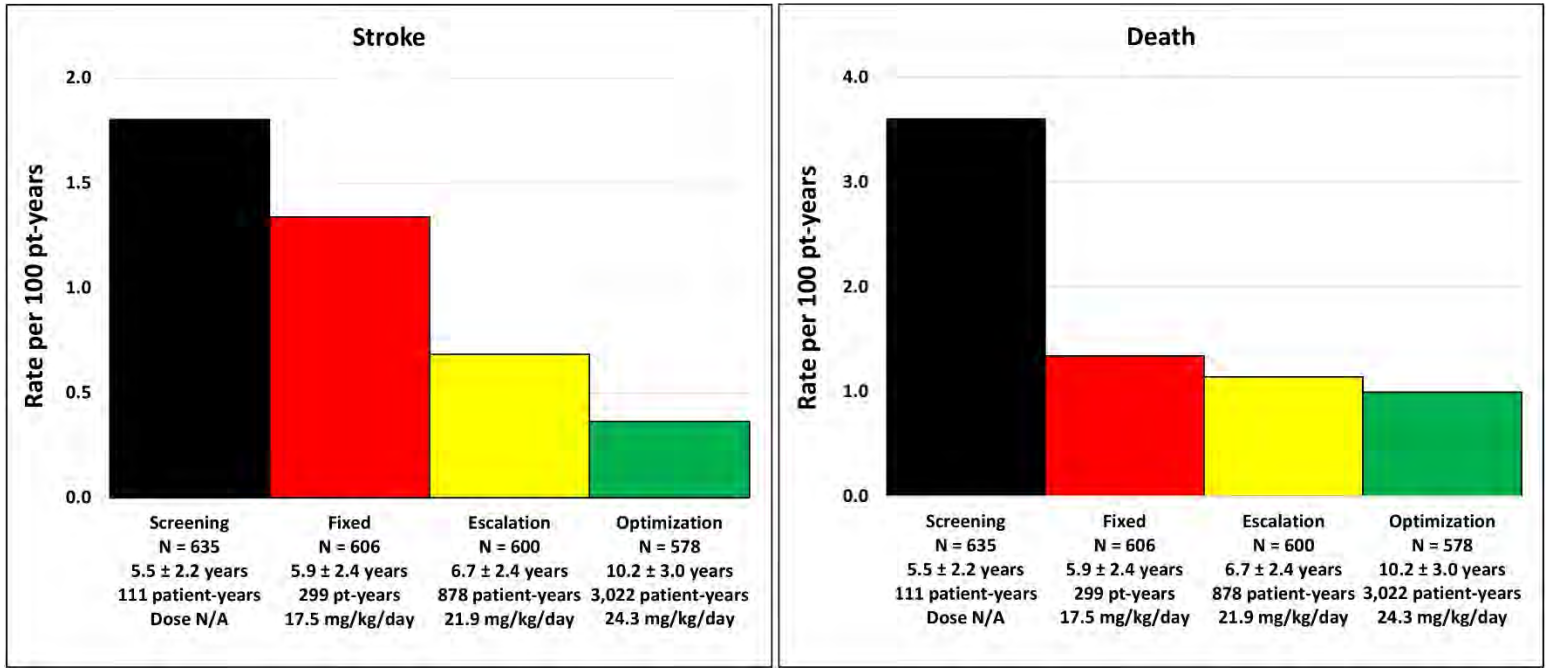
BMT CTN 1507

Comparison of the 2 curative therapies for adults with severe SCD (cont).

Variables	Haploidentical BMT with Post-Transplant Cyclophosphamide	Current Gene Therapy Approaches
Toxicity of regimen	High-dose Cytoxan- short-term toxicity (hemorrhagic cystitis, cardiotoxicity, pulmonary fibrosis, immunosuppression, increased hepatic enzymes SIADH	busulfan toxicity (short-term—seizures, cardiovascular, GI, bronchopulmonary dysplasia with pulmonary fibrosis and hepatic SOS).
Outcomes	Evidence that a successful transplant attenuates progressive vasculopathy and end-organ damage	Unknown impact on progressive vasculopathy and end-organ damage in adults
Complications	Risk of GVHD and graft rejection	Avoids immunologic complications; Poor phenotypic correction & consistency, integration, Poor-level expression of inserted gene Poor erythroid lineage specificity;.
Late-effects	Long-term—less risk of ovarian failure, puberty, amenorrhea, or development of myeloid disorders from recipient derived clonal hematopoiesis of indeterminate potential (CHIP) in engrafted patients with current NMA approaches.	Long-term—ovarian failure, failure to achieve puberty and amenorrhea, secondary malignancies Chromosomal alterations may also occur; possible genotoxic effects; risk of clonal hematopoiesis of indeterminate potential (CHIP) prior to HSCT

Abst. #6: Hydroxyurea Dose Optimization Is Safe and Improves Outcomes for Children with Sickle Cell Anemia Living in Sub-Saharan Africa: The Reach Experience, Aygun et al

Children, age 1-10, SCA enrolled; n = 635
Hydroxyurea 15-20 mg/kg/d x 6 months, then escalate q 2 wks to MTD;
HU increased if ANC >3.0 x 10^9/L, Hb >5.0 g/dL, reticulocytes >100 x 10^9/L and platelets >100 x 10^9/L.
Results: 606 started HU; 527 remain; avg duration of Rx = 83 months
Optimal dose established range 27-29 mg/kg
VOE, Acute Chest syndrome, CVA, splenic sequestration → all decreased
Conclusions: SAFE and BENEFICIAL



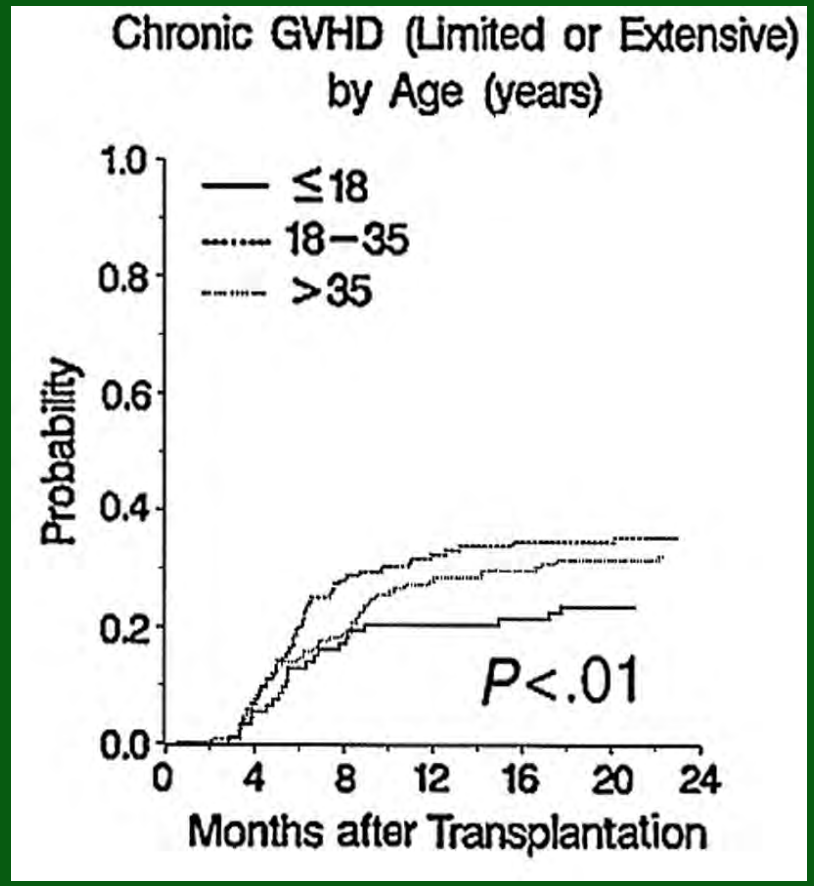
Hematopoietic Cell Transplantation

Thoughts: allo HCT

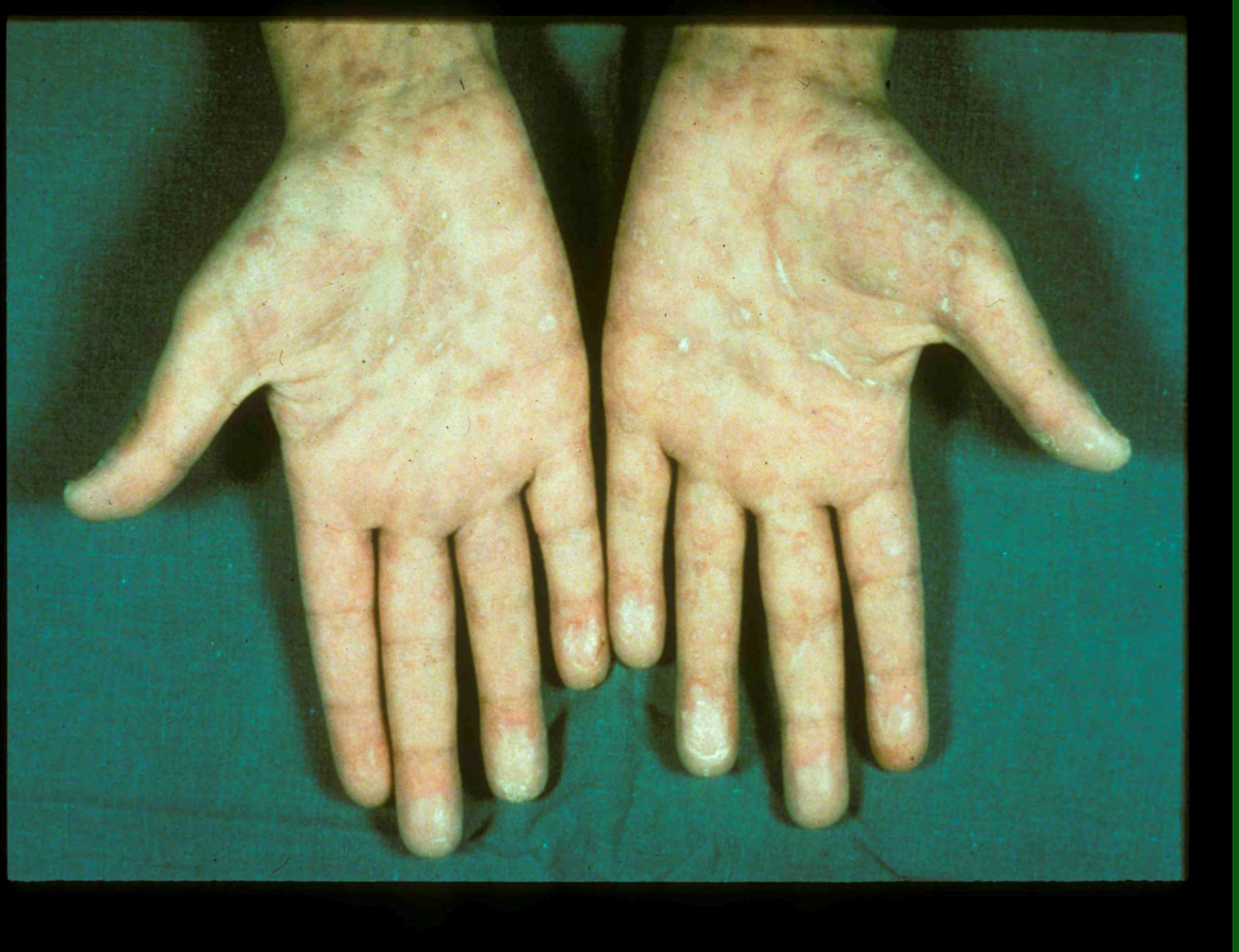
- Still the mainstay of activity
- Major advances in the past half decade
- New grading scales- Minnesota/Ann Arbor aGVHD; NCI cGVHD
- FDA approvals for acute & chronic GVHD
  - Prophylaxis: Abatacept
  - Treatment: MSC, ruxolitinib in aGVHD; ibrutinib, ruxolitinib, belumosodil in cGVHD

CHRONIC GVHD
Mechanism and Clinical Staging

- Onset beyond 100 days after hematopoietic cell infusion
- Attack by T cells derived from donor stem cells
- Older subjects have higher probability
- Recognized contribution by B dysfunctional cells
- Dysregulated thymic conditioning
- Mimics collagen-vascular & autoimmune diseases
- Organs involved (epithelial & mesenchymal):
  - skin & Liver
  - muscle
  - GI tract
  - lung
  - eye, salivary glands

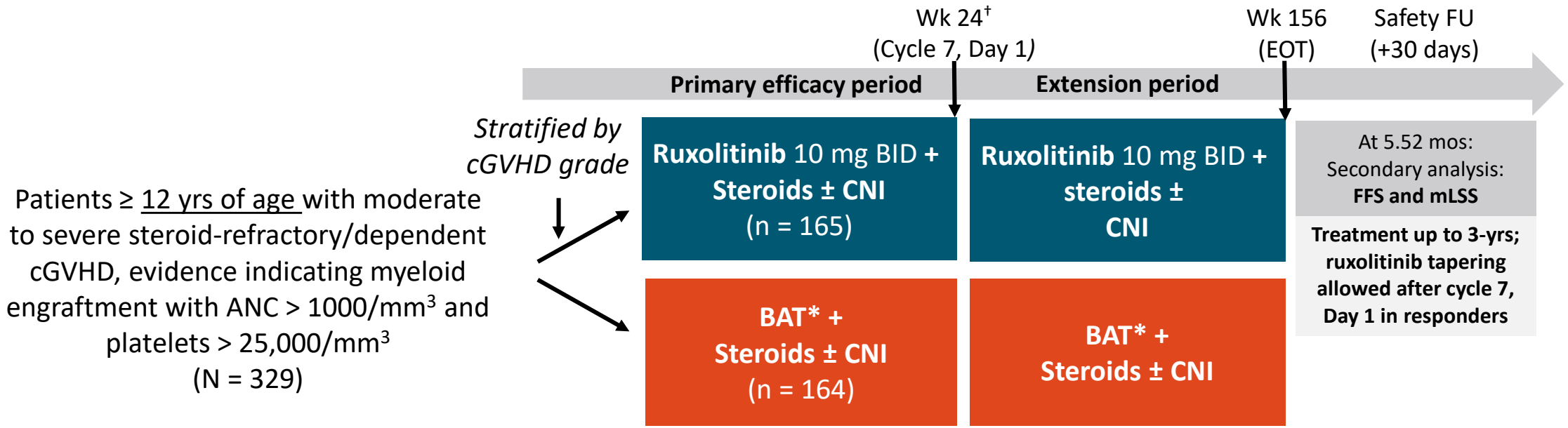


Pavletic, NHLBI. Blood 106: 3308-3313, 2005



REACH3: Ruxolitinib vs Best Available Therapy

- Multicenter, open-label, randomized phase III trial[1,2]



*Investigator choice of BAT: ECP, low-dose methotrexate, mycophenolate mofetil, everolimus, sirolimus, infliximab, rituximab, pentostatin, imatinib, or ibrutinib.
†Patients receiving BAT who progressed, had mixed or unchanged response, developed toxicity to BAT, or experienced a cGVHD flare could cross over to ruxolitinib.

- Primary endpoint: ORR at Wk 24 by NIH consensus criteria for response[3]
- Key Secondary endpoint: FFS

1. Zeiser. NEJM

REACH3: ORR at Wk 24 (Primary Endpoint)

Characteristic, n (%)	RUX (n = 165)	BAT (n = 164)	OR (95% CI)
Responders	82 (49.7)	42 (25.6)	2.99 (1.86-4.80; *P* < .0001)
▪ CR	11 (6.7)	5 (3.0)	
▪ PR	71 (43.0)	37 (22.6)	
Nonresponders			
▪ Unchanged response	9 (5.5)	15 (9.1)	
▪ Mixed response	10 (6.1)	17 (10.4)	
▪ Progression	4 (2.4)	21 (12.8)	
▪ Other*	5 (3.0)	9 (5.5)	
▪ Unknown†	55 (33.3)	60 (36.6)	

*Patients with additional systemic therapies and investigator-assessed CR/PR. †Death, early discontinuation, or missing data.

- Median duration of best overall response was not reached in the RUX arm vs 6.24 in the BAT arm

Zeiser. ASH 2020. Abstr 77.

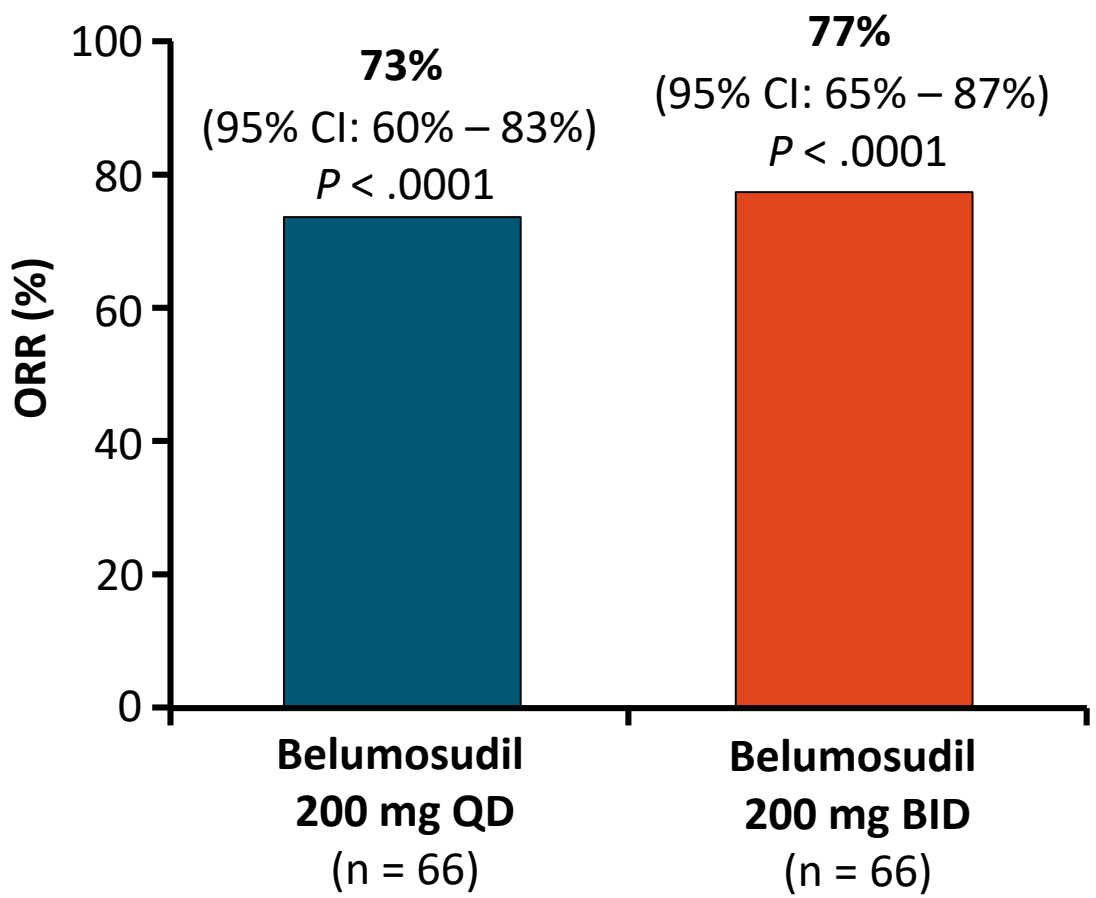
Slide credit: clinicaloptions.com

ROCKstar Trial: Background

- ROCK is a serine/threonine kinase with 2 isoforms (ROCK1 and ROCK2), which regulate transcription of profibrotic genes and mediate stress fiber formation in myofibroblasts[1,2]
- Belumosudil (KD025) is an oral selective inhibitor of ROCK2
- In the earlier phase IIa KD025-208 study, belumosudil yielded an **ORR of 65%** in patients with chronic GVHD (cGVHD) who had previously received 1-3 prior lines of systemic therapy[4]
- KD025-213 (ROCKstar) reports top-line results for safety and efficacy of belumosudil as daily or twice daily treatment for cGVHD after 2-5 prior lines of systemic therapy[5]

1. Zanin-Zhorov. Proc Natl Acad Sci USA. 2014;111:16814. 2. Riches. Am J Pathol. 2015;185:909. 3. Flynn. Blood. 2016;127:2144.
4. Jagasia. ASH 2019. Abstr 872. 5. Cutler. ASH 2020. Abstr 353.

ROCKstar: ORR (Primary Endpoint)



- Primary endpoint met at follow up
  - 12-month follow-up after last patient enrolled
- Clinically meaningful and statistically significant ORRs (defined as lower bound of 95% CI > 30%) for both QD and BID schedule
  - CR in all affected organs: n = 7
  - Median time to response: 4 wks

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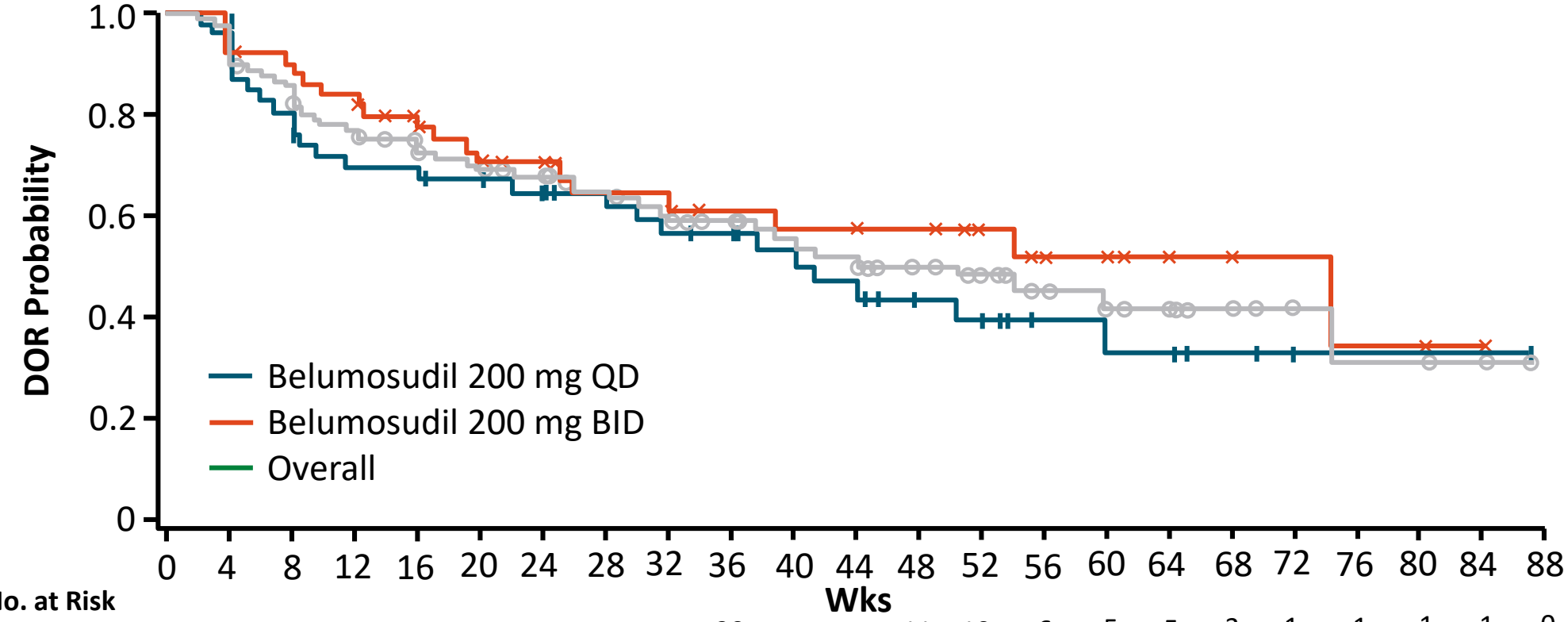
ROCKstar: DoR

- Median DoR: 50 wks; 60% of patients maintained response ≥ 20 wks



No. at Risk																						
Belumosudil 200 mg QD	48	43	37	31	31	29	26	24	21	20	17	15	11	10	6	5	5	3	1	1	1	0
Belumosudil 200 mg BID	51	48	44	41	35	30	28	21	19	16	15	15	14	11	9	7	5	4	3	2	2	1	0
Overall	99	91	81	72	66	59	54	45	40	36	32	30	25	21	15	12	10	7	4	3	3	2	0

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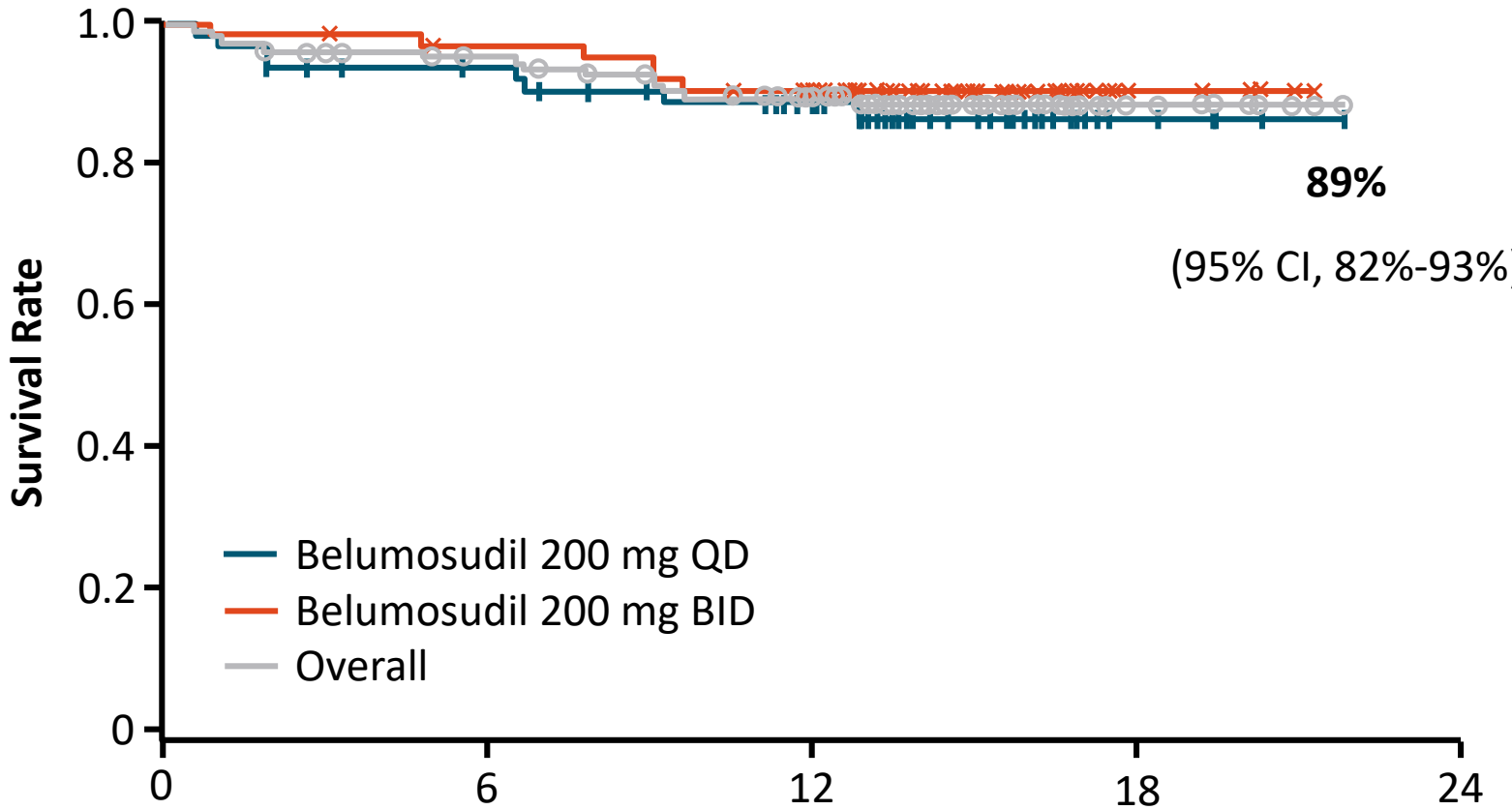
ROCKstar: OS



No. at Risk					
Belumosudil 200 mg QD	66	58	44	6	0
Belumosudil 200 mg BID	66	62	50	5	0
Overall	132	120	94	11	0

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Abst. #1: Safety and Efficacy of Axatilimab at 3 Different Doses in Patients with Chronic Graft-Versus-Host Disease (AGAVE-201), Wolff et al.

- Colony-stimulating factor 1 receptor (CSF-1R)–dependent monocytes and macrophages - key role in cGVHD inflammation and fibrosis. Axatilimab (SNDX-6352) -investigational, high-affinity anti–CSF-1R Mab targets monocytes and macrophages
- Pivotal phase 2, open-label, randomized, multicenter study evaluated axatilimab at 3 different doses in alloHCT patients with recurrent or refractory cGVHD
- Eligible patients were randomized 1:1:1 to receive intravenous (IV) axatilimab at 0.3 mg/kg every 2 weeks (Q2W), 1 mg/kg Q2W, or 3 mg/kg every 4 weeks (Q4W).
- Concomitant use of corticosteroids, calcineurin inhibitors, or mammalian target of rapamycin inhibitors (sirolimus or everolimus) was allowed
- 1^{o} efficacy endpoint was ORR in 1st 6 cycles (24 weeks), NIH 2014 consensus criteria
- Results: ORR (95% CI) was 74% (63, 83) with 0.3 mg/kg Q2W, 67% (55, 77) with 1 mg/kg Q2W, and 50% (39, 61) with 3 mg/kg Q4W.
  - Highest ORR and least toxicity at the 0.3 mg/kg Q2W dose

Abst. #1: Safety and Efficacy of Axatilimab at 3 Different Doses in Patients with Chronic Graft-Versus-Host Disease (AGAVE-201), Wolff et al.

Table 1. Patient Demographics and Response to Axatilimab

Parameter	0.3 mg/kg Q2W (n=80)	1 mg/kg Q2W (n=81)	3 mg/kg Q4W (n=80)
Median age, y (range)	50 (7, 76)[a]	56 (26, 81)	53 (7, 79)[b]
Male, n (%)	47 (59)	51 (63)	53 (66)
Race, white, n (%)	68 (85)	70 (86)	62 (78)
Time from cGVHD diagnosis to randomization, median, y (range)	3.9 (0.4, 17.6)	4.1 (0.6, 17.1)	3.8 (0.4, 15.4)
Number of prior lines of therapy, median (range)	4 (2, 12)	4 (2, 14)	4 (2, 15)
≥4	54 (68)	51 (63)	51 (64)
≥5	37 (46)	34 (42)	36 (45)
≥ 4 Organs involved, n (%)	45 (56)	46 (57)	39 (49)
Lung	32 (40)	41 (51)	35 (44)
Prior ibrutinib, n (%)	27 (34)	19 (24)	29 (36)
Prior ruxolitinib, n (%)	57 (71)	64 (79)	58 (73)
Prior belumosudil, n (%)	16 (20)	19 (24)	21 (26)
Summary of Response by Dose Cohort			
Objective response in first 6 cycles, n (%), (95% CI for ORR)	59 (74), (63, 83)	54 (67), (55, 77)	40 (50), (39, 61)
Complete response	1 (1.3)	0 (0)	1 (1.3)
Partial Response	58 (72)	54 (67)	39 (49)
mLSS reduction ≥7 points in first 6 cycles, n (%), (95% CI)	43 (55) (43, 66)	43 (54) (42, 65)	28 (36) (25, 48)
Median time to first response, mos (range)	1.5 (0.9, 5.1)	1.1 (0.9, 6.1)	1.4 (0.9, 5.6)
Median DOR SA1, mo (95% CI)[c]	7.1 (2.3, NE)	5.5 (3.6, 6.9)	4.9 (2.8, 9.5)
Median DOR SA2, mo (95% CI)[d]	NE (8.5, NE)	NE (6.9, NE)	NE (8.2, NE)
Durability of response at 12-mo, % (95% CI)[e]	60 (43, 74)	60 (43, 74)	53 (30, 71)
Sustained response ≥20 wk, % (95% CI)	50 (39, 61)	49 (38, 61)	38 (27, 49)

cGVHD, chronic graft-versus host disease; DOR, duration of response; mLSS, modified Lee Symptom Scale; NE, not estimable; ORR, overall response rate; Q2W, every 2 weeks; Q4W, every 4 weeks; SA, sensitivity analysis. [a]4 pediatric patients: ages 7, 12, 14, 15 years. [b]3 pediatric patients: ages 7, 7, 14 years. [c]Time from first response of either complete response or partial response until progression of cGVHD, start of another systemic treatment, or death, whichever is earlier. [d]Time from first response of either complete response or partial response until start of another systemic treatment, or death, whichever is earlier. [e]Event-free probability estimates.

Abst. #4797: Single cell transcriptomics of BOS, Mellors et al

- Bronchiolitis obliterans syndrome: associated with morbidity and mortality after allogeneic HCT and also lung transplantation
- Path: fibrotic obliteration of small airways→ progressive respiratory failure
- Methods: lung tissue obtained surgically or at autopsy- BOS & Control Pts
- Single cell libraries generated: cell origins identified by single cell transcriptomics
- Genes implicated in fibrosis and wound healing were upregulated in stromal cells in BOS patients
- Results reveal signaling from stromal cells to CD45+ve cells; stromal derived signaling associated with both fibrotic (collagen and fibronectin) and anti-fibrotic programs.
- Summary: There exists interplay between pro- and anti-fibrotic programs even in end-stage BOS lungs→ in future, could one intervene therapeutically in this dyshomeostatic balance????

Abst. #4797: Single cell transcriptomics of BOS, Mellors et al

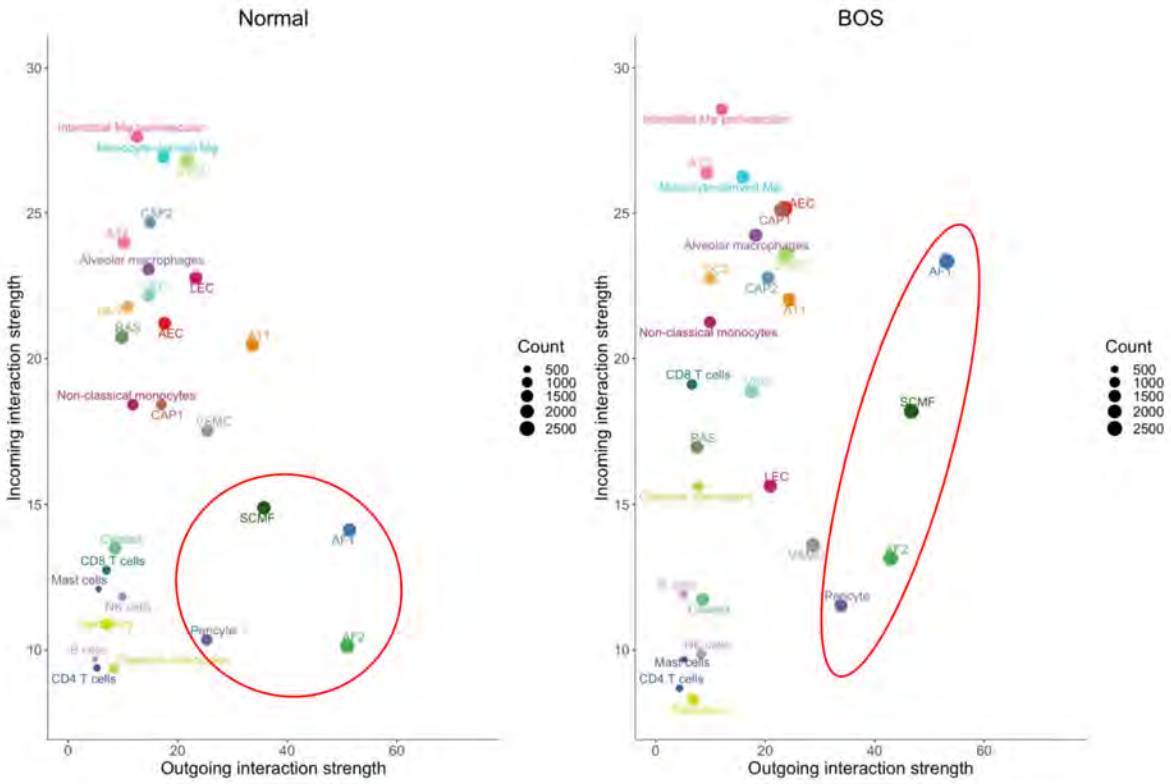


Figure 1: Scatter plot of incoming (Y axis) versus outgoing (X axis) interaction strength from normal (left) and BOS lungs (right). Red circles highlight stromal cells including pericytes, secondary crest myofibroblasts (SCMF), type 1 alveolar fibroblasts (AF1), and type 2 alveolar fibroblasts (AF2).

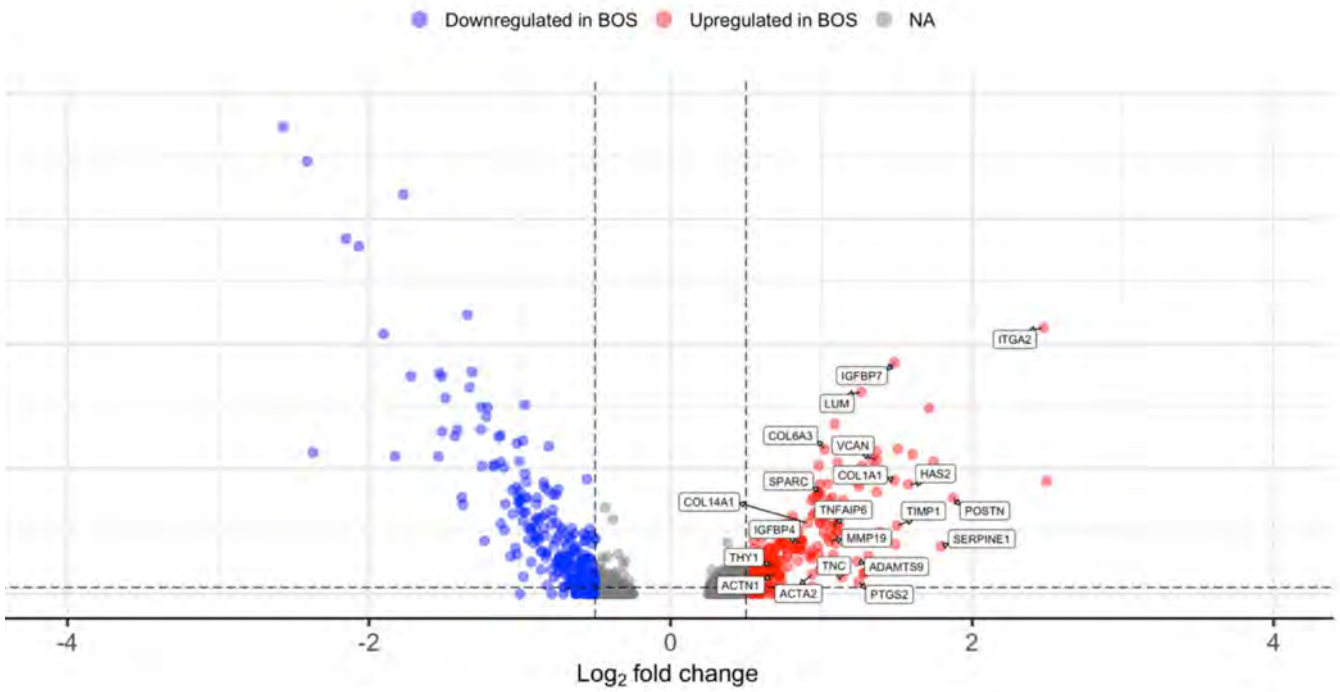


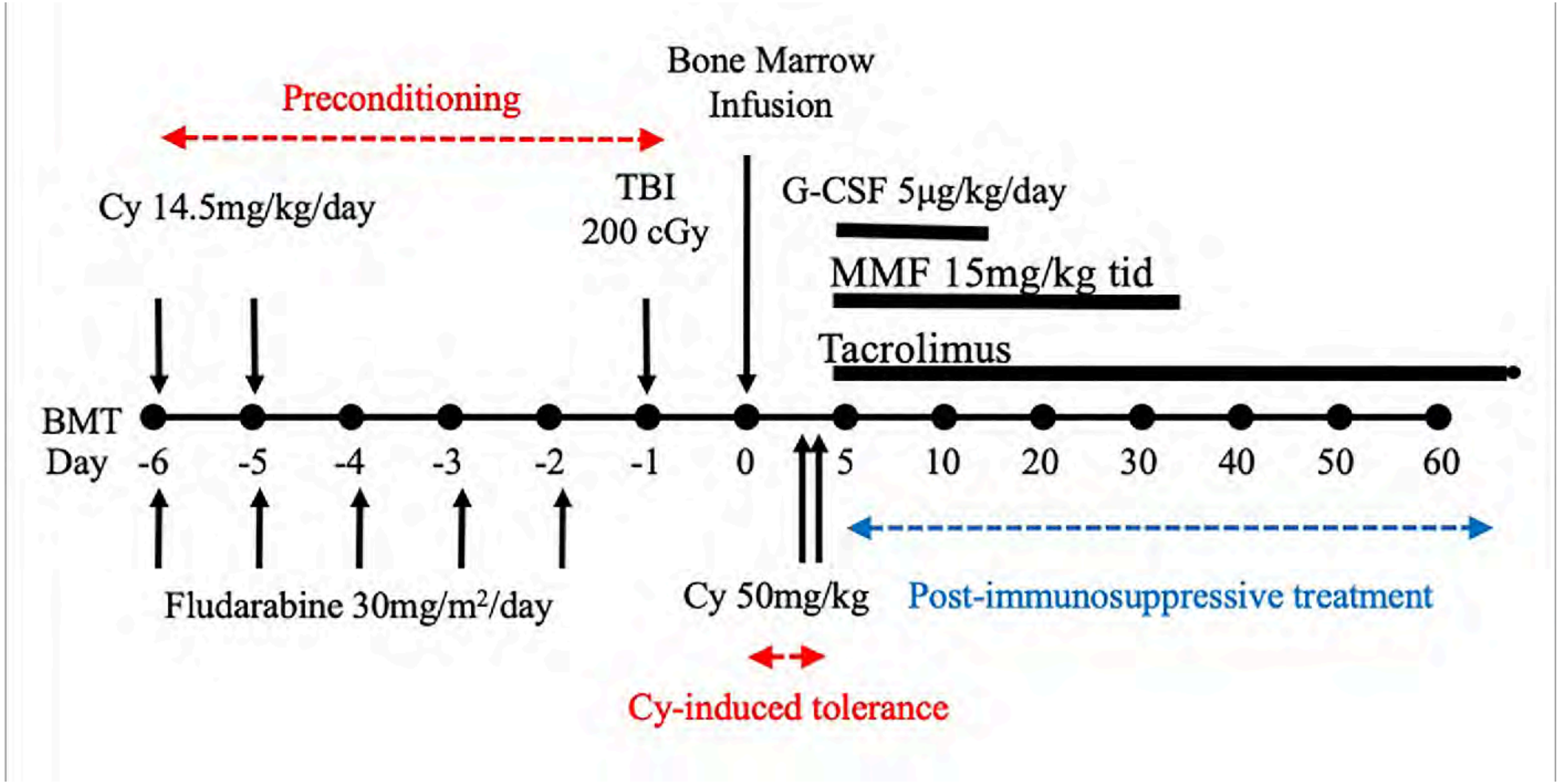
Figure 2: Volcano plot illustrating upregulation of genes implicated in fibrogenesis in BOS compared to normal controls

Stromal cell populations

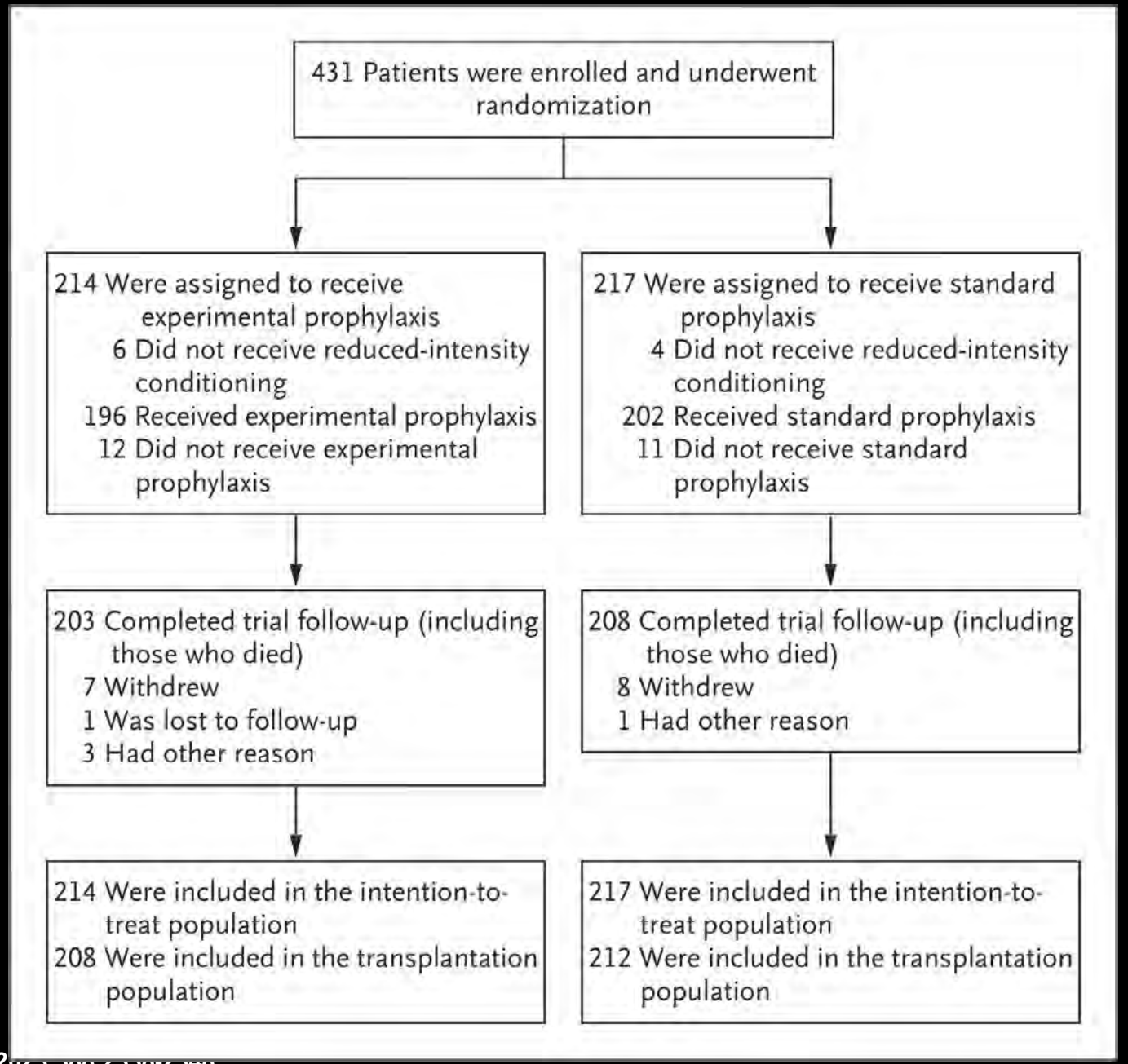
Acute GVHD:

- Many trials, limited success in new GVHD prophylaxis strategies over the past 3 decades
- Calcineurin inhibitor and MTX remained standard
- Other regimens equivalent outcomes- different toxicity profiles
- Previous 4 arm randomized phase II national trial- BMT CTN 1202: contemporary Tac/MTX vs Tac/MTX/Marivaroc vs Tac/MTX/Bortezomib vs Tac/MMF/ post HCT CTX
- Results: Tac/MMF/post HCT CTX appeared superior to marivaroc or bortezomib arms
- Phase III trial needed

GVHD prophylaxis with post-HCT CTX



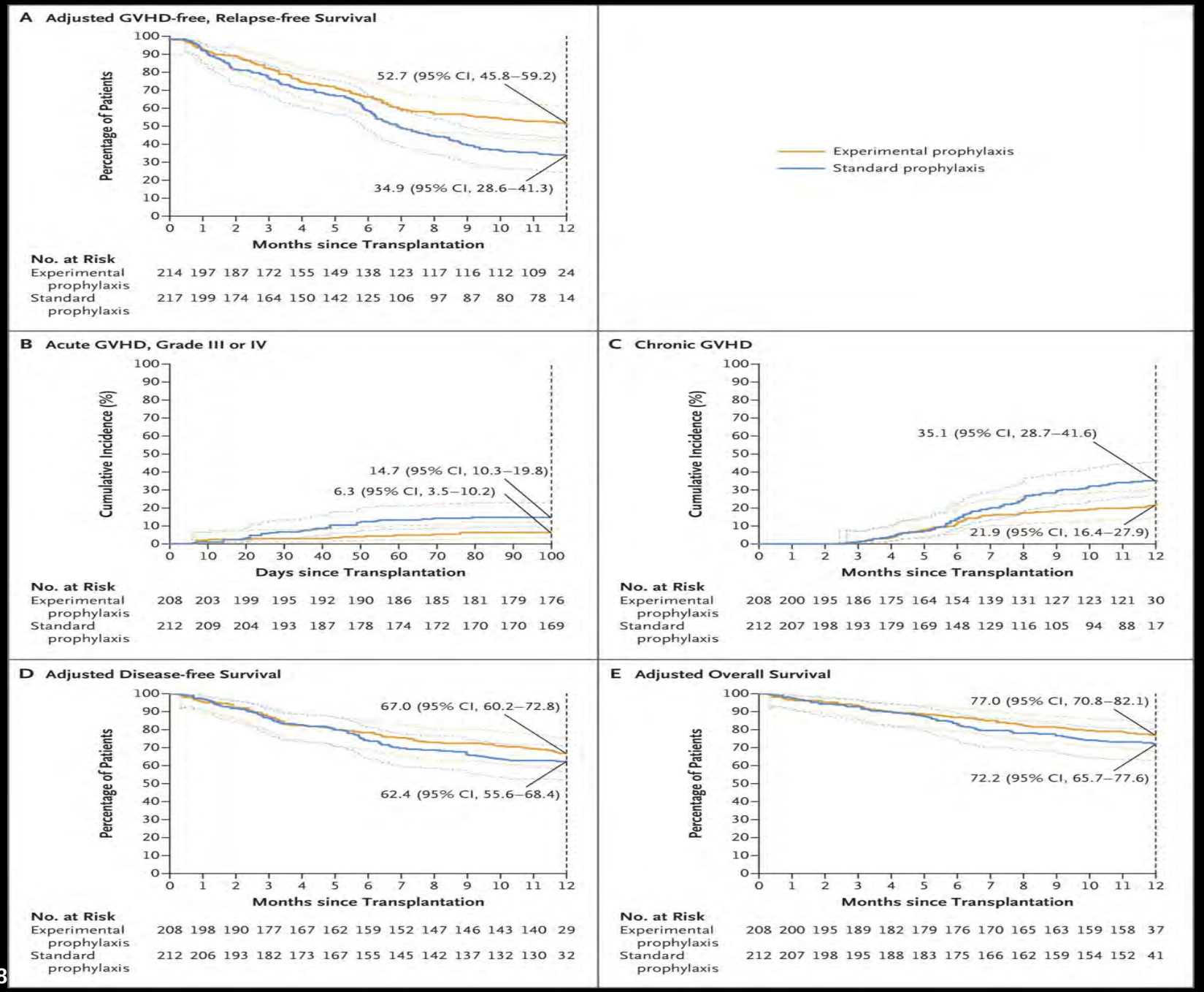
BMT CTN 1703: RIC Allo HCT Randomization, Treatment, and Follow-up.



Bolaños-Meade J et al. N Engl J Med2023;388:2338-2348

The NEW ENGLAND JOURNAL of MEDICINE

Adjusted Survival Probabilities and the Cumulative Incidence of Primary and Secondary End-Point Events.



Bolaños-Meade J et al. N Engl J Med2023;388:2338

Causes of Death in Patients in the Intention-to-Treat Population.

Table 3. Causes of Death in Patients in the Intention-to-Treat Population.

Cause of Death	Experimental-Prophylaxis Group (N=214)	Standard-Prophylaxis Group (N=217)
	number/total number (percent)	
Recurrence or persistence of disease	19/48 (40)	24/56 (43)
Primary graft failure	2/48 (4)	0
Acute GVHD	2/48 (4)	8/56 (14)
Chronic GVHD	0	1/56 (2)
Infection	8/48 (17)	10/56 (18)
Organ failure	11/48 (23)	6/56 (11)
Hemorrhage	3/48 (6)	1/56 (2)
Acute respiratory distress syndrome	0	1/56 (2)
Other*	3/48 (6)	5/56 (9)

* The "other" category includes accident, septic shock, thrombotic microangiopathy, and unknown.

Among patients undergoing allogeneic HLA-matched HSCT with reduced-intensity conditioning, **GVHD-free, relapse-free survival at 1 year was significantly more common** among those who received cyclophosphamide–tacrolimus–mycophenolate mofetil than among those who received tacrolimus–methotrexate.

Bolaños-Meade J et al. N Engl J Med2023;388:2338-2348

The NEW ENGLAND JOURNAL of MEDICINE

Abst. #2179: **Post-Transplant Cyclophosphamide or ATG As Gvhd Prophylaxis in Mismatched Unrelated Stem Cell Transplantation? – a Registry Analysis By the EBMT Transplant Complications Working Party, Penack et al.**

N = 2123 9/10 ag mMUD
PT Cy: 583; rATG: 1540

The incidences of cGVHD & aGVHD - not significantly different.
(2-years cGVHD: PTCy 31.7% [27.4 – 36] vs. rATG 30.3% [27.8 - 32.8]; HR 0.95, p=0.67.

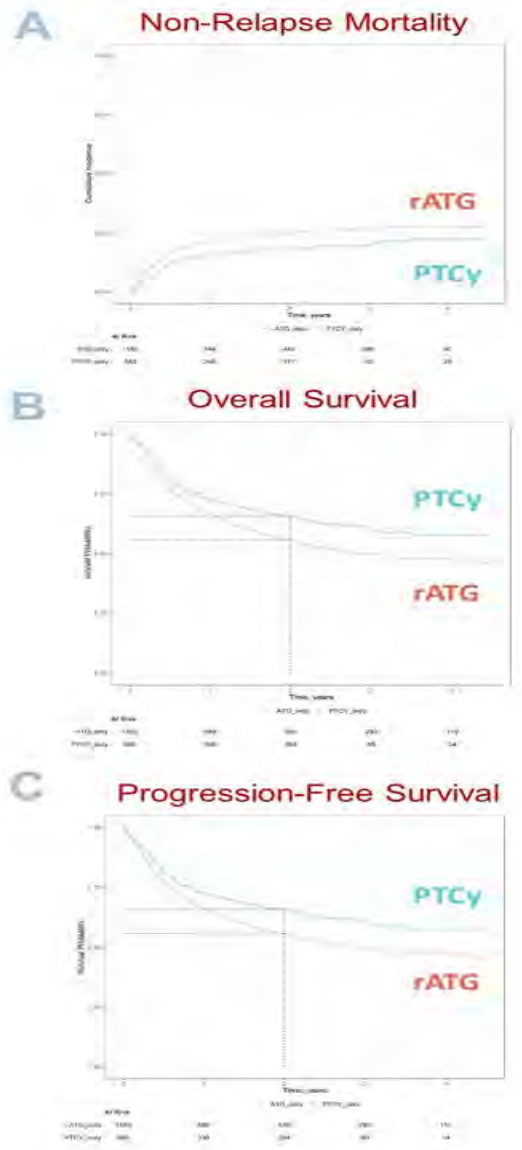
100-days aGVHD grades II-IV: PTCy 29.9% [25.9-34.1] vs. rATG 32.5% [30-34.9]; HR 0.83, p=0.11)

Conclusions: PtCy assoc with higher OS in mMUD recipients

Table 1

	ATG_only (N=1540)	PTCy_only (N=583)	Total (N=2123)	p value
Patient Gender				0.48[1]
Male	893 (58.0%)	348 (59.7%)	1241 (58.5%)	
Female	647 (42.0%)	235 (40.3%)	882 (41.5%)	
Age at Transplant, yrs				< 0.01[2]
median [Q1, Q3]	56.1 (44.7, 63.8)	51.7 (40.0, 62.2)	55.3 (43.6, 63.3)	
[Min, Max]	18.1 - 80.4	18.2 - 79.2	18.1 - 80.4	
Age at Diagnosis, yrs				< 0.01[2]
median [Q1, Q3]	53.9 (42.6, 62.1)	49.0 (37.0, 60.3)	52.8 (40.6, 61.6)	
[Min, Max]	10.0 - 79.9	10.6 - 78.6	10.0 - 79.9	
Missing count	2	0	2	
Karnofsky =>90				0.30[1]
< 90	375 (25.5%)	132 (23.3%)	507 (24.9%)	
>= 90	1094 (74.5%)	434 (76.7%)	1528 (75.1%)	
Missing count	71	17	88	
HCT Comorbidity Index				0.35[1]
0	716 (51.2%)	265 (49.6%)	981 (50.8%)	
1-2	324 (23.2%)	115 (21.5%)	439 (22.7%)	
>=3	359 (25.7%)	154 (28.8%)	513 (26.5%)	
Missing count	141	49	190	
DRI				0.14[1]
Low	128 (8.3%)	56 (9.6%)	184 (8.7%)	
Int	975 (63.3%)	362 (62.1%)	1337 (63.0%)	
High	355 (23.1%)	146 (25.0%)	501 (23.6%)	
Very high	82 (5.3%)	19 (3.3%)	101 (4.8%)	
Hematological Malignancies				
AML	768 (49.9%)	257 (44.1%)	1025 (48.3%)	
MDS	215 (14.0%)	83 (14.2%)	298 (14.0%)	
ALL	187 (12.1%)	86 (14.8%)	273 (12.9%)	
MPN	142 (9.2%)	36 (6.2%)	178 (8.4%)	
MDS & MPN overlap	49 (3.2%)	16 (2.7%)	65 (3.1%)	
CML	31 (2.0%)	16 (2.7%)	47 (2.2%)	
NHL	103 (6.7%)	55 (9.4%)	158 (7.4%)	
Hodgkins	30 (1.9%)	26 (4.5%)	56 (2.6%)	
CLL	15 (1.0%)	8 (1.4%)	23 (1.1%)	
Transplant Year				< 0.01[1]
2018	487 (31.6%)	145 (24.9%)	632 (29.8%)	
2019	455 (29.5%)	160 (27.4%)	615 (29.0%)	
2020	359 (23.3%)	172 (29.5%)	531 (25.0%)	
2021	239 (15.5%)	106 (18.2%)	345 (16.3%)	
Myeloablative Conditioning				0.49[1]
No	678 (44.2%)	247 (42.5%)	925 (43.7%)	
Yes	857 (55.8%)	334 (57.5%)	1191 (56.3%)	
Missing count	5	2	7	
TBI				< 0.01[1]
No	1320 (85.7%)	464 (79.6%)	1784 (84.0%)	
Yes	220 (14.3%)	119 (20.4%)	339 (16.0%)	
GVHD Prevention Regimen				
CSA+MTX based	881 (57.2%)	3 (0.5%)	884 (41.6%)	
CSA+MMF based	446 (29.0%)	313 (53.7%)	759 (35.8%)	
MMF+TACRO/SIRO based	95 (6.2%)	174 (29.8%)	269 (12.7%)	
CSA based	47 (3.1%)	15 (2.6%)	62 (2.9%)	
TACRO/SIRO based	4 (0.3%)	54 (9.3%)	58 (2.7%)	
MTX+TACRO based	54 (3.5%)	0 (0.0%)	54 (2.5%)	
Other	13 (0.8%)	24 (4.1%)	37 (1.7%)	

Figure 1



Abst. #3558: **Post-Transplant CTX or ATG As Gvhd Prophylaxis in Matched Unrelated Stem Cell Transplantation? – a Registry Analysis By the EBMT Transplant Complications Working Party, Penack et al.**

N = 8764 MUD
PT Cy: 1039; rATG: 7725

Chronic GVHD lower in the PTCy arm (2-years cGVHD: PTCy 28.4% [25.2 - 31.7] vs. rATG 31.4% [30.3 - 32.6]; HR 0.77, p=0.012)

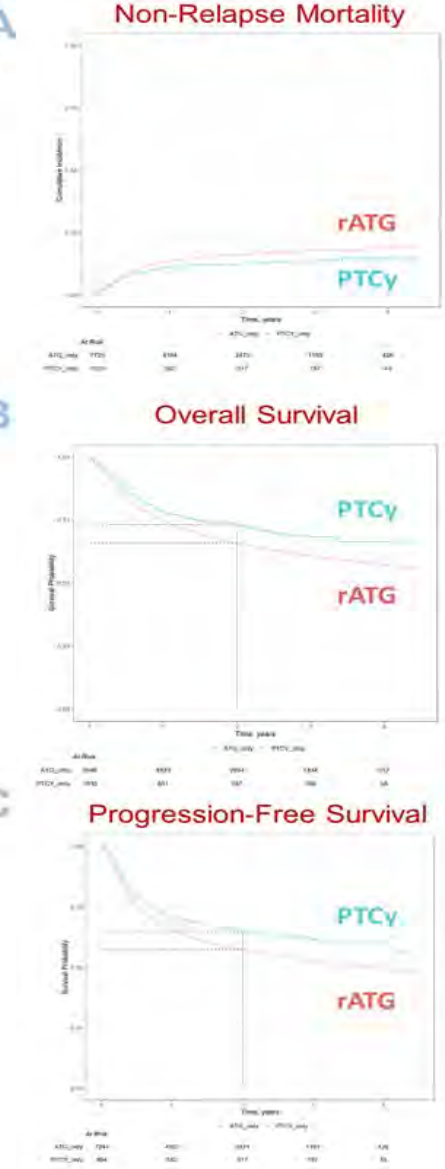
Acute GVHD grades II-IV not significantly different between the two arms (100-day aGVHD: PTCy 24.1% [21.3 - 27] vs. rATG 26.5% [25.5 - 27.6]; HR 0.85, p=0.11)

Conclusions: PtCy assoc with higher OS in MUD recipients

Table 1

	ATG_only (N=7725)	PTCy_only (N=1039)	Total (N=8764)	p value
Patient Gender				0.33[1]
Male	4427 (57.3%)	612 (58.9%)	5039 (57.5%)	
Female	3298 (42.7%)	427 (41.1%)	3725 (42.5%)	
Age at Transplant, yrs				< 0.01[2]
median [Q1, Q3]	58.6 (48.1, 65.4)	53.0 (38.6, 62.3)	58.1 (46.9, 65.1)	
[Min, Max]	18.0 - 79.1	18.2 - 79.5	18.0 - 79.5	
Karnofsky =>90				0.83[1]
< 90	2271 (31.0%)	311 (31.4%)	2582 (31.1%)	
>= 90	5045 (69.0%)	680 (68.6%)	5725 (68.9%)	
Missing count	409	48	457	
SORROR Comorbidity Index				0.14[1]
0	3367 (48.6%)	494 (50.7%)	3861 (48.9%)	
1-2	1694 (24.5%)	210 (21.6%)	1904 (24.1%)	
>=3	1861 (26.9%)	270 (27.7%)	2131 (27.0%)	
Missing count	803	65	868	
DRI				< 0.01[1]
Low	585 (7.6%)	124 (11.9%)	709 (8.1%)	
Int	4959 (64.2%)	649 (62.5%)	5608 (64.0%)	
High	1839 (23.8%)	243 (23.4%)	2082 (23.8%)	
Very high	342 (4.4%)	23 (2.2%)	365 (4.2%)	
Hematological Malignancies				
AML	3728 (48.3%)	412 (39.7%)	4140 (47.2%)	
MDS	1185 (15.3%)	158 (15.2%)	1343 (15.3%)	
ALL	791 (10.2%)	157 (15.1%)	948 (10.8%)	
MPN	781 (10.1%)	67 (6.4%)	848 (9.7%)	
NHL	543 (7.0%)	123 (11.8%)	666 (7.6%)	
MDS & MPN	350 (4.5%)	34 (3.3%)	384 (4.4%)	
CML	189 (2.4%)	35 (3.4%)	224 (2.6%)	
Hodgkins	84 (1.1%)	36 (3.5%)	120 (1.4%)	
CLL	74 (1.0%)	17 (1.6%)	91 (1.0%)	
Transplant Year				0.03[1]
2018	2132 (27.6%)	242 (23.3%)	2374 (27.1%)	
2019	2311 (29.9%)	333 (32.1%)	2644 (30.2%)	
2020	2086 (27.0%)	302 (29.1%)	2388 (27.2%)	
2021	1196 (15.5%)	162 (15.6%)	1358 (15.5%)	
Myeloablative Conditioning				< 0.01[1]
No	3664 (48.0%)	391 (37.7%)	4055 (46.7%)	
Yes	3975 (52.0%)	646 (62.3%)	4621 (53.3%)	
Missing count	86	2	88	
TBI				< 0.01[1]
No	6607 (85.5%)	782 (75.3%)	7389 (84.3%)	
Yes	1118 (14.5%)	257 (24.7%)	1375 (15.7%)	
GVHD Prevention Regimen				
CSA+MTX	3849 (49.8%)	6 (0.6%)	3855 (44.0%)	
CSA+MMF	2690 (34.8%)	260 (25.0%)	2950 (33.7%)	
MMF+TACRO/SIRO	459 (5.9%)	461 (44.4%)	920 (10.5%)	
CSA	470 (6.1%)	101 (9.7%)	571 (6.5%)	
TACRO/SIRO	36 (0.5%)	159 (15.3%)	195 (2.2%)	
MTX+TACRO	143 (1.9%)	0 (0.0%)	143 (1.6%)	
Other	78 (1.0%)	52 (5.0%)	130 (1.5%)	

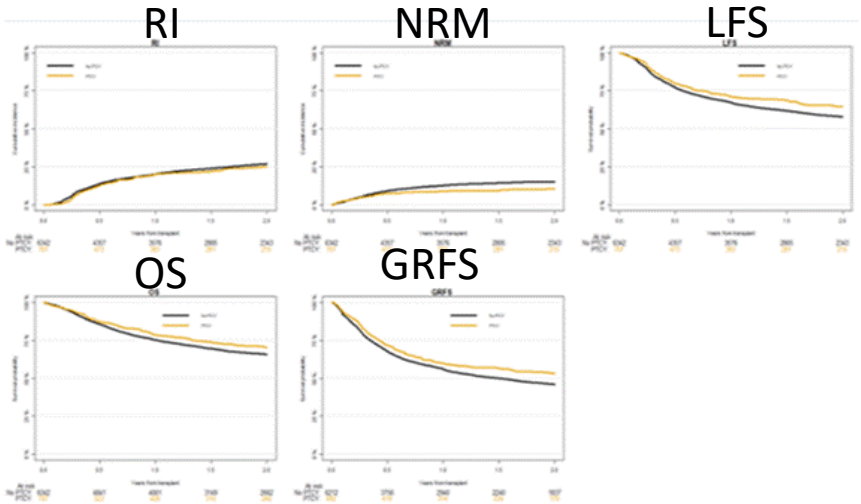
Figure 1



Abstr #237: Relapse post URD in AML- PTCy vs conventional GVHD prophylaxis, Nagler et al

- SOC (n = 5648; blue) with Tac/MTX/ATG vs CNI/MMF vs PTCy (n = 402; yellow)

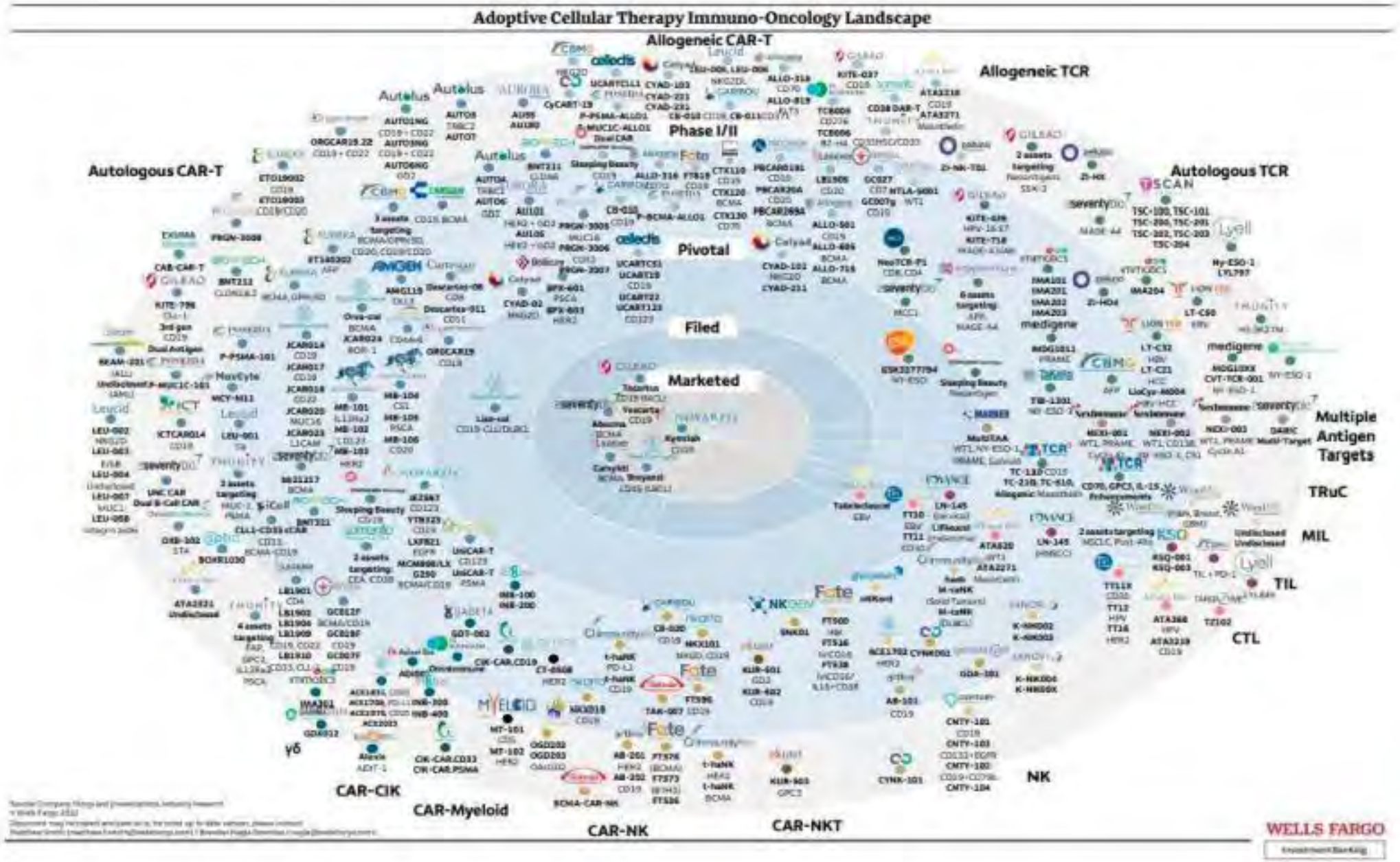
Figure: Transplantation outcome – Relapse incidence (RI), non-relapse mortality (NRM), leukemia-free survival (LFS), overall survival (OS), and graft-versus-host disease (GVHD)-free, relapse-free survival (GRFS) in acute leukemia patients undergoing unrelated allogeneic stem cell transplantation with post-transplant cyclophosphamide (PTCy) compared to no PTCy (*in vivo* T-cell depletion or calcineurin inhibitor-based GVHD prophylaxis)



In this registry-based retrospective analysis, comparing PTCy in combination with TAC or CSA and MMF to ATG in combination with TAC and MTX as GVHD prophylaxis, similar incidence and severity observed of both aGVHD and cGVHD. NRM was significantly lower with the PTCy-based GVHD prophylaxis, while all other transplant outcome parameters were similar.

Immune Effector Cell Therapies

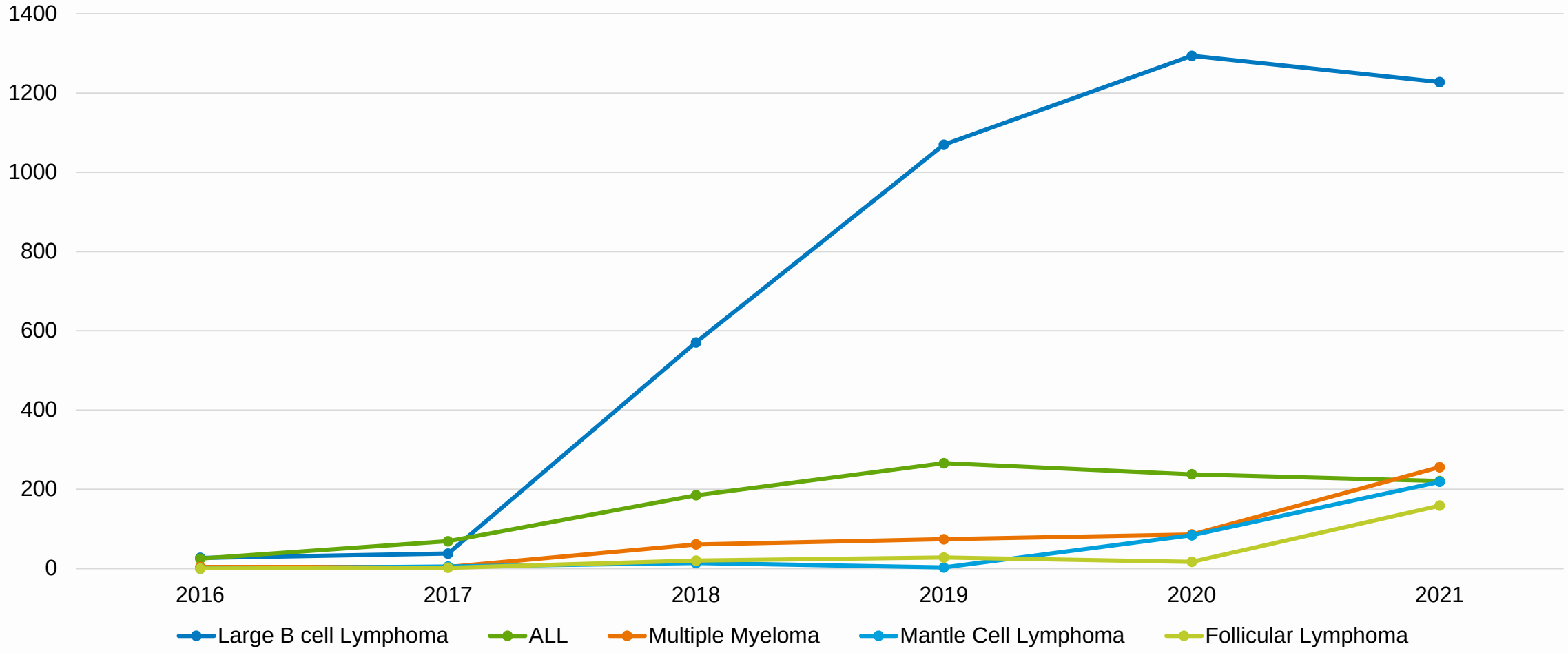
Cell Therapy Landscape: 2018-2023 View



July 31, 1978

"The potential for misadventure is limitless. What if we got an otherwise perfectly formed individual that was a cyclops? Who is responsible? The parents? The doctor? The government?" Marshall, MD, LA County

CAR T-Cell Indications Annually: 2016-2021



Data Incomplete for 2021

OHSU Adult HCT & Cell RX activity

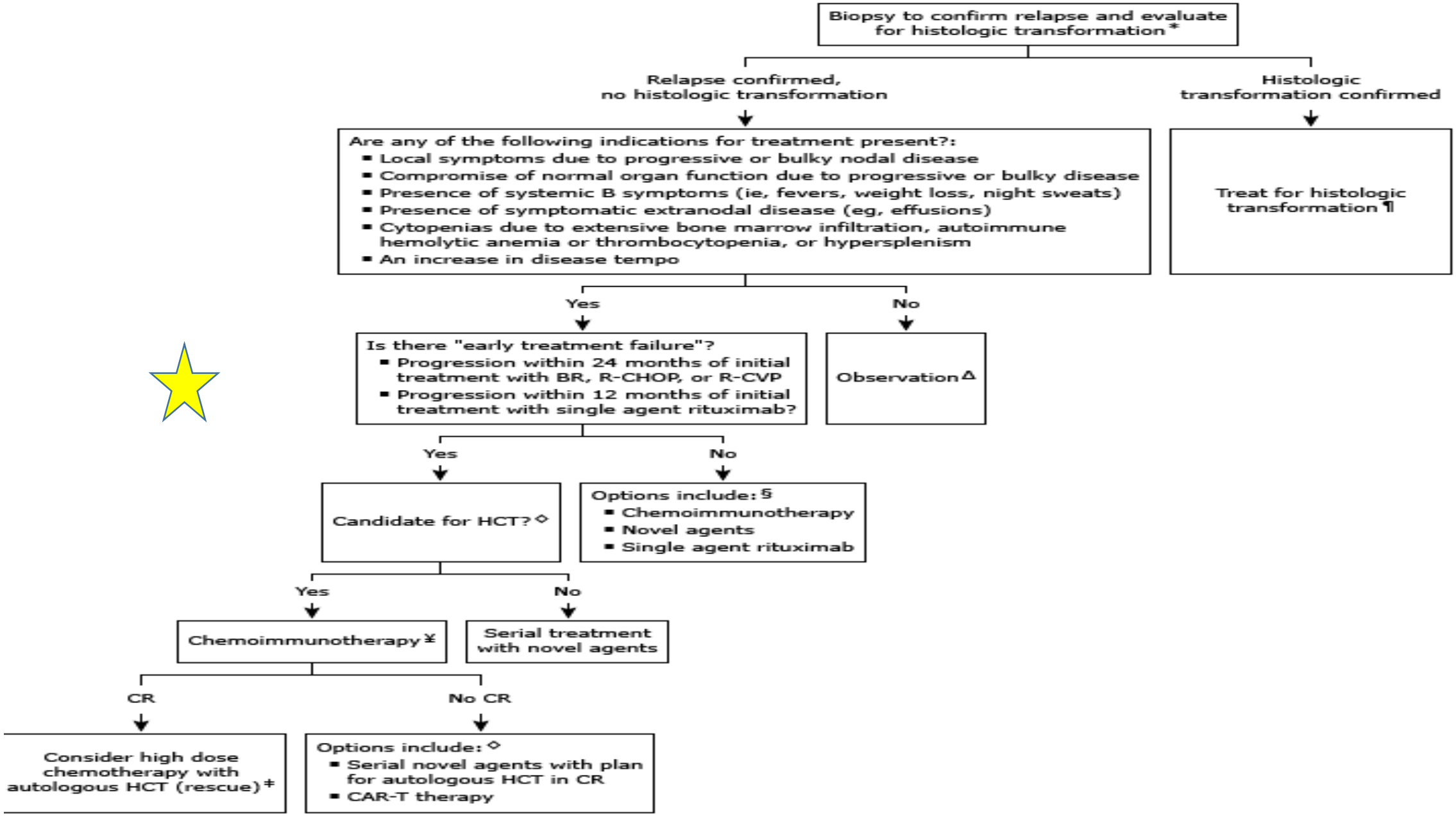
2018:	233	17
2019:	234	18
2020:	216	27
2021:	230	43
2022:	236	68
2023:	*250*	*91*

Over 30,000 CAR T-cell procedures reported performed since commercialization

Transplant Center Code	Center Name
160	Froedtert & Medical College of Wisconsin
161	Baylor College of Medicine
162	The University of Michigan
163	University of Kansas
164	Barnes Jewish Hospital
165	Abramson Cancer Center University - Pennsylvania Medical Center
166	Oregon Health and Science University
167	Hackensack University Medical Center
168	Memorial Sloan Kettering Cancer Center - Adults
169	Moffitt Cancer Center
170	Stanford University Medical Center
171	The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
172	Fred Hutchinson Cancer Center
173	Dana-Farber Brigham Cancer Center
174	MD Anderson Cancer Center
175	City of Hope National Medical Center

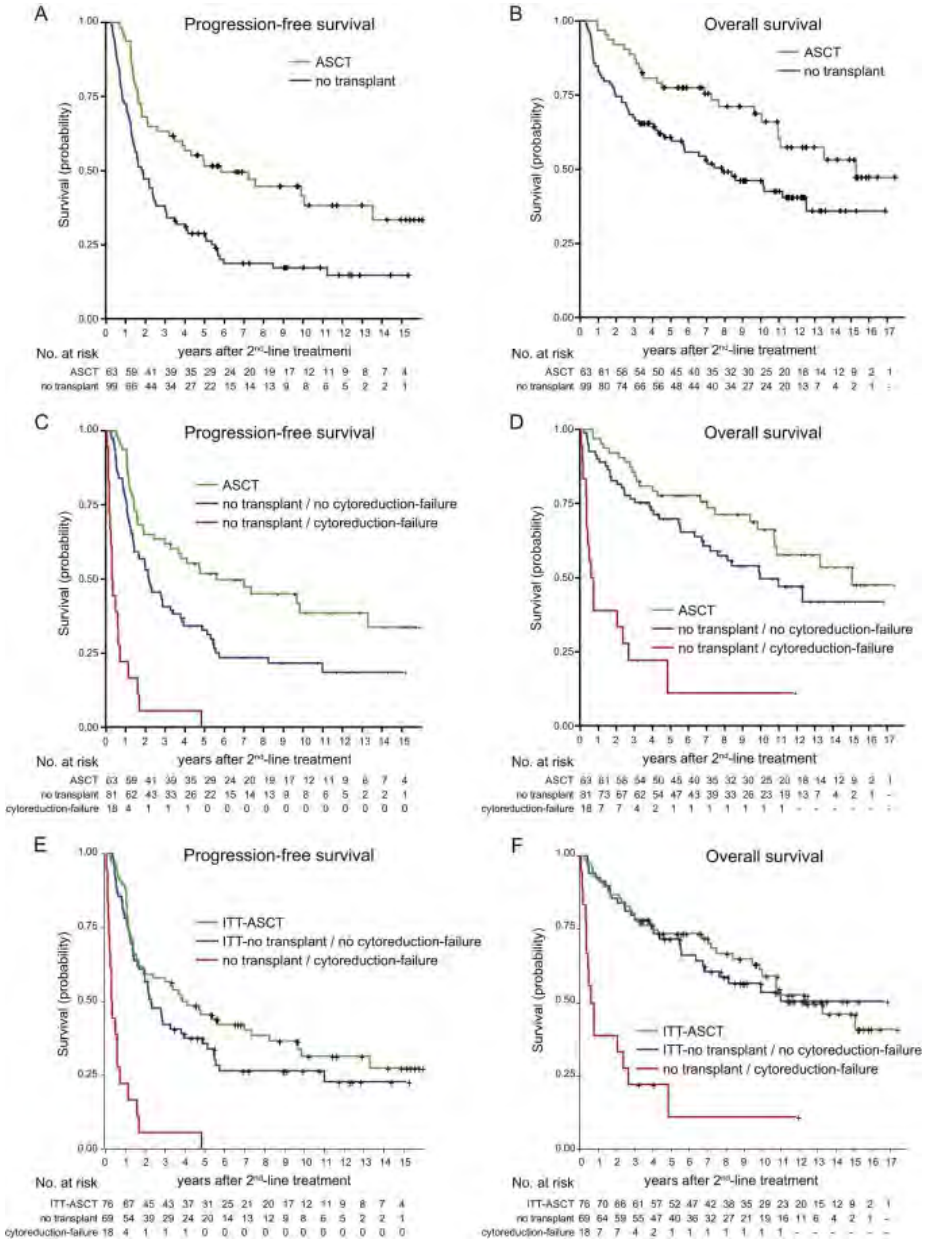
Solid line indicates predicted survival and box indicates 95% confidence interval. Dot indicates a center's actual survival; a dot below (above) the box indicates an under (over)-performing center relative to the network.

Follicular Lymphoma



Follicular Lymphoma

Auto HCT vs SOC for POD24, Jurinovic et al, BBMT, 2018



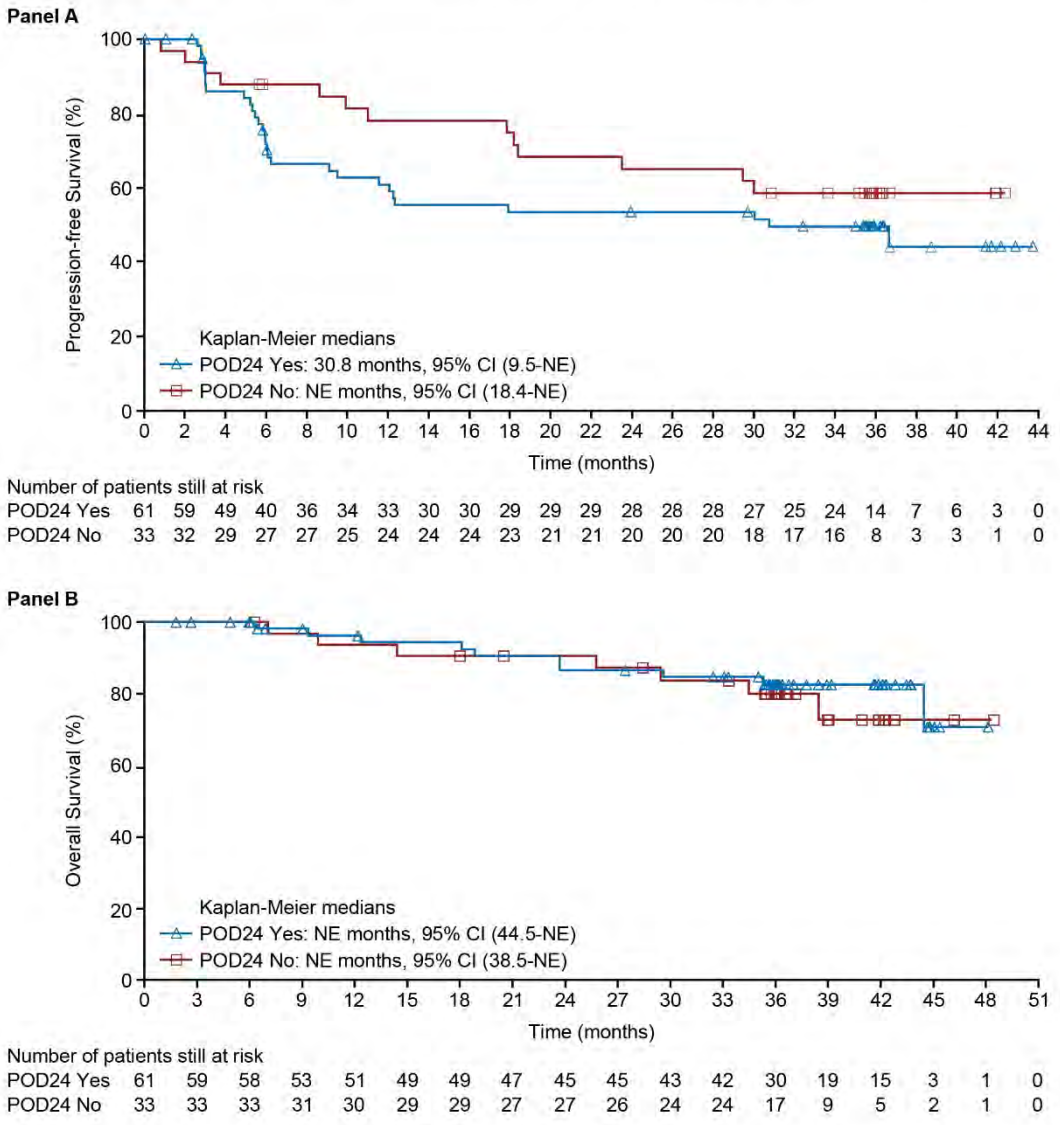
Outcomes after RIC-allotransplant for FL as first transplant approach

Series	Years	*N*	Prior ASCT, %	Median prior lines, *n*	3-year NRM, %	3-year RR, %	3-year OS, %	3-year EFS/PFS, %	aGVHD/cGVH %
Sureda *et al.*[117]	2001–2011	1567	29	Missing	25	17	66	58	20/45
Klyuchnikov *et al.*[115]	2000–2012	268	0	4	23	19	69	61	28/60
Robinson *et al.*[103]	1998–2005	149	0	3	22	17	68	62	47·2/51·7
Klyuchnikov *et al.*[116]	2000–2012	61	0	3	21	20	61	58	25/53
Smith *et al.*[104]	2002–2014	105 MSD	0	3	MSD 15	MSD 27	MSD 75	MSD 59	MSD 35/54
		95 MUD	0	3	MUD 29	MUD 23	MUD 55	MUD 47	MUD 35/58
Hari *et al.*[118]	1997–2002	120 MAC	6	3	MAC 25	MAC 8	MAC 71	MAC 67	MAC 36/46
		88	10	3	RIC	RIC	RIC	RIC 55	RIC 44/62

Abst. #601: Clinical Outcomes of Patients with R/R Follicular Lymphoma Treated with Tisagenlecleucel: Ph 2 Elara 3-Yr FU, Schuster et al

- R/R FL, Gr 1-3A, ≥ 2L of Rx
- N = 97, med f/u 41 mos
- Results: BOR 86%; CR 68%
- Med PFS: 37%; (69% for CR subjects)
- OS: 82% at 3 yr
- Safety signals: CRS 20%, PNA 11%

Figure. (A) Progression-free survival by POD24, (B) Overall survival by POD24.
NE, not evaluable; POD24, progression of disease within 2 years of frontline systemic therapy.



Abst. #4394: Real World Results of Brexucabtagene Autoleucel for Patients with Relapsed/Refractory Mantle Cell Lymphoma - First German/Swiss Analysis, Hess et al.

- N =111; Med age 64.3 yrs (42-79.5); 50 subjects > age 70. MIPI inter/hi (72%); 33% blastoid variant; TP53 alteration in 22%. Time from start last RX= 7.7 mos. Med # of prior RX = 3 (1-9). Prior auto HCT 56%.
- Results:
- ORR 86%; BOR CR (62%), PR(24%). Med DFS: 8 mos. Projected med OS: 1.9 yrs.
- Safety: CRS 83% overall; 19% Gr 3-5. ICANS: 51%, 25% Gr 2-4.
- 9% death within 28 days; 20/111 with NRM: 11 infection; 4 direct CAR related; 5 other/unknown.

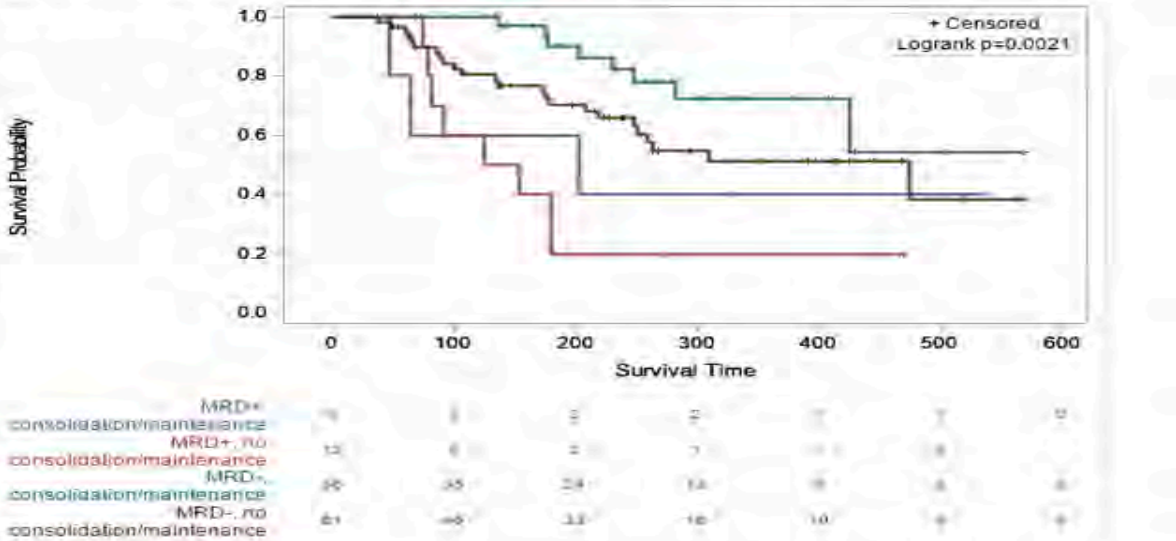
Abst, # 1030: Real World experience with Brexu-cel for adults with R/R ALL, Roloff et al.

Baseline Characteristics	N	%
Age at infusion, years		
Median (Range)	46 (18-81)	
Sex		
Male	87	57
Race/Ethnicity		
Non-Hispanic White	77	51
Hispanic	52	34
Asian/PI	10	7
Black	9	6
Other	4	3
ALL Sub-Type		
Ph+	47	31
Ph-	102	67
MPAL	3	2
Prior Therapies		
Lines of Prior Therapy: median (range)	4 (1-12)	
Blinatumomab	88	58
Inotuzumab	72	47
Allogeneic HCT	62	41
Other CAR T-Cell	3	2
Pre-Apheresis Disease Burden		
High Burden (>=5% marrow blasts and/or extra-medullary disease)	78	51
Low Burden (<5% marrow blasts), MRD-Positive	35	23
Low Burden, MRD-Negative	23	15
Low Burden, MRD Unknown	3	2
Unknown	13	9

Toxicity	N	%
CRS (ASTCT Criteria)		
Any CRS	124	82
Grade 1	58	38
Grade 2	53	35
Grade 3	9	6
Grade 4	4	3
Unknown	5	3
ICANS (ASTCT Criteria)		
Any ICANS	83	55
Grade 1	14	9
Grade 2	21	14
Grade 3	34	23
Grade 4	14	9
Unknown	4	3

Outcomes	N	%
Response (among N=133 with response data)		
CR/CRi	120	90
MRD+ among CR/CRi	18	15
MRD- among CR/CRi	98	82
MRD unknown among CR/CRi	4	3
Less than CR/CRi	13	10
Unknown/Unavailable (of total N=152 in cohort)	19	13
Duration of Response (DOR, among N=120 responders)		
Median DOR	Not Reached	
6-month DOR	70% (59, 78)	
12-month DOR	62% (50, 71)	
Progression-Free Survival (PFS)		
Median PFS	8.6 months	
6-month PFS	61% (52, 68)	
12-month PFS	47% (37, 56)	
Overall Survival (OS)		
Median OS	15.6 months	
6-month OS	81% (73, 87)	
12-month OS	63% (53, 72)	
Death in Remission by Day +28	8	5
Loss of CD19 at Relapse (among N= 45 relapsed)	15	33
Post-CAR T-Cell Consolidation/Maintenance		
Total Receiving Consolidation/Maintenance	44	29
Allogeneic HCT	25	16
TKI	15	10
POMP	2	1
Other	3	2

Figure 1. PFS by Post-CAR MRD Response and Use of Post-CAR Consolidation/Maintenance



N = 189

19% went to CAR T with active CNS disease

Lisocabtagene Maraleucel in Relapsed/Refractory Large B-Cell Lymphoma: Real World Analysis from the Cell Therapy Consortium

Peter A. Riedell, Connor Grady, Loretta J. Nastoupil, Alejandro Luna, Nausheen Ahmed, Richard T. Maziarz, Marie Hu, Jamie Brower, Wei-Ting Hwang, Stephen J. Schuster, Andy Chen, Olalekan O. Oluwole, Veronika Bachanova, Joseph P. McGuirk, Miguel-Angel Perales, Michael R. Bishop, and David L. Porter

Baseline Patient Characteristics

Characteristic	N=101
Age at apheresis	
Median, years (range)	71 (30-85)
<65, (%)	28%
65-74, (%)	38%
≥ 75, (%)	35%
Male, (%)	60%
Diagnosis, (%)	
DLBCL	86%
HGBL	7%
TFL	5%
PMBCL	2%
Disease stage III/IV, (%)	80%
Missing, n	15
Bulky disease (≥10 cm), (%)	18%
Missing, n	1
ECOG 0/1, (%)	84%
Missing, n	15

Characteristic	N=101
Active secondary CNS involvement, (%)	11%
Baseline comorbidities	
Diabetes, (%)	18%
Stage IV chronic kidney disease, (%)	5%
Cerebrovascular disease, (%)	5%
Impaired cardiac ejection fraction, (%)	2%
Pulmonary dysfunction, (%)	2%
Impaired hepatic function, (%)	2%
Active infection, (%)	3%
Charlson Comorbidity Index	
0-1	7%
2	25%
≥3	68%
Ineligible for TRANSCEND[1] due to comorbidities, (%)	30%

[1]Ineligible if any of the following criteria are met at apheresis: ECOG >1, GFR <30 mL/min, bilirubin >2 mg/dL, Grade ≥2 dyspnea or pulse Ox ≤91% on room air, LVEF< 40%, active infection including HIV or Hepatitis B or C, history of seizure disorder, cerebellar disease, Parkinson's disease, or psychosis.

CELL THERAPY Consortium

Baseline Patient Characteristics Cont’

Characteristic	N=101
Prior lines of therapies	
Median, n (range)	3 (1-8)
1, (%)	16%
2, (%)	31%
3, (%)	26%
4+, (%)	28%
Prior autologous transplant, (%)	16%
Bridging therapy, (%)	62%
Bridging therapy regimen, (%)	
Polatuzumab-based	41%
Chemotherapy	24%
Radiation therapy	21%
Targeted therapy	13%
Steroids	1%
Days from leukapheresis to infusion, median (IQR)	39 (34-43)

Characteristic	N=101
Out of specification, (%)	7%
Pre-LDc LDH > institutional ULN, (%)	44%
Missing, n	8
Disease status at time of LDc, (%)	
Active disease	82%
Complete response	18%
Missing, n	11
LDc regimen, (%)	
Fludarabine/cyclophosphamide	74%
Bendamustine	26%

CELL THERAPY Consortium

Efficacy

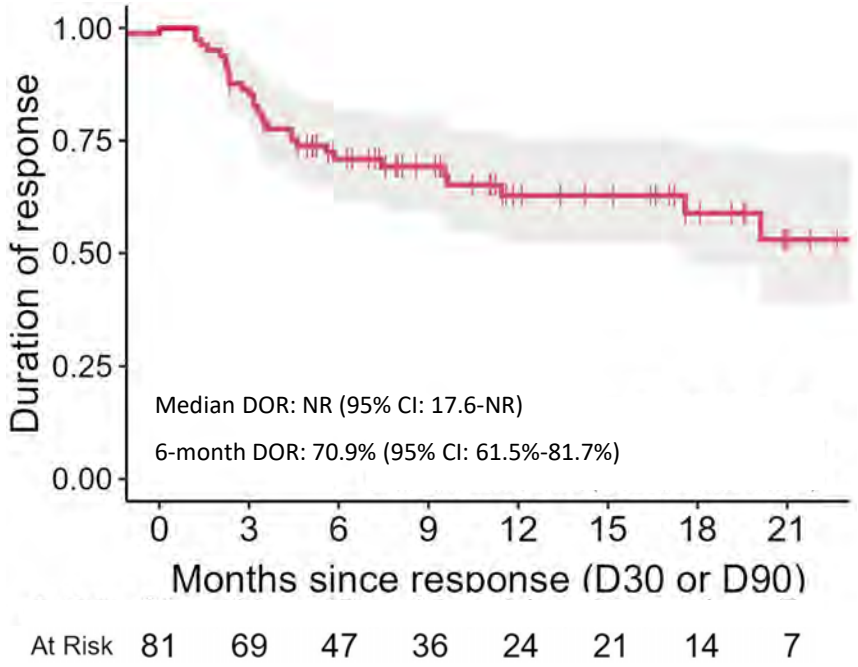
Endpoint	
Bridging therapy evaluable, n	52
ORR, (%)	46%
CR rate, (%)	19%
Response by bridging regimen	
Chemotherapy evaluable, n	10
ORR/CR rate, (%)	30% / 0%
Polatuzumab-based evaluable, n	22
ORR/CR rate, (%)	55% / 36%
Radiation therapy evaluable, n	8
ORR/CR rate, (%)	50% / 0%

Endpoint	
Median follow-up, months (range)	12.4 (0.3-25.1)
D+30 evaluable, n	89
Day +30 ORR, (%)	81%
Day+30 CR rate, (%)	63%
D+90 evaluable, n	91
D+90 ORR, (%)	67%
D+90 CR rate, (%)	60%

CELL THERAPY Consortium

Duration of Response

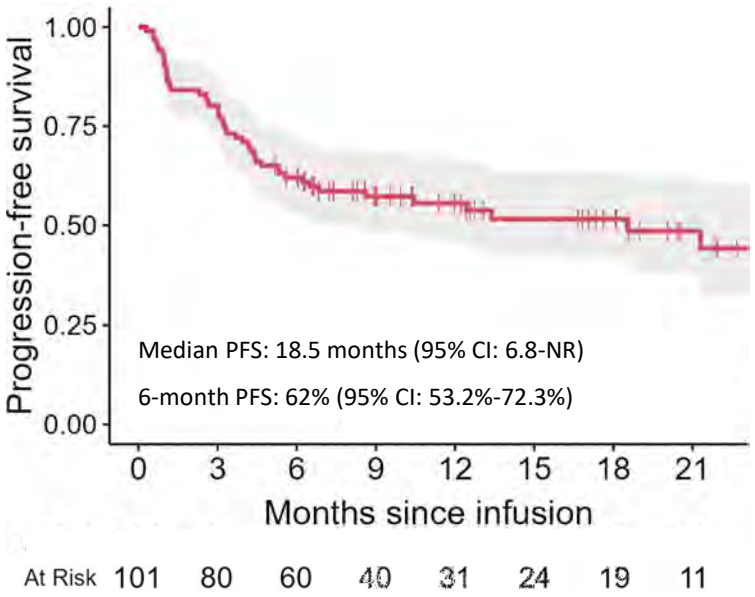
- Median follow-up: 12.4m



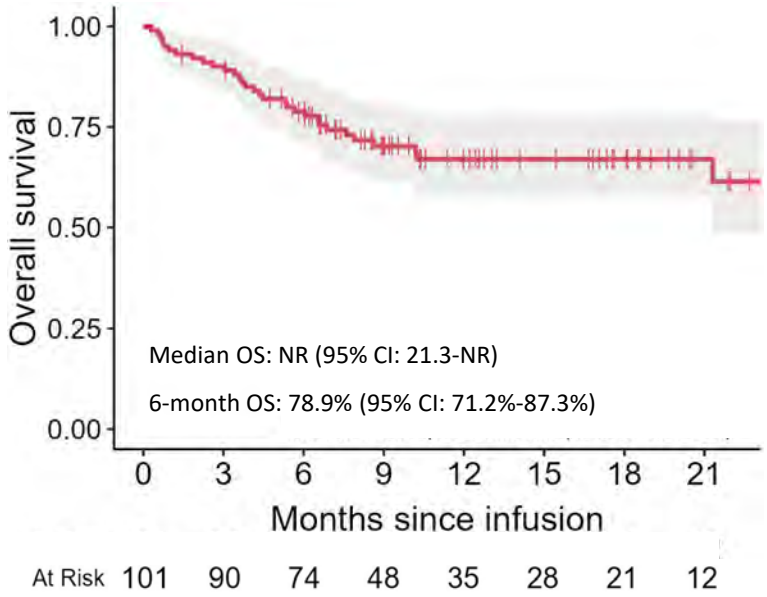
CELL THERAPY Consortium

PFS and OS of SOC Liso-cel

Progression-free Survival



Overall Survival



CELL THERAPY Consortium

Conclusions

- Commercial liso-cel recipients were likely to be of advanced age and harbor a significant comorbid burden
- Liso-cel demonstrated durable responses in patients with high-risk DLBCL
  - Entire population→6-month PFS: 62% (95% CI: 53.2%-72.3%)
  - Secondary CNS lymphoma→ 6-month PFS: 72.7% (95% CI: 50.6%-100%)
- Response to bridging therapy (i.e.,CR/PR) was associated with improved PFS
- Roughly 1/3 of patients would have been ineligible for TRANSCEND
- Advancements in patient selection, toxicity management, and the utilization of bridging therapy likely contributed to favorable outcomes in this real world population

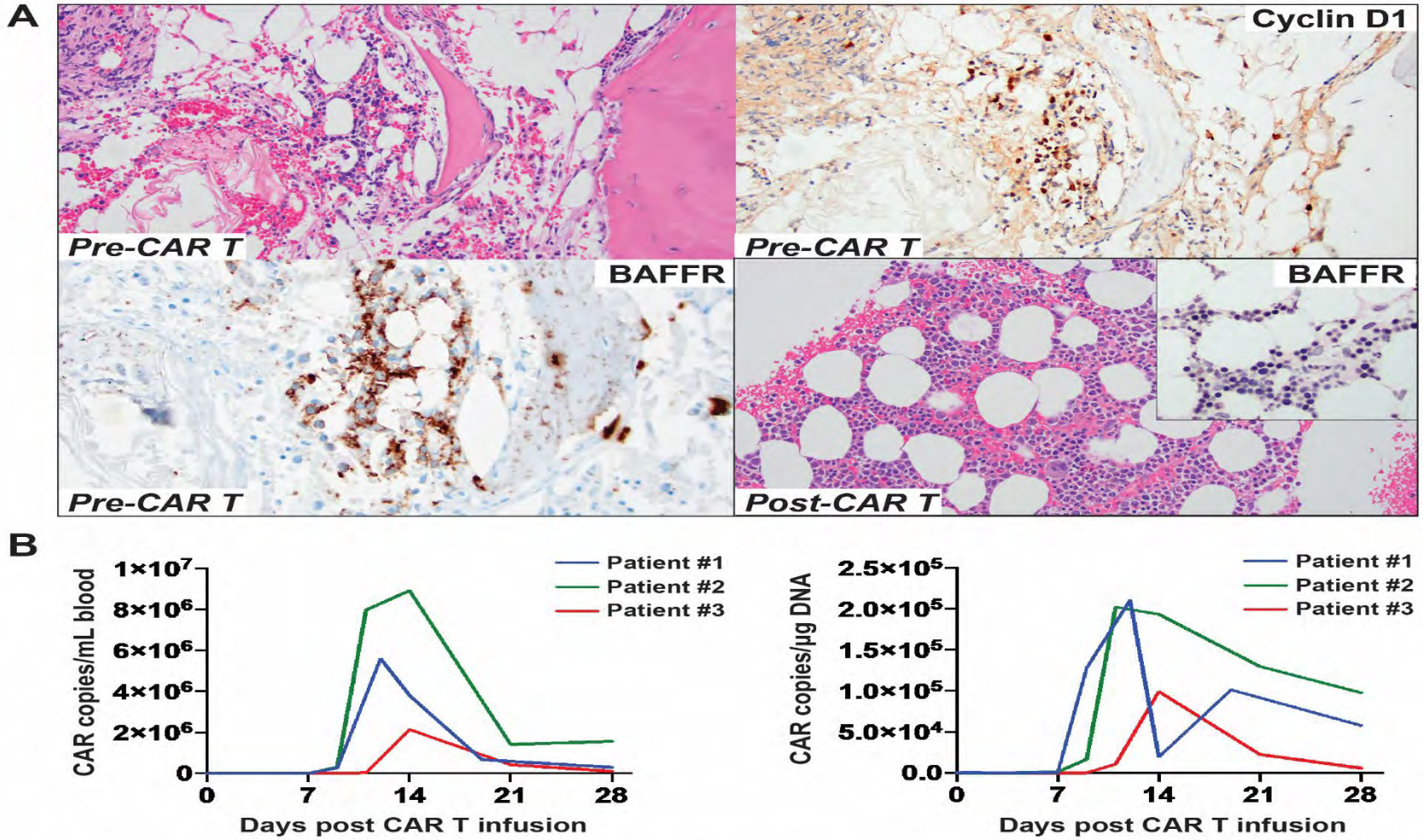
CELL THERAPY Consortium

Abst. #221: Promising Safety and Anti-Lymphoma Efficacy of Autologous Pmb-CT01 (BAFFRCAR T Cell) Therapy in a First-in-Human Phase 1 Study, Budde et al, COH

- CD19 CAR T-cell can be curative, but long term, only in 30-40%
- Other target options under study: CD20, CD22, single or dual-targets
- BAFF-R signaling - driver of B cell and malignant growth and survival
- BAFF-R expression is independent of CD19 expression on malignant B cells
- Phase I, dose escalation
- Results: N = 3; MCL (2)- failed prior CAR T; T cell rich DLBCL (1)- CD19-, CD20-
- 3/3 pts with response (100%) 2 MCL pts→ CR; DLBCL with PR
- CRS Gr 1 in 3/3; ICANS Gr1 in 2/3

- Potential new target for future interventions

Abst. #221: Promising Safety and Anti-Lymphoma Efficacy of Autologous Pmb-CT01 (BAFFRCAR T Cell) Therapy in a First-in-Human Phase 1 Study, Budde et al, COH



A. Clearance of lymphoma in the bone marrow of Patient #1 (MCL). Staining (H&E, Cyclin D1, BAFFR) is shown before CAR T treatment. Clearance of lymphoma is demonstrated by H&E staining and absence of BAFFR expression (bottom right panel). **B. Post-infusion expansion of CAR T cells in the peripheral blood of the 3 patients.** Copy number is shown per mL of blood and per µg of DNA.

Updates on Myeloma CAR T cell Therapy

- Currently approved for pts beyond 4 lines of therapy
- Emerging data suggest that pts with R/R MM after 2-3 lines of therapy may gain benefit with earlier application of CAR T-cell therapy
- There may be evidence to suggest better outcomes in antigen target naïve subjects

Clin Pharmacol Thera 2023 Sep 26. doi: 10.1002/cpt.3057. Online ahead of print.

CAR T-cell therapy for multiple myeloma: A clinical practice-oriented review

Norah Layla Sadek[#1], Bruno Almeida Costa[#1], Karthik Nath[2], Sham Mailankody

Table 1: Clinical studies of chimeric antigen receptor T-cell therapy in patients with relapsed/refractory multiple myeloma

Setting	Trial ID	Phase	Study	Drug(s)	Target	n	ORR (≥CR), %	mDOR, mo	mPFS, mo	CRS, %	Neurotoxicity, %
≥ fourth LOT	NCT03361748	II	KarMMA	Ide-cel	BCMA	128	73 (33)	10.7	8.8	84	18
	NCT03548207	I/II	CARTITUDE-1	Cilta-cel	BCMA	97	98 (83)	33.9	34.9	95	21
	NCT04555551	I	-	MCARH109	GPRC5D	17	71 (35)	7.8	NA	88	6
	NCT05016778	I	POLARIS	OriCAR-017	GPRC5D	9	100 (60)	NA	NR	100	0
	NCT04155749	I	-	CART-ddBCMA	BCMA	12	100 (75)	NR	NR	100	17
	NCT04093596	I	UNIVERSAL	ALLO-715	BCMA	43	56 (25)	8.3	NA	56	14
2-4 prior LOTs	NCT03651128	III	KarMMA-3	Ide-cel *vs* standard regimens	BCMA	386	71 (39) *vs* 42 (5)	14.8 *vs* 9.7	13.3 *vs* 4.4	88	15
≥ second LOT	NCT03090659	I	LEGEND-2	LCAR-B38M	BCMA	57	88 (68)	14.0	15.0	90	2
	ChiCTR2100048888	II	-	Anti-GPRC5D CAR-T	GPRC5D	33	91 (64)	NA	NA	76	9
	NCT02546167	I	-	CART-BCMA ± huCART19 †	BCMA, CD19	30	67 (20)	NA	9.8	90	3
	NCT04181827	III	CARTITUDE-4	Cilta-cel *vs* standard regimens	BCMA	419	85 (73) *vs* 67 (22)	NA	NR *vs* 11.8	76	5
	NCT04309981	I/II	CARTBCMA-HCB-01	ARI0002h	BCMA	30	100 (67)	NR	14.5	80	0
	NCT03502577	I	-	FCARH143 + crenigacestat	BCMA	18	89 (56)	14.4	11.0	94	39
first LOT	NCT03455972	I	-	Anti-BCMA CAR-T + Anti-CD19 CAR-T §†	BCMA, CD19	10	100 (100)	NA	NR	100	0

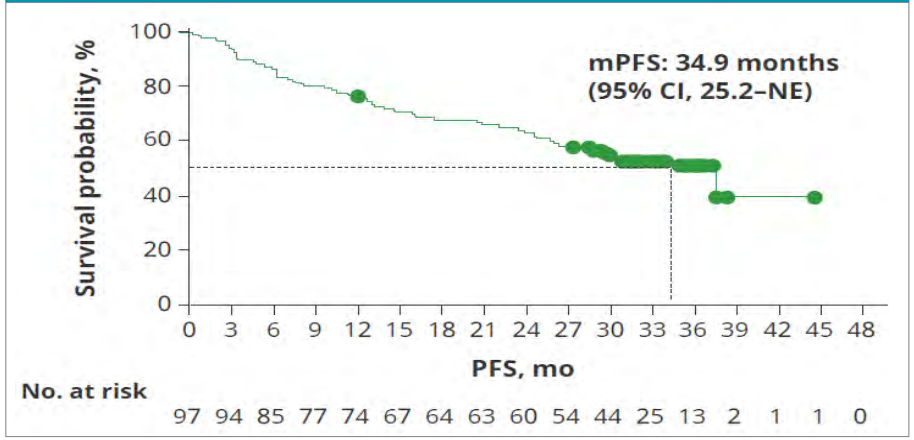
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS, cytokine release syndrome; GPRC5D, G protein-coupled receptor, class-C, group-5, member-D; ide-cel, idecabtagene vicleucel; LOT, line of therapy; mDOR, median duration of response; MM, multiple myeloma; mo, months; mPFS, median progression-free survival; n, number of enrolled patients; NA, not available; NR, not reached; ORR, overall response rate.

† Followed by immunomodulatory drug maintenance; § Preceded by bortezomib/doxorubicin/dexamethasone induction, busulfan/cyclophosphamide conditioning, and autologous stem cell transplantation.

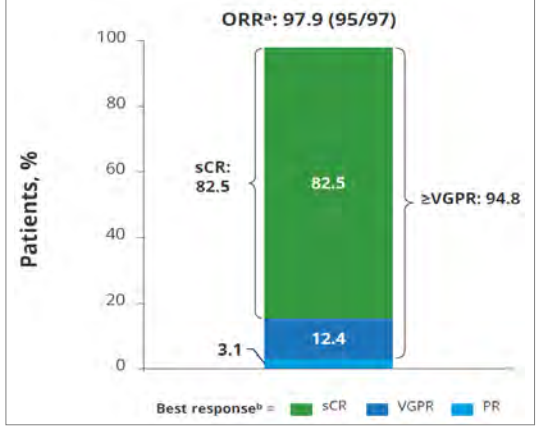
CARTITUDE-1: Cilta-Cel in Patients With RRMM

Efficacy and Safety[1,2]

PFS



ORR by IRC



- Median DOR: 33.9 months (95% CI, 25.5-NE)
- An estimated 62.9% of patients were alive at 3-year follow-up

Deaths, n		Total (N=97)	Time of Death Post–Cilta-Cel Infusion, Days
Total deaths during the study		35	45-980
Deaths due to PD		17	253-980
AEs unrelated to treatment (n=12)	Pneumonia	2	109, 887
	AML	3	418, 582, 718
	Ascites	1	445
	MDS	1	803
	Respiratory failure	3	733, 793, 829
	Septic shock and/or sepsis	2	917, 945
AEs related to treatment (n=6)	Septic shock and/or sepsis	2	45, 162
	CRS/HLH	1	99
	Lung abscess	1	119
	Respiratory failure	1	121
	Neurotoxicity	1	247

[a] ORR assessed by IRC. [b] No patient had CR or stable disease.

1. Lin Y, et al. ASCO 2023. Abstract 8009. **2.** Munshi N, et al. EHA 2023. Abstract S202.

CARTITUDE-2 Cohort C: Cilta-Cel in Patients With RRMM Previously Exposed to Noncellular BCMA-Directed Therapies

Study Design and Patients

Key Eligibility Criteria: Cohort C

- Progressive MM after ≥4 prior lines of therapy, including a PI and IMiD, an anti-CD38 mAb, and a noncellular BCMA-directed therapy

Screening (1-28 days)

Apheresis

Bridging therapy (as needed)

Cy (300 mg/m^2) + Flu (30 mg/m^2), day -5 to -3

Cilta-cel infusion (day 1)
Target dose 0.75×10^6 (range, 0.5-1.0×10^6) CAR+ viable T cells/kg

Postinfusion assessments (day 1-100)
Safety, efficacy, PK, PD, biomarker

Posttreatment assessments
(day 101 up to end of cohort) Safety, efficacy, PK, PD, biomarker

Follow-up

Primary Objective: MRD-neg (10^{-5}) by NGS
Secondary Objectives: ORR, VGPR, CR, sCR, DOR, TTR, AEs

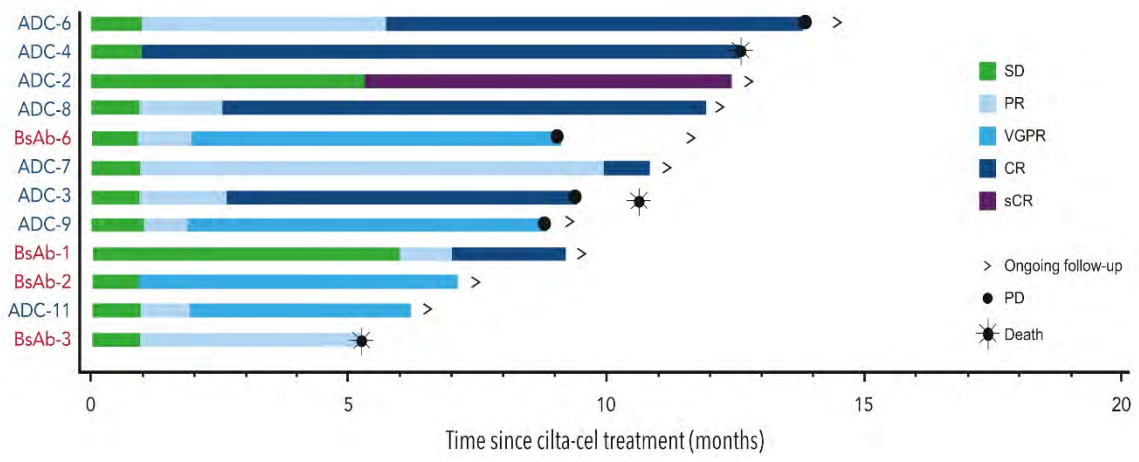
Patient Characteristics	Cohort C (N=20)
Median age (range), years	62.5 (44-81)
Median time from initial MM diagnosis (range), years	6.3 (2.5-16.3)
ISS stage at study entry, n (%)	
I	8 (40)
II	4 (20)
III	8 (40)
Plasmacytoma, n (%)	5 (25)
BM plasma cells ≥60%, n (%)	6 (32)
High-risk cytogenetics (all del[17p]), n (%)	3 (15)
Median number of prior LOT (range)	8 (4-13)
Prior ASCT, n (%)	20 (100)
Refractory to last line of prior therapy, n (%)	19 (95)
Triple-class refractory, n (%)	18 (90)
Penta-refractory, n (%)	11 (55)
Anti-BCMA treatment refractory	16 (80)

Cohen AD, et al. *Blood*. 2023;141(3):219-230.

CARTITUDE-2 Cohort C: Cilta-Cel in Patients With RRMM Previously Exposed to Noncellular BCMA-Directed Therapies

Efficacy and Safety

Response Among Responders



		Total Evaluated (N=18[a])	
		Responders (n=12)	Nonresponders (n=6)
Duration of last anti-BCMA treatment, days	Median	29.5	63.5
	Range	1-277	22-527
Time from last anti-BCMA treatment to apheresis, days	Median	161.0	56.5
	Range	26-695	40-895
Time from last anti-BCMA treatment and Cilta-cel infusion, days	Median	235.0	117.5
	Range	62-749	95-944

Response to Cilta-Cel	Full Cohort (N=20)	ADC Exposed (n=13)	Bispecific Antibody Exposed (n=7)
ORR, % (95% CI)	60.0 (36.1-80.9)	61.5 (31.6-86.1)	57.1 (18.4-90.1)
Median DOR (95% CI), mo	11.5 (7.9-NE)	11.5 (7.9-NE)	8.2 (4.4-NE)
MRD negativity, n (%)			
No. of patients evaluable at 10^{-5}	10	7	3
Rate, n (%)	7 (70.0)	5 (71.4)	2 (66.7)

TEAEs, n (%)		Full Cohort (N=20)	
		Any Grade	Grade 3/4
Hematologic (≥20%)	Neutropenia	17 (85)	17 (85)
	Thrombocytopenia	16 (80)	14 (70)
	Anemia	14 (70)	11 (55)
	Leukopenia	11 (55)	11 (55)
	Lymphopenia	6 (30)	6 (30)
CRS and neurotoxicity	CRS	12 (60)	0
	ICANS	4 (20)	2 (10)
	Other neurotoxicity	0	0

[a] Two patients died before confirmed disease evaluations and were excluded from the analysis.

Cohen AD, et al. *Blood.* 2023;141(3):219-230.

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RESEARCH SUMMARY

Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Rodriguez-Otero P et al. DOI: 10.1056/NEJMoa2213614

CLINICAL PROBLEM

Idecabtagene vicleucel (ide-cel) — a chimeric antigen receptor (CAR) T-cell therapy that targets B-cell maturation antigen expressed on myeloma cells — is approved in the United States for the treatment of relapsed or refractory multiple myeloma after the receipt of at least four previous lines of therapy. Its efficacy in less heavily pretreated disease is unclear.

CLINICAL TRIAL

Design: An international, phase 3, open-label, randomized trial assessed the efficacy and safety of ide-cel, as compared with standard regimens, in adults with triple-class–exposed relapsed and refractory multiple myeloma who had received two to four lines of therapy previously and who had disease refractory to the most recent regimen.

Intervention: 386 patients whose previous lines of therapy included daratumumab, immunomodulatory agents, and proteasome inhibitors and who had progressive disease within 60 days after completing the last therapy were assigned in a 2:1 ratio to receive a single infusion of ide-cel or to one of five standard regimens. The primary end point was progression-free survival. Key secondary end points were overall response (partial response or better) and overall survival.

RESULTS

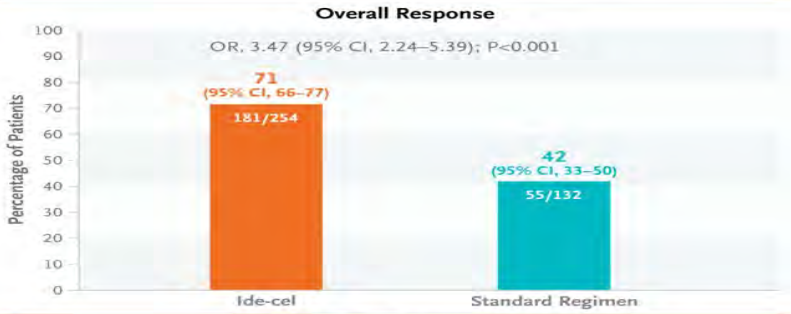
Efficacy: At a median follow-up of 18.6 months, progression-free survival was significantly longer in the ide-cel group than in the standard-regimen group.

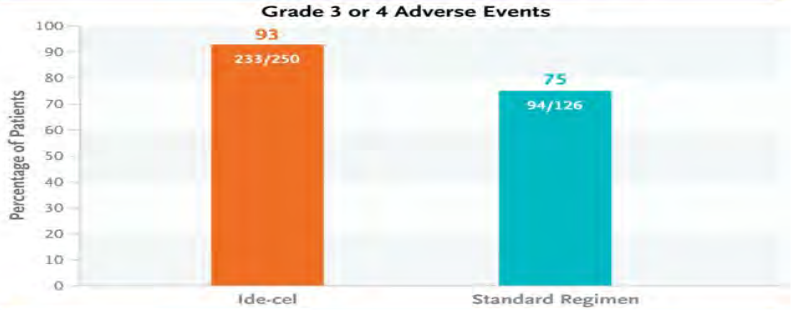
Safety: Grade 3 or 4 adverse events occurred more often with ide-cel than with standard regimens. Most ide-cel recipients had cytokine release syndrome, which usually was low-grade. Neurotoxic effects also occurred in the ide-cel group.

LIMITATIONS AND REMAINING QUESTIONS

- The proportion of Black patients was not balanced between the groups.
- The investigators' choice of standard regimens may have introduced treatment heterogeneity in that group.
- Mechanisms underlying ide-cel resistance remain unknown.

Links: Full Article | NEJM Quick Take





CONCLUSIONS

Among adults with heavily pretreated relapsed and refractory multiple myeloma who had received two to four lines of therapy previously, the CAR T-cell therapy ide-cel led to significantly longer progression-free survival than standard regimens.

A phase 3 trial of BCMA-specific CAR T cells in R/R MM showed advantage over standard therapy (PFS 13.3 vs. 4.4 months); 39% of patients in the ide-cel group had a CR

Rodriguez-Otero P et al. N Engl J Med2023;388:1002-1014

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

San-Miguel J et al. DOI: 10.1056/NEJMoa2303379

CLINICAL PROBLEM

Among patients with multiple myeloma, early resistance to lenalidomide is becoming more common, and effective treatments are needed. Ciltacabtagene autoleucel (cilta-cel), a B-cell maturation antigen (BCMA)–directed CAR T-cell therapy, is effective in heavily pretreated patients with relapsed or refractory multiple myeloma, but its activity earlier in the treatment course is unknown.

CLINICAL TRIAL

Design: A phase 3, open-label, randomized trial compared the efficacy and safety of cilta-cel with the physician's choice of two standard treatments among patients with lenalidomide-refractory multiple myeloma who had received one to three lines of therapy.

Intervention: 419 patients were randomly assigned either to receive a single infusion of cilta-cel following bridging therapy with pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd) or to receive the physician's choice of standard care (PVd or DPd). The primary outcome was progression-free survival.

RESULTS

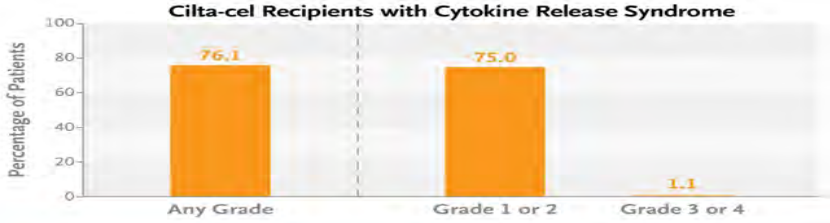
Efficacy: At the 12-month follow-up in the intention-to-treat population, progression-free survival was 75.9% in the cilta-cel group and 48.6% in the standard-care group.

Safety: Three quarters of cilta-cel recipients had cytokine release syndrome, mostly of grade 1 or 2 severity.

LIMITATIONS AND REMAINING QUESTIONS

- Longer follow-up is needed, as the median progression-free survival was not reached in the cilta-cel group.
- Two other highly efficacious triplet regimens — daratumumab, carfilzomib, and dexamethasone and isatuximab, carfilzomib, and dexamethasone — were not approved by the time the trial began and could not be included as standard-care options.

Links: Full Article | NEJM Quick Take



CONCLUSIONS

A single infusion of cilta-cel following bridging therapy reduced the risk of disease progression or death among patients with lenalidomide-refractory multiple myeloma who had received one to three previous therapies.

Patients with lenalidomide-refractory disease who received ciltacabtagene autoleucel had significantly longer PFS than those who received standard therapy.

San-Miguel J et al. N Engl J Med2023;389:335-347

Original Article

GPRC5D-Targeted CAR T Cells for Myeloma

Sham Mailankody, M.B., B.S., Sean M. Devlin, Ph.D., Jonathan Landa, D.O., Karthik Nath, M.B., B.S., Ph.D., Claudia Diamonte, B.S.N., R.N., O.C.N., Elizabeth J. Carstens, M.D., Douglas Russo, M.S., Romany Auclair, M.D., Lisa Fitzgerald, M.S.N., Briana Cadzin, B.S.N., R.N., Xiuyan Wang, Ph.D., Devanjan Sikder, Ph.D., Brigitte Senechal, Ph.D., Vladimir P. Bermudez, Ph.D., Terence J. Purdon, M.S., Kinga Hosszu, Ph.D., Devin P. McAvoy, B.S., Tasmin Farzana, M.P.H., Elena Mead, M.D., Jessica A. Wilcox, M.D., Bianca D. Santomasso, M.D., Ph.D., Gunjan L. Shah, M.D., Urvi A. Shah, M.D., Neha Korde, M.D., Alexander Lesokhin, M.D., Carlyn R. Tan, M.D., Malin Hultcrantz, M.D., Ph.D., Hani Hassoun, M.D., Mikhail Roshal, M.D., Filiz Sen, M.D., Ahmet Dogan, M.D., Ph.D., Ola Landgren, M.D., Ph.D., Sergio A. Giralt, M.D., Jae H. Park, M.D., Saad Z. Usmani, M.D., Isabelle Rivière, Ph.D., Renier J. Brentjens, M.D., Ph.D., and Eric L. Smith, M.D., Ph.D.

N Engl J Med
Volume 387(13):1196-1206
September 29, 2022

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Characteristics of the Patients at Baseline.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	25×10^6 CAR T cells (N=3)	50×10^6 CAR T cells (N=3)	150×10^6 CAR T cells (N=6)	450×10^6 CAR T cells (N=5)	Total (N=17)
Median age (range) — yr	60 (38–76)	50 (39–56)	59 (40–74)	65 (63–73)	60 (38–76)
Male sex — no. (%)	2 (67)	3 (100)	4 (67)	4 (80)	13 (76)
High-risk cytogenetic feature — no. (%)†	3 (100)	2 (67)	3 (50)	5 (100)	13 (76)
Extramedullary plasmacytoma — no. (%)	3 (100)	1 (33)	4 (67)	0	8 (47)
Nonsecretory myeloma — no. (%)	2 (67)	0	1 (17)	0	3 (18)
Previous lines of therapy — median (range)	6 (6–8)	5 (4–8)	7 (5–14)	6 (5–12)	6 (4–14)
Disease refractory to last line of therapy — no. (%)	3 (100)	3 (100)	5 (83)	3 (60)	14 (82)
Penta-exposed — no. (%)‡	3 (100)	3 (100)	6 (100)	5 (100)	17 (100)
Triple-refractory disease — no. (%)§	3 (100)	3 (100)	6 (100)	4 (80)	16 (94)
Previous autologous transplantation — no. (%)	3 (100)	3 (100)	6 (100)	5 (100)	17 (100)
Previous allogeneic transplantation — no. (%)	0	2 (67)	1 (17)	0	3 (18)
Previous BCMA therapy — no. (%)¶	1 (33)	1 (33)	4 (67)	4 (80)	10 (59)
Previous CAR T-cell therapy — no. (%)	0	1 (33)	3 (50)	4 (80)	8 (47)
Bridging therapy — no. (%)	3 (100)	3 (100)	6 (100)	4 (80)	16 (94)
Disease refractory to bridging therapy — no./total no. (%)	3/3 (100)	3/3 (100)	5/6 (83)	4/5 (80)	15/16 (94)

* BCMA denotes B-cell maturation antigen, and CAR chimeric antigen receptor.
† High-risk cytogenetic features included del(17p), t(4;14), t(14;16), and 1q gain.
‡ Penta-exposed patients were those who had received previous treatment with two proteasome inhibitors, two immunomodulatory drugs, and one anti-CD38 antibody.
§ Triple-refractory disease was defined as refractory to a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody.
¶ Included are BCMA-targeted antibody–drug conjugates, bispecific antibodies, and CAR T-cell therapies.

Mailankody S et al. N Engl J Med2022;387:1196-1206

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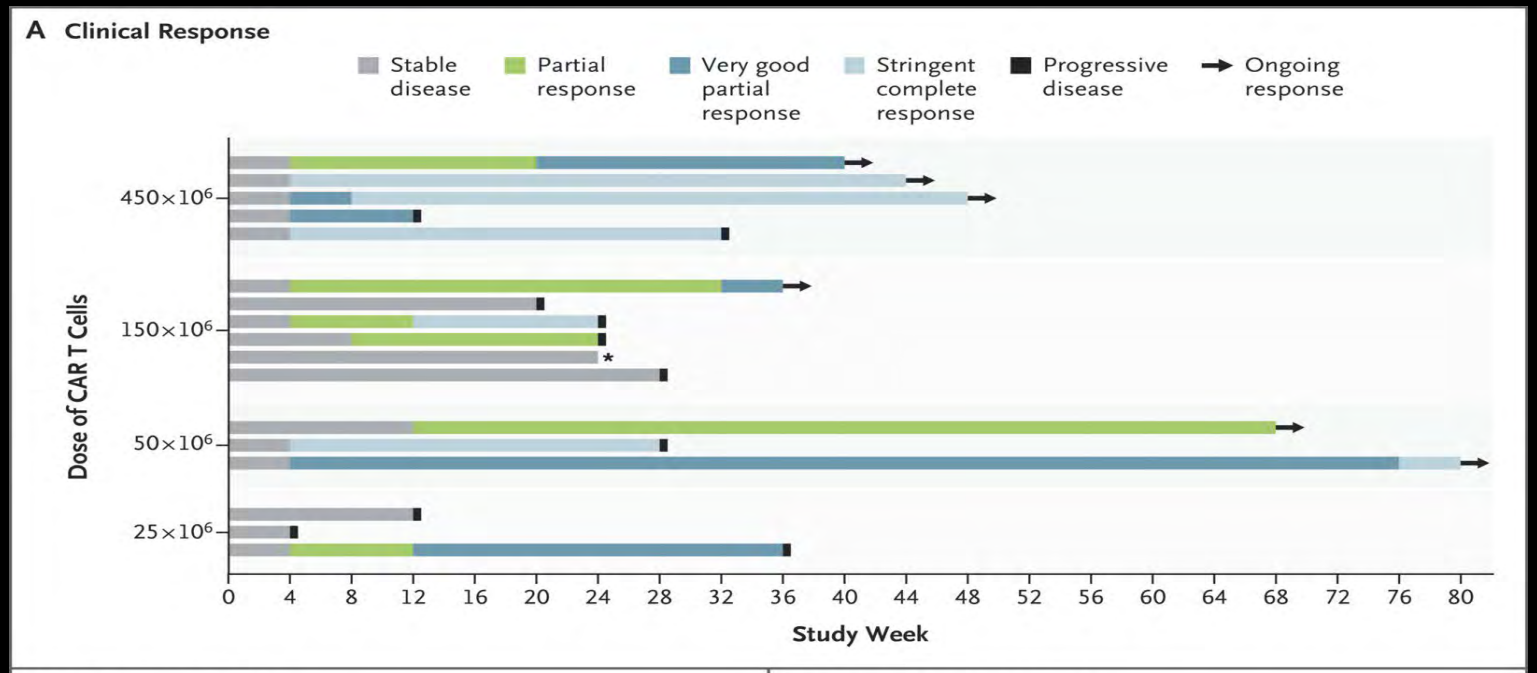
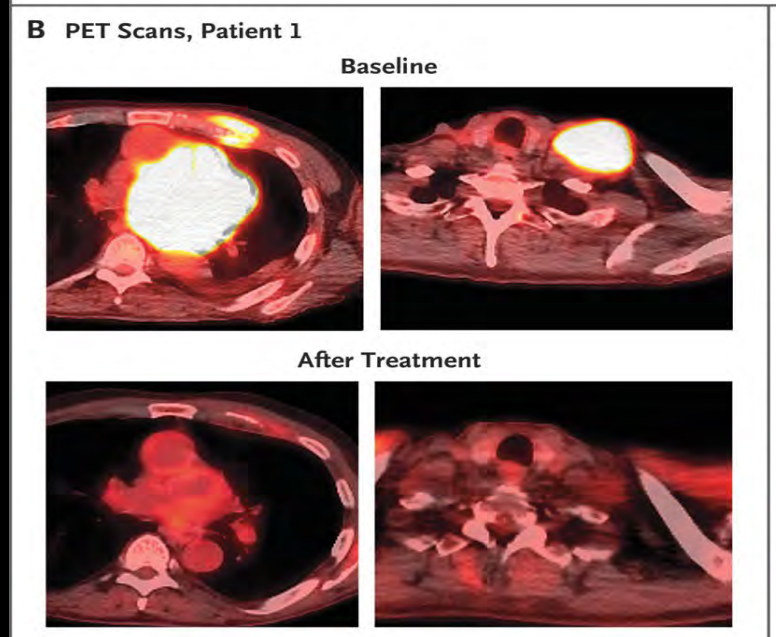
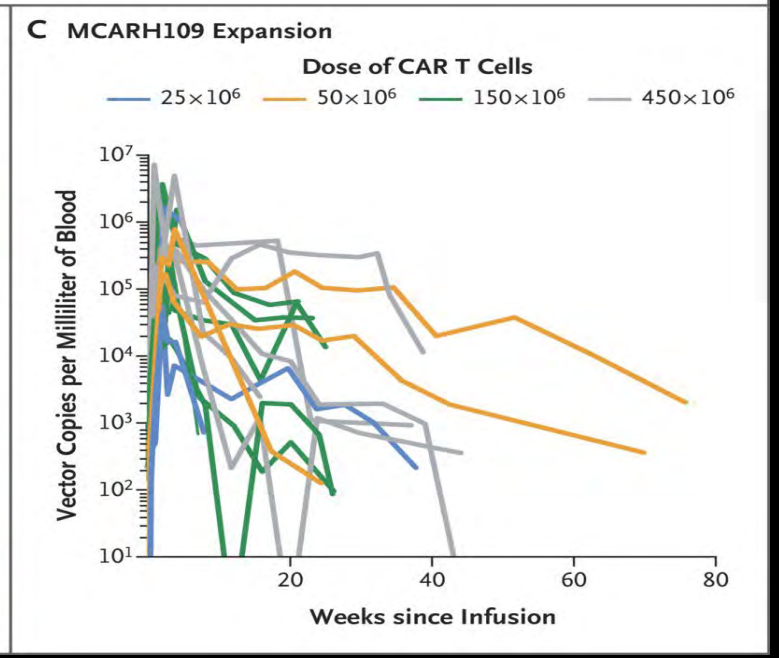
Clinical Responses to GPRC5D-Targeted Chimeric Antigen Receptor (CAR) T-Cell Therapy.







Mailankody S et al. N Engl J Med2022;387:1196-1206

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Clinical Responses in All Patients and in Patients with or without Previous BCMA-Directed Therapies.

Table 3. Clinical Responses in All Patients and in Patients with or without Previous BCMA-Directed Therapies.

Response	All Patients		Previous BCMA Therapies		No Previous BCMA Therapies	
	All Dose Levels (N=17)	25×10^6–150×10^6 CAR T Cells (N=12)	All Dose Levels (N=10)	25×10^6–150×10^6 CAR T Cells (N=6)	All Dose Levels (N=7)	25×10^6–150×10^6 CAR T Cells (N=6)
	number (percent)					
Partial response or better	12 (71)	7 (58)	7 (70)	3 (50)	5 (71)	4 (67)
Very good partial response or better	10 (59)	5 (42)	6 (60)	2 (33)	4 (57)	3 (50)
Complete response or better	6 (35)	3 (25)	4 (40)	2 (33)	2 (29)	1 (17)
Negativity for MRD in bone marrow*	8 (47)	6 (50)	3 (30)	2 (33)	5 (71)	4 (67)

* Negativity for minimal residual disease (MRD) in bone marrow was assessed by means of 10-color flow cytometry with a sensitivity of 1 in 10^5 at 4 weeks after CAR T-cell therapy, at the occurrence of a complete response, and as clinically indicated.

Mailankody S et al. N Engl J Med2022;387:1196-1206

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Conclusions

- The results of this study of a GPRC5D-targeted CAR T-cell therapy (MCARH109) confirm that GPRC5D is an active immunotherapeutic target in multiple myeloma.

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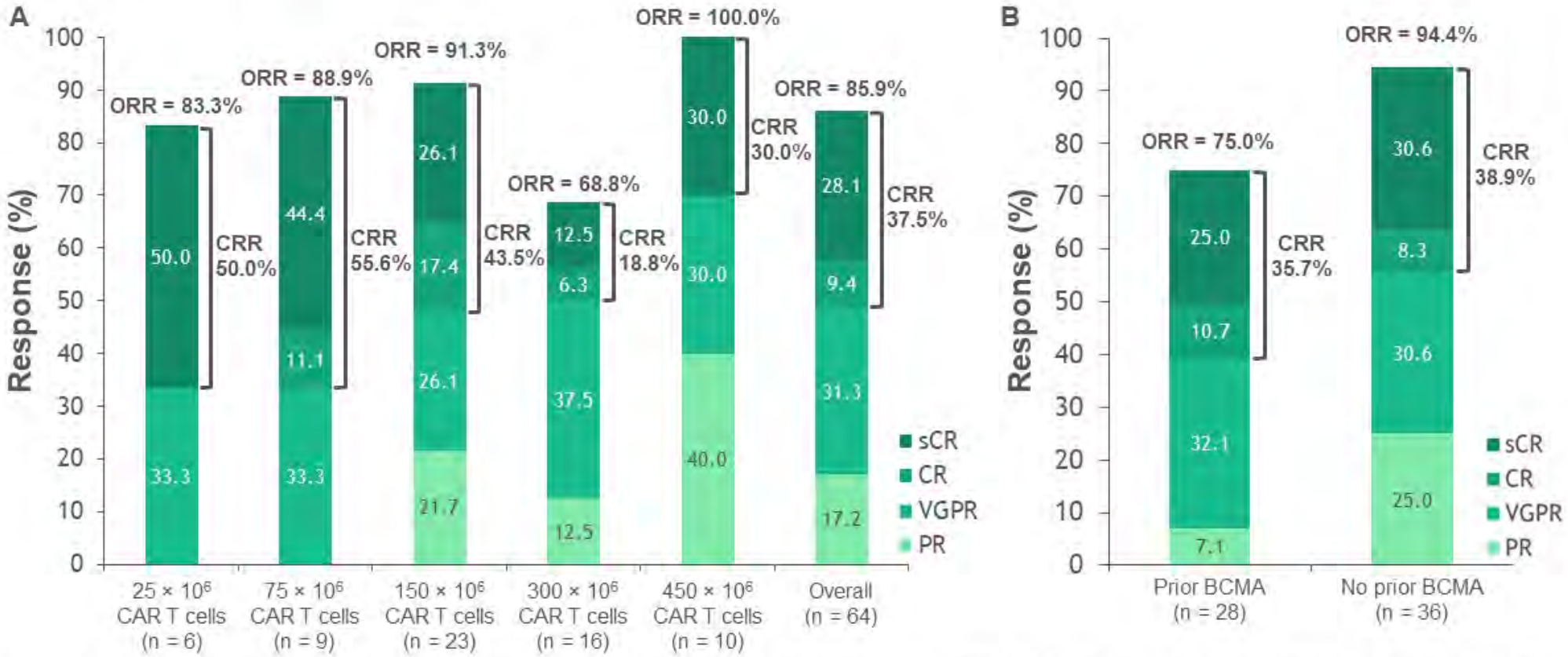
Abst. #219: BMS-986393 (CC-95266), a G Protein–Coupled Receptor Class C Group 5 Member D (GPRC5D)–Targeted CAR T-Cell Therapy for R/R MM -Updated Results of Phase 1 Study

- Multiple advances exist for advanced R/R MM;CAR-T and bi-specific Mabs
- Talquetamab recently approved by FDA in US, targets GPRC5D
- CAR-T in development- BMS - NCT046674813
- Eligibility: $\geq$ 3 prior regimens with imide, PI, anti-CD38, auto HCT in eligible pts
- Dose escalation study; N = 70 pts. 46% hi risk; 46% prior BCMA (36% prior CAR T), 34% penta-refrac
- DL2 selected: 150 x 10e6 CAR T
- Cytopenias, infections common.
- CRS 88.5%; 4% $\geq$ Gr 3; ICANS 11%; 3% Gr3; On target tox- skin 24%, nails 16%, GI 3%
- Efficacy: ORR 88% (75% in BCMA exposed pts); CR 45%. (Med DOR 13 mos)
- 10 pts with CR had MRD neg status at 3 months ($< 1 \times 10^{-5}$)
- Responses not dependent on Baseline GPRC5D expression levels

Abst. #219: BMS-986393 (CC-95266), a G Protein–Coupled Receptor Class C Group 5 Member D (GPRC5D)–Targeted CAR T-Cell Therapy for R/R MM -Updated Results of Phase 1 Study

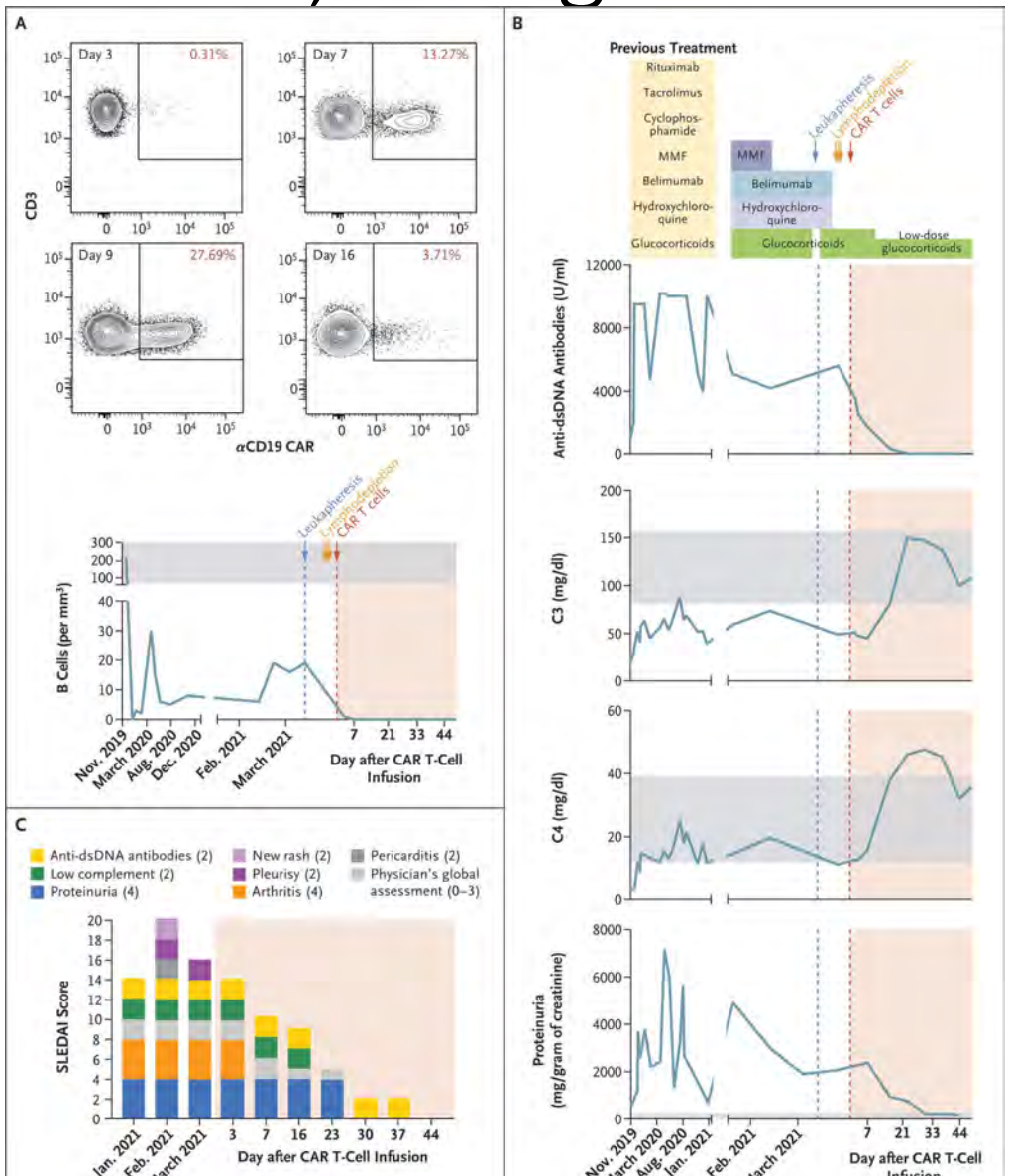
Figure. Best overall response (A) by dose level and (B) according to prior BCMA treatment (efficacy-evaluable analysis set)[a].



[a]CC-95266 efficacy-evaluable population includes all patients who received conforming BMS 986393 cell product, had measurable disease at the last disease assessment prior to BMS-986393 infusion, and had ≥ 1 post-infusion disease response assessment.
Responses were assessed per International Myeloma Working Group criteria. CR, complete response; CRR, complete response rate; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

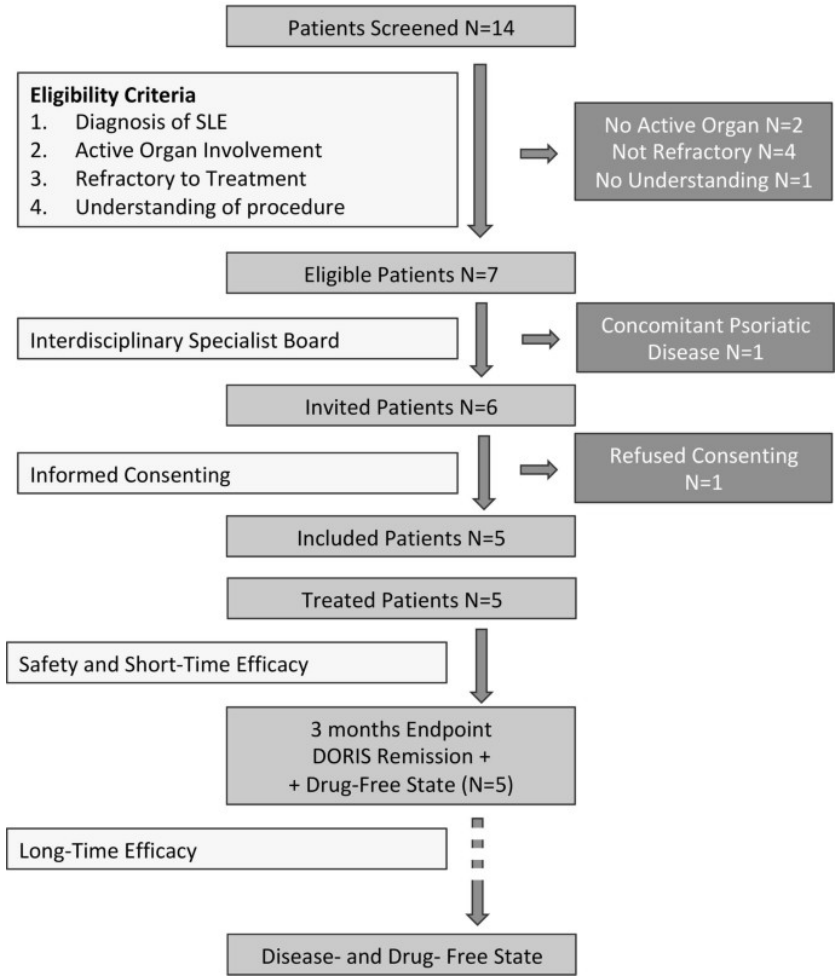
FUTURES??????????

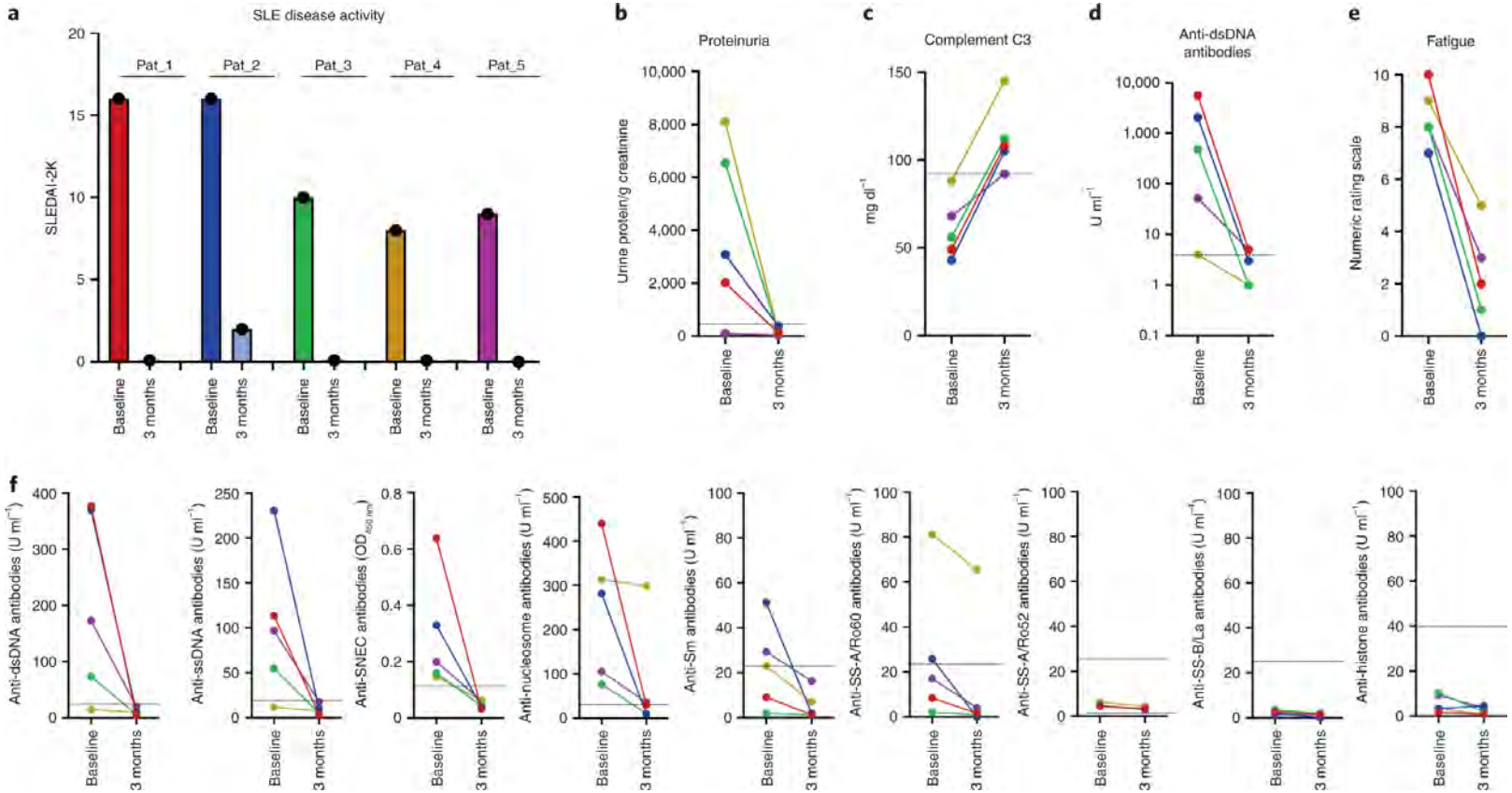
CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus, Mougiakakos et al, Letter: NEJM, 2021



Anti-CD19 CAR T cell therapy for refractory SLE, Mackensen et al, Nat Med, 2022

CONSORT Flow Diagram





ASH 2023: Abst #220- CD19-Targeted CAR-T Cells in Refractory Systemic Autoimmune Diseases: A Monocentric Experience from the First Fifteen Patients, Mueller et al.

- **Background:** CD19 CAR T cells target autoreactive B cells that trigger autoimmune diseases (AID) including systemic lupus erythematosus (SLE), idiopahtic inflammatory myositis (IIM) and systemic sclerosis (SSc).
- **Aim:** To test whether CD19 CAR T cells achieve a deeper reset of B cells, eradicate autoimmunity, and achieve lasting drug-free remission in autoantibody-dependent AID.
- **Methods:** Treatment-refractory SLE, IIM and SSc eligible→signs of active organ involvement, failure of multiple immunomodulatory therapies, and serious or immediately life-threatening disease.
- Autologous CD19 CAR T cells MB-CART19.1 (Miltenyi prodigy platform). Leukapheresis on day -13; LDC with flu 25 mg/m2 D-5 to -3 and CTX 1000 mg/m2/on D-3. D1: patients 1x10e6 CAR T cells / kg body weight.

ASH 2023: Abst #220- CD19-Targeted CAR-T Cells in Refractory Systemic Autoimmune Diseases: A Monocentric Experience from the First Fifteen Patients, Mueller et al.

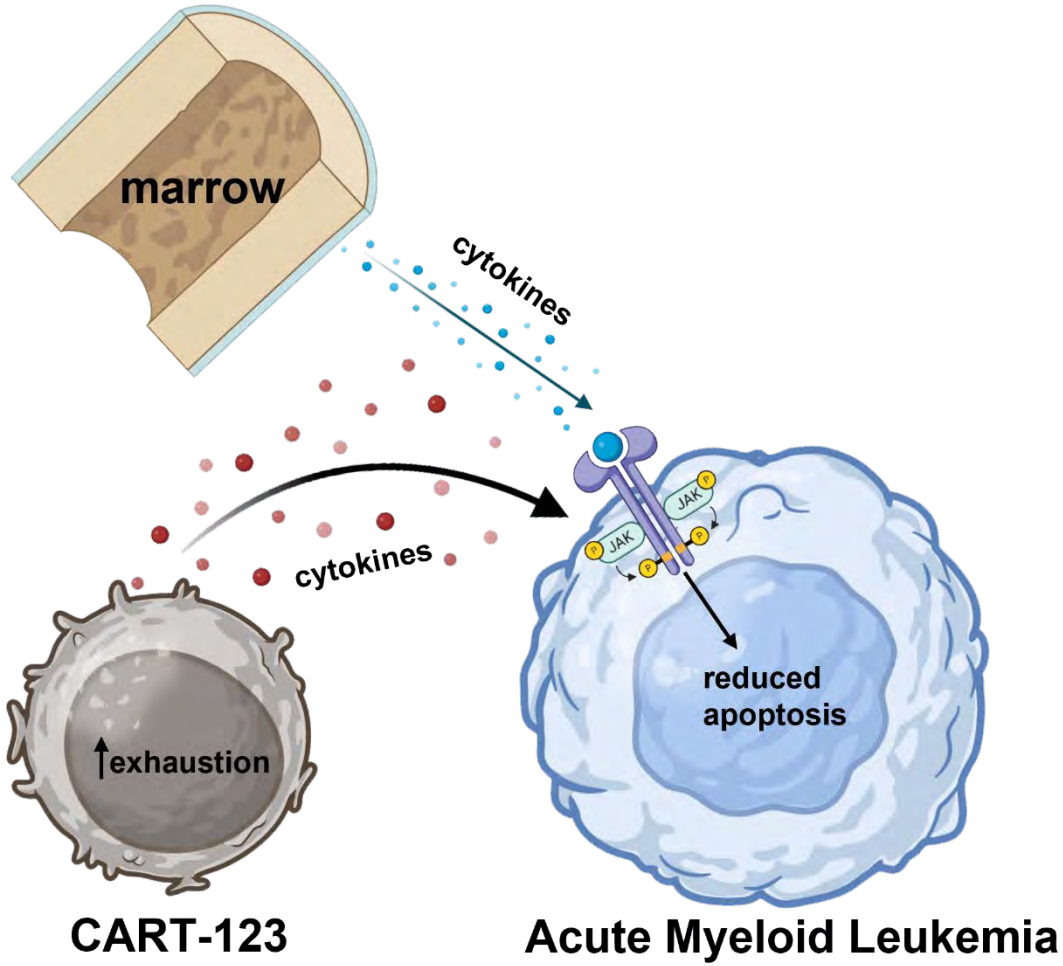
- ***Results:*** 15 patients : 8 SLE, 4 SSc, and 3 IIM (Med age = 36); 15./15 with autoabs; at least 2 organ involvement
- Median disease duration before CAR T was 4 years [1-20], median f/u post CAR T 12 months [2-28]. Median # prior RX= 5 [2-14
- No Immune meds except max pred 10 mg qd
- CAR T cell expansion with peak day 8.6 ± 0.8.
- Clearance of host CD19+ B cells: mean of 5.9 ± 2.2 days
- 8 SLE pts → CR at 3 mo; ongoing SLE Disease Activity Index (SLEDAI) of 0.
- 3/3 IIM pts→ major improvement and normalization of CK at 3 mos; ongoing response.
- 4 SSc patients, 3 patients with >3 months → decreased sx by EULAR AI by -4.3 [-4.3; -3.6].
- All 15 patients entirely stopped immunosuppressive drugs.
- CRS 11/15; 10 Gr1; 1 gr 2. 6/156 → toci. ICANS 1/15, Gr 1 (vertigo sx)
- Five SLE patients at 14-24 months in CR, with B cell recovery seen. Total B cell numbers gradually increased to a median of 230 cells/µl at month 12; mostly naïve phenotype. The early drop of CD19+CD27+ memory B cells increased again at month 12 indicating maturation of the B cells emerging after CAR T treatment.

Abst. #217: CRS results in reduced AML killing by CD123 CAR T cells, Bhagwat et al

- AML CAR T-cell therapy has been assoc with multiple failures
- Penn Pilot study: CD123 directed CAR T-cells
- 20 candidates with R/R AML; 12 infused
- Cy/Flu LDC; CAR T Rx outcomes→

  4 CRi, 3 PD, 5 stable, 2 NRM 2^{o} CRS;

  Only 2 alive longterm
- CRS 10/12 subjects
- Link between hi CRS, lo response?
- Lab RNASeq analysis:
  - 1. AML samples with CRS cytokines→ Upregulation signalling (Jak/Stat) and survival pathways in blasts
  - 2. GM-CSF → decrease AML sensitivity to CAR T
  - 3. Ongoing antigen exposure→ T cell exhaustion
  - 4. Ruxolitinib could restore AML blast killing, by blocking JAK/STAT pathway in blasts
  - 5. Different biology than in Lymphoid blasts



Apologies that these selections are but a snapshot of ASH
There is always more, coming around the corner