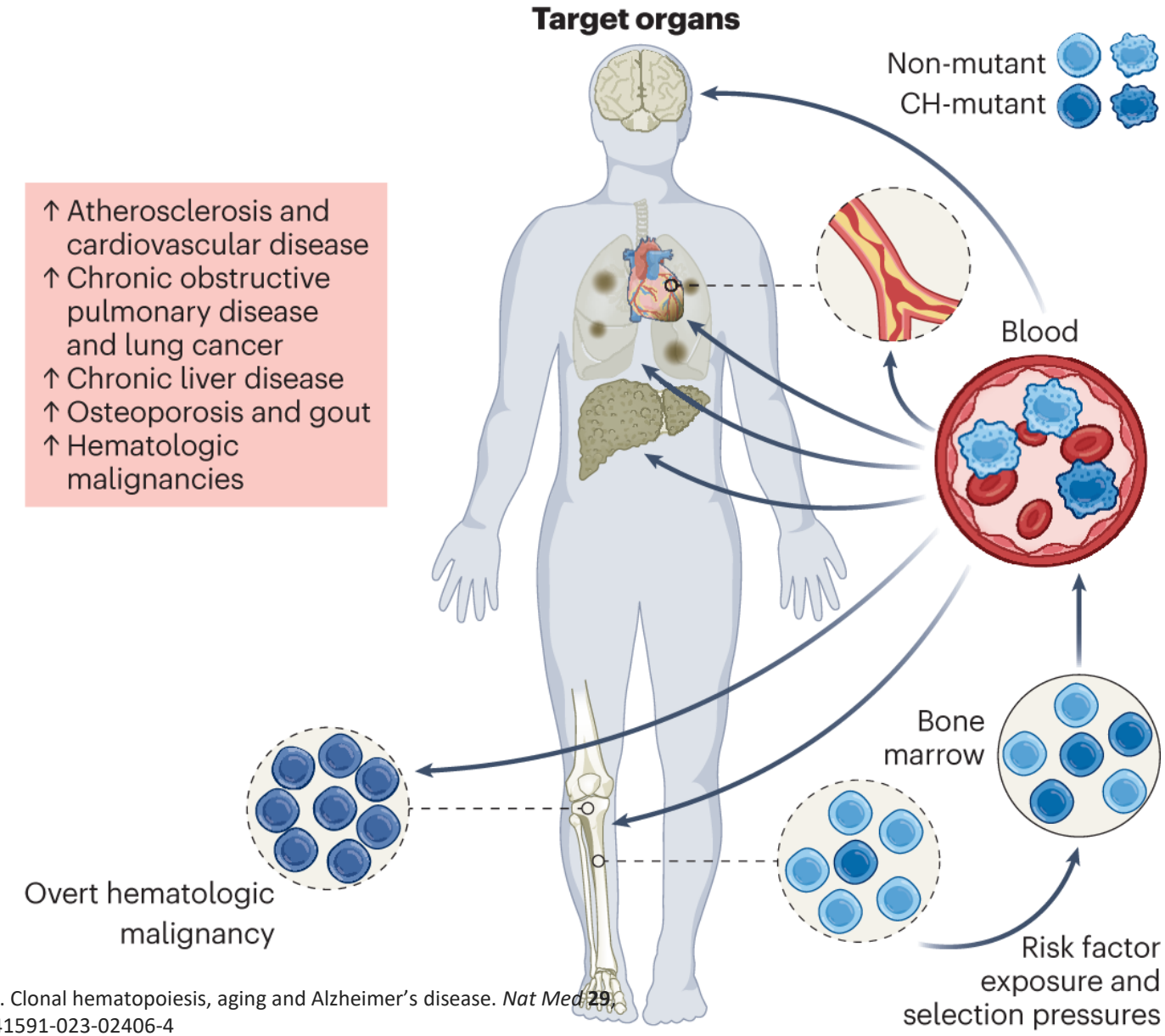
V7 Das Beste aus der Hämatologie

Best of Haematology

Thorsten Zenz (Zürich, CH)

CHIP

Klonale Hämatopoiese



Clonal hematopoiesis of indeterminate potential (CHIP) is an age-associated expansion of hematopoietic stem cells (HSCs) found in 10–30% of those older than 70

Sánchez Vela, P., Trowbridge, J.J. & Levine, R.L. Clonal hematopoiesis, aging and Alzheimer's disease. *Nat Med* 29, 1605–1606 (2023). https://doi.org/10.1038/s41591-023-02406-4

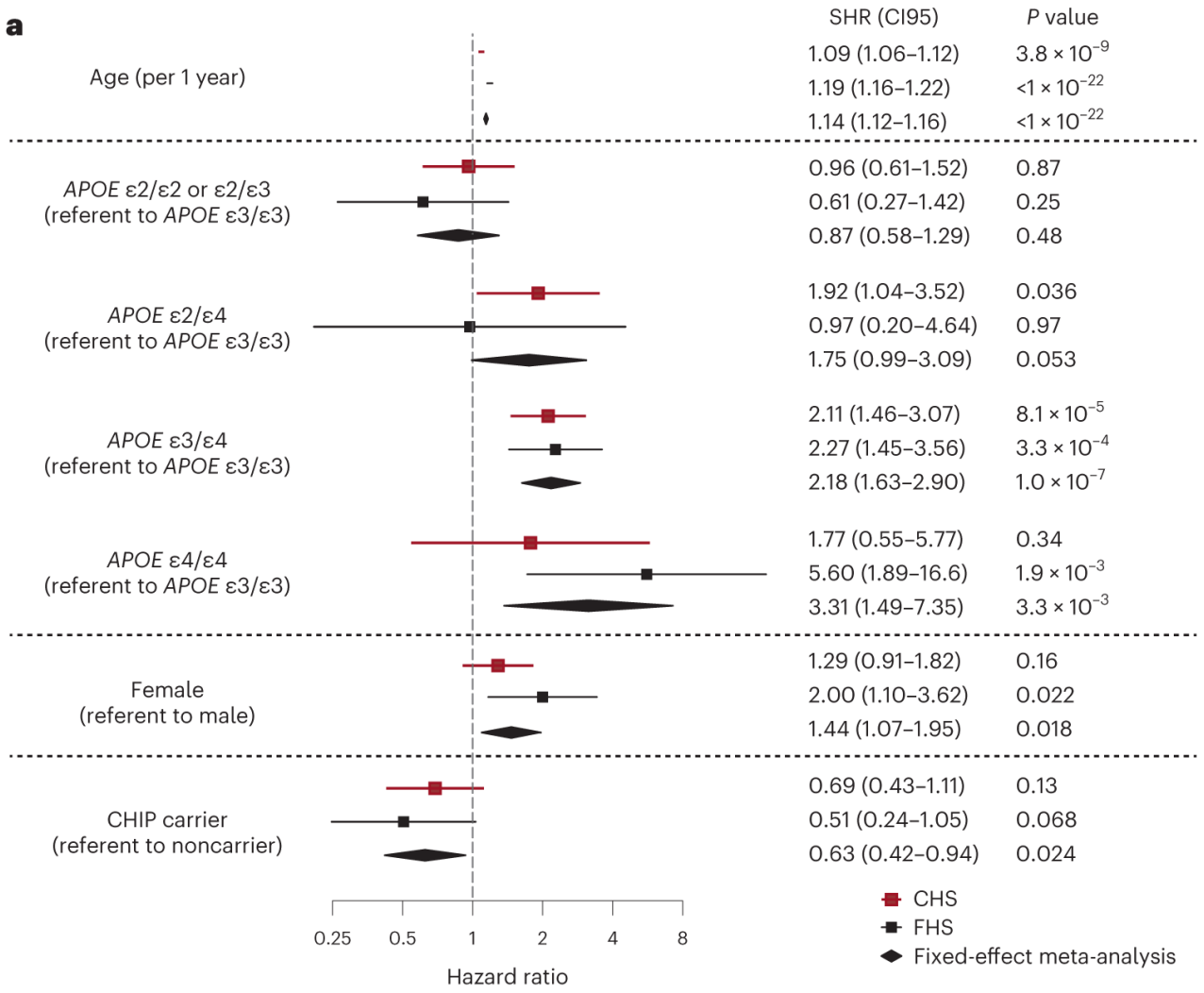
Association between CHIP and AD dementia

- To perform association tests between CHIP and AD dementia, we analyzed blood DNA sequencing data from 1,362 individuals with AD and 4,368 individuals without AD.
- Individuals with CHIP had a lower risk of AD dementia (meta-analysis odds ratio (OR) = 0.64, P = 3.8 × 10−5), and Mendelian randomization analyses supported a potential causal association.
- We observed that the same mutations found in blood were also detected in microglia-enriched fraction of the brain in seven of eight CHIP carriers. Single-nucleus chromatin accessibility profiling of brain-derived nuclei in six CHIP carriers revealed that the mutated cells comprised a large proportion of the microglial pool in the samples examined.
- These results suggest that CHIP may have a role in attenuating the risk of AD

Bouzid, H., Belk, J.A., Jan, M. *et al.* Clonal hematopoiesis is associated with protection from Alzheimer's disease. *Nat Med* **29**, 1662–1670 (2023). https://doi.org/10.1038/s41591-023-02397-2

Association of CHIP and AD in longitudinal cohorts.

Framingham Heart Study (FHS) and the Cardiovascular Health Study (CHS)



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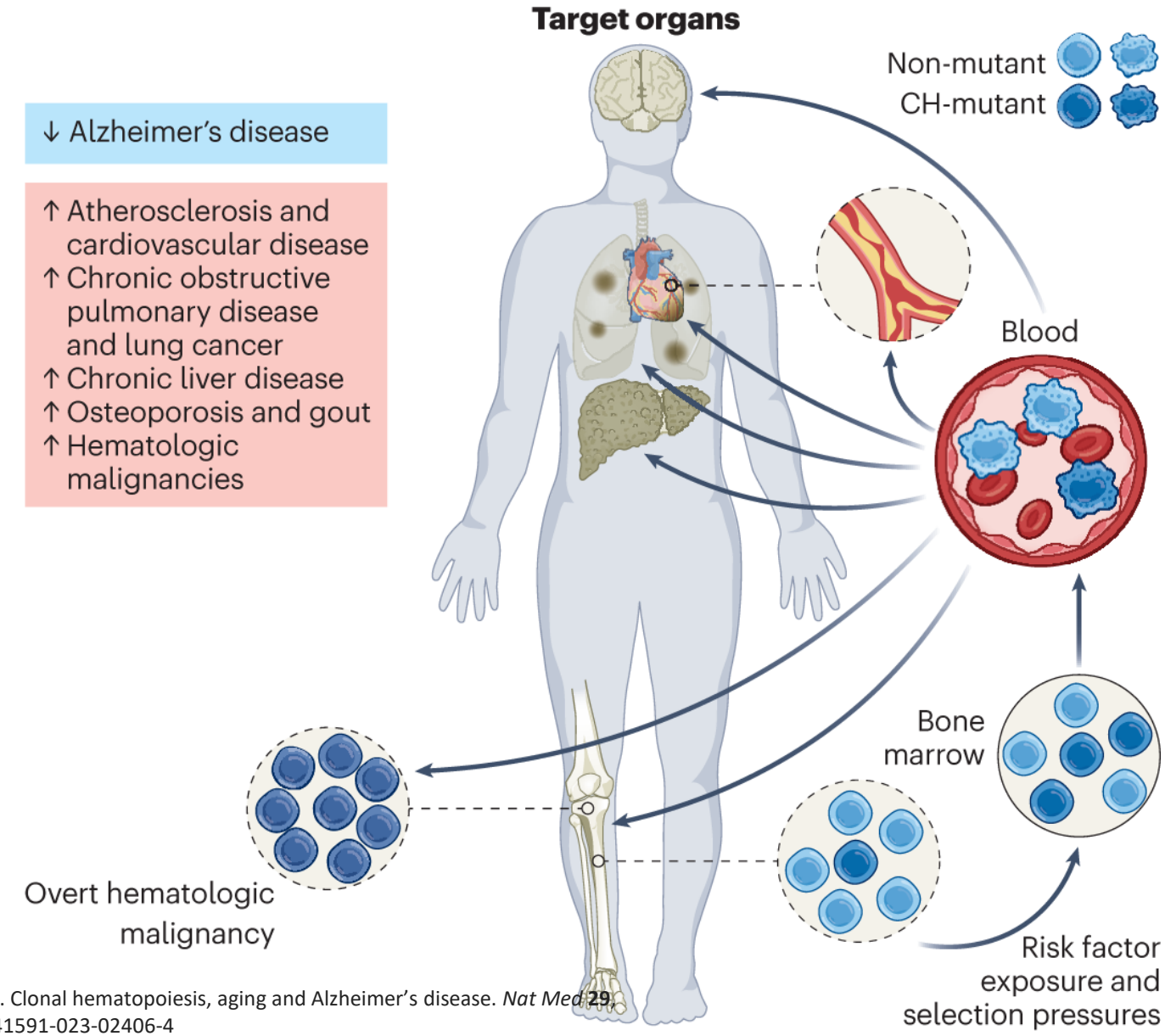
CHIP

Klonale Hämatopoiese



Clonal hematopoiesis of indeterminate potential (CHIP) is an age-associated expansion of hematopoietic stem cells (HSCs) found in 10–30% of those older than 70

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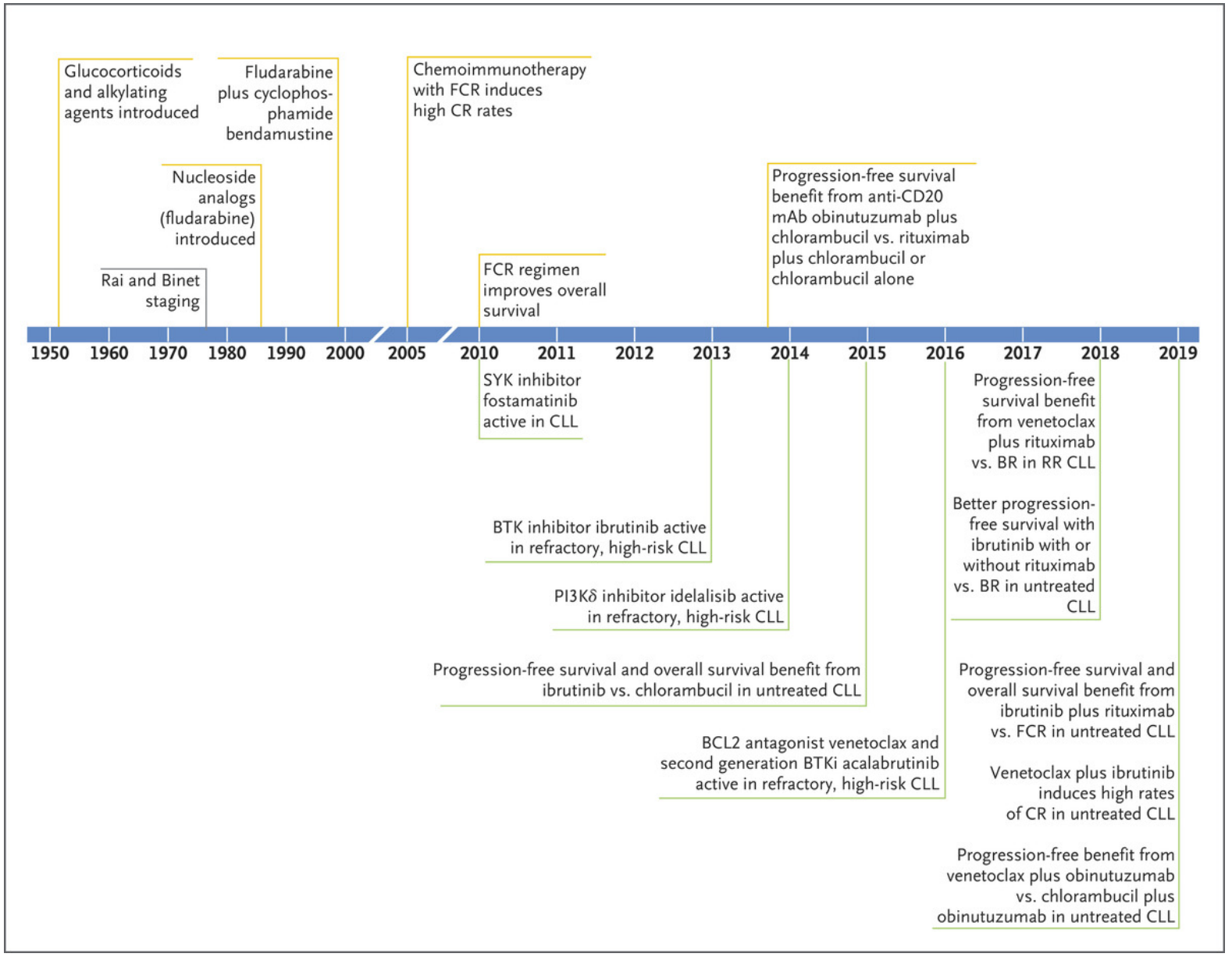
Milestones in Clinical CLL Research

Role of targeted drugs

MRD



JA Burger. N Engl J Med 2020;383:460-473.

The NEW ENGLAND JOURNAL of MEDICINE

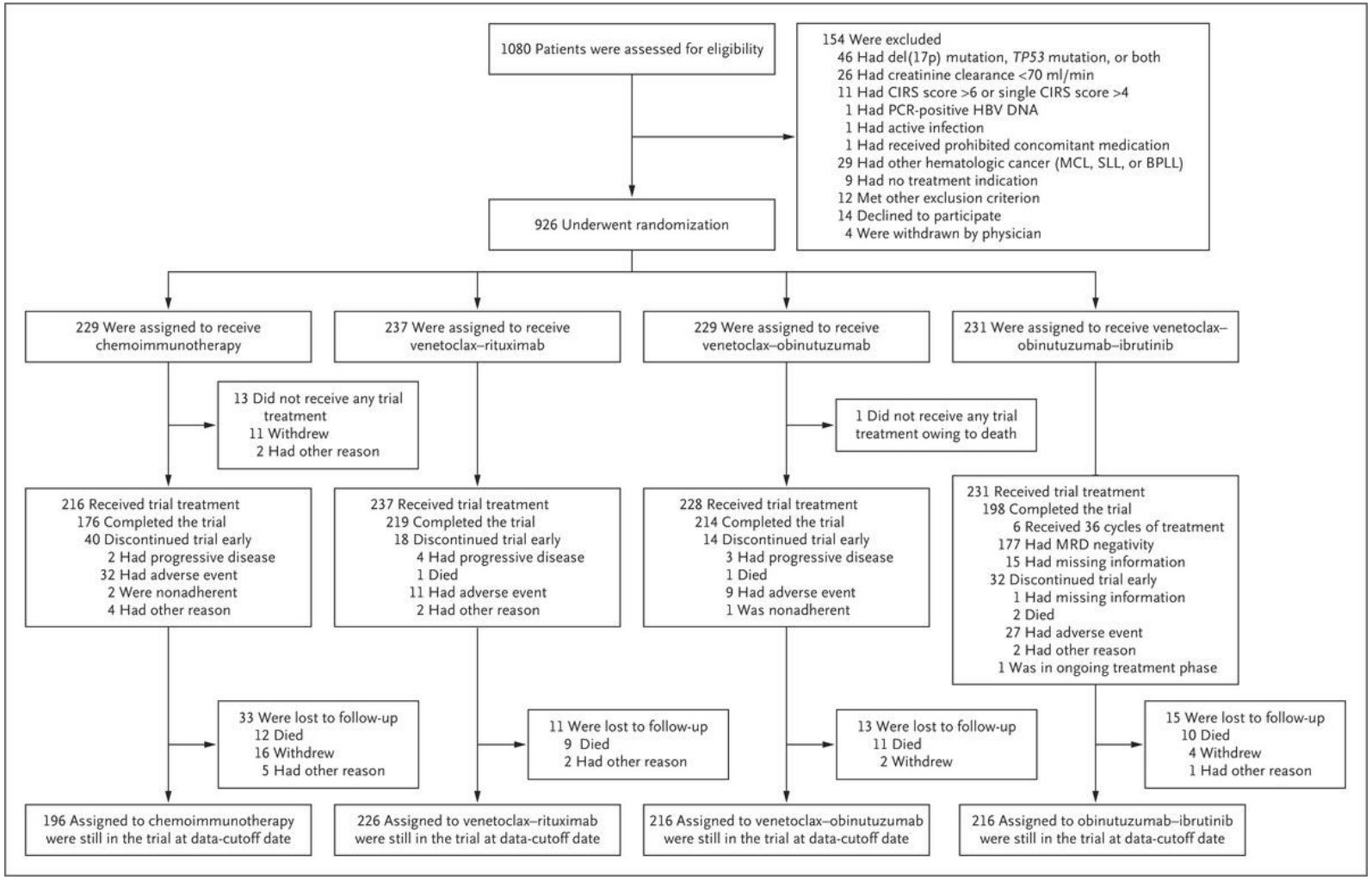
ESTABLISHED IN 1812 MAY 11, 2023 VOL. 388 NO. 19

First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia

B. Eichhorst, C.U. Niemann, A.P. Kater, M. Fürstenau, J. von Tresckow, C. Zhang, S. Robrecht, M. Gregor, G. Juliusson, P. Thornton, P.B. Staber, T. Tadmor, V. Lindström, C. da Cunha-Bang, C. Schneider, C.B. Poulsen, T. Illmer, B. Schöttker, T. Nösslinger, A. Janssens, I. Christiansen, M. Baumann, H. Frederiksen, M. van der Klift, U. Jäger, M.B.L. Leys, M. Hoogendoorn, K. Lotfi, H. Hebart, T. Gaska, H. Koene, L. Enggaard, J. Goede, J.C. Regelink, A. Widmer, F. Simon, N. De Silva, A.-M. Fink, J. Bahlo, K. Fischer, C.-M. Wendtner, K.A. Kreuzer, M. Ritgen, M. Brüggemann, E. Tausch, M.-D. Levin, M. van Oers, C. Geisler, S. Stilgenbauer, and M. Hallek, for the GCLLSG, the HOVON and Nordic CLL Study Groups, the SAKK, the Israeli CLL Association, and Cancer Trials Ireland*

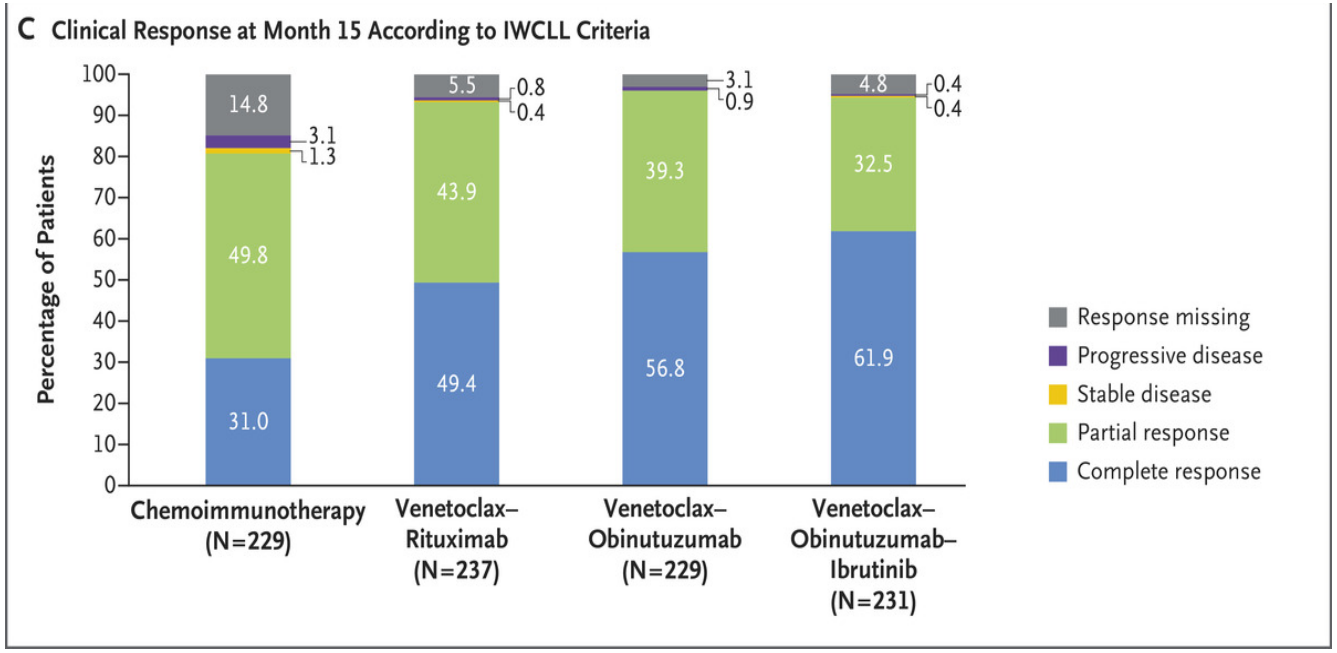
FCR/BR vs. RVen vs. GVen vs. GIVe

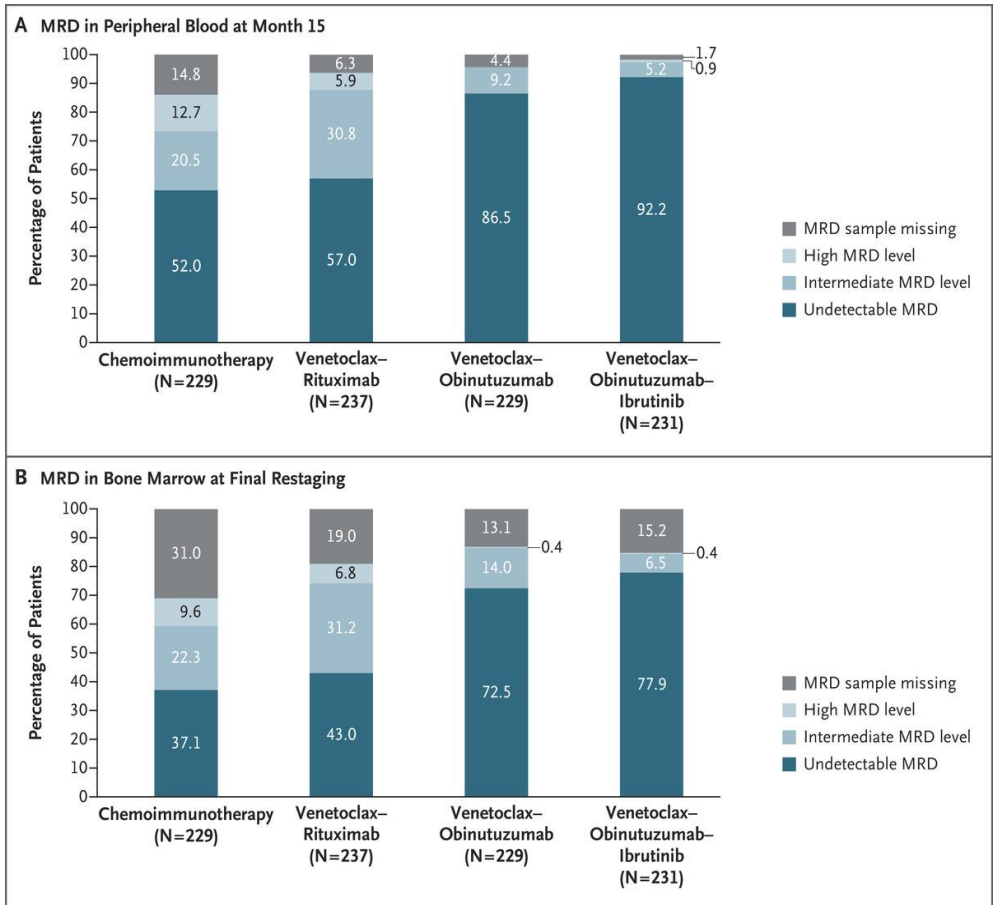
Screening, Randomization, and Follow-up.



B Eichhorst et al. N Engl J Med 2023;388:1739-1754.

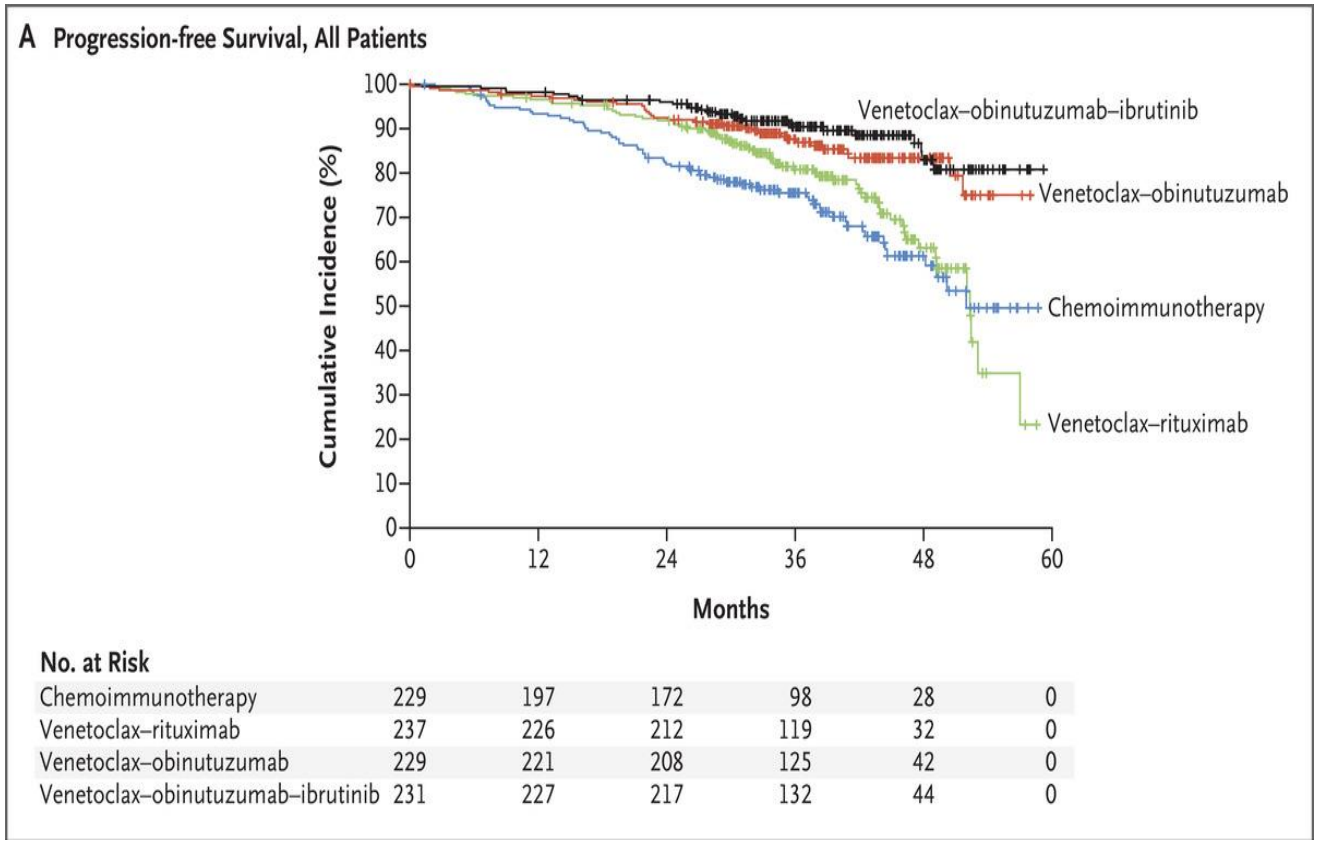
MRD Measured by Flow Cytometry





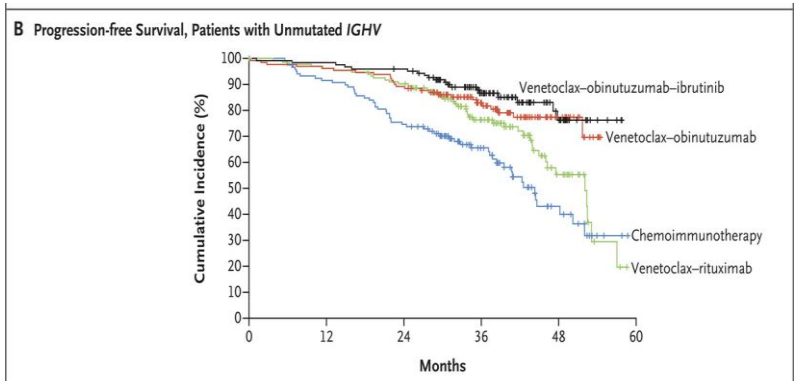
B Eichhorst et al. N Engl J Med 2023;388:1739-1754.

Progression-free Survival at 3 Years



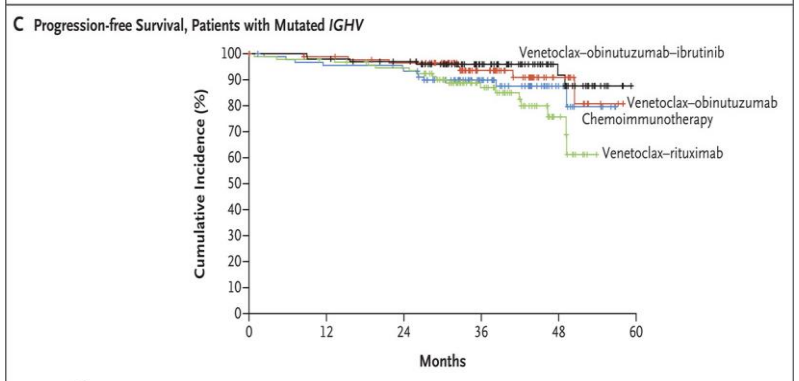
No. at Risk

Chemoimmunotherapy	229	197	172	98	28	0
Venetoclax–rituximab	237	226	212	119	32	0
Venetoclax–obinutuzumab	229	221	208	125	42	0
Venetoclax–obinutuzumab–ibrutinib	231	227	217	132	44	0



No. at Risk

Chemoimmunotherapy	131	108	88	48	14	0
Venetoclax–rituximab	134	128	119	67	20	0
Venetoclax–obinutuzumab	130	125	116	71	21	0
Venetoclax–obinutuzumab–ibrutinib	123	121	117	70	22	0



No. at Risk

Chemoimmunotherapy	95	86	83	50	14	0
Venetoclax–rituximab	95	91	86	49	12	0
Venetoclax–obinutuzumab	89	86	82	48	17	0
Venetoclax–obinutuzumab–ibrutinib	101	99	94	59	22	0

B Eichhorst et al. N Engl J Med 2023;388:1739-1754.

Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia

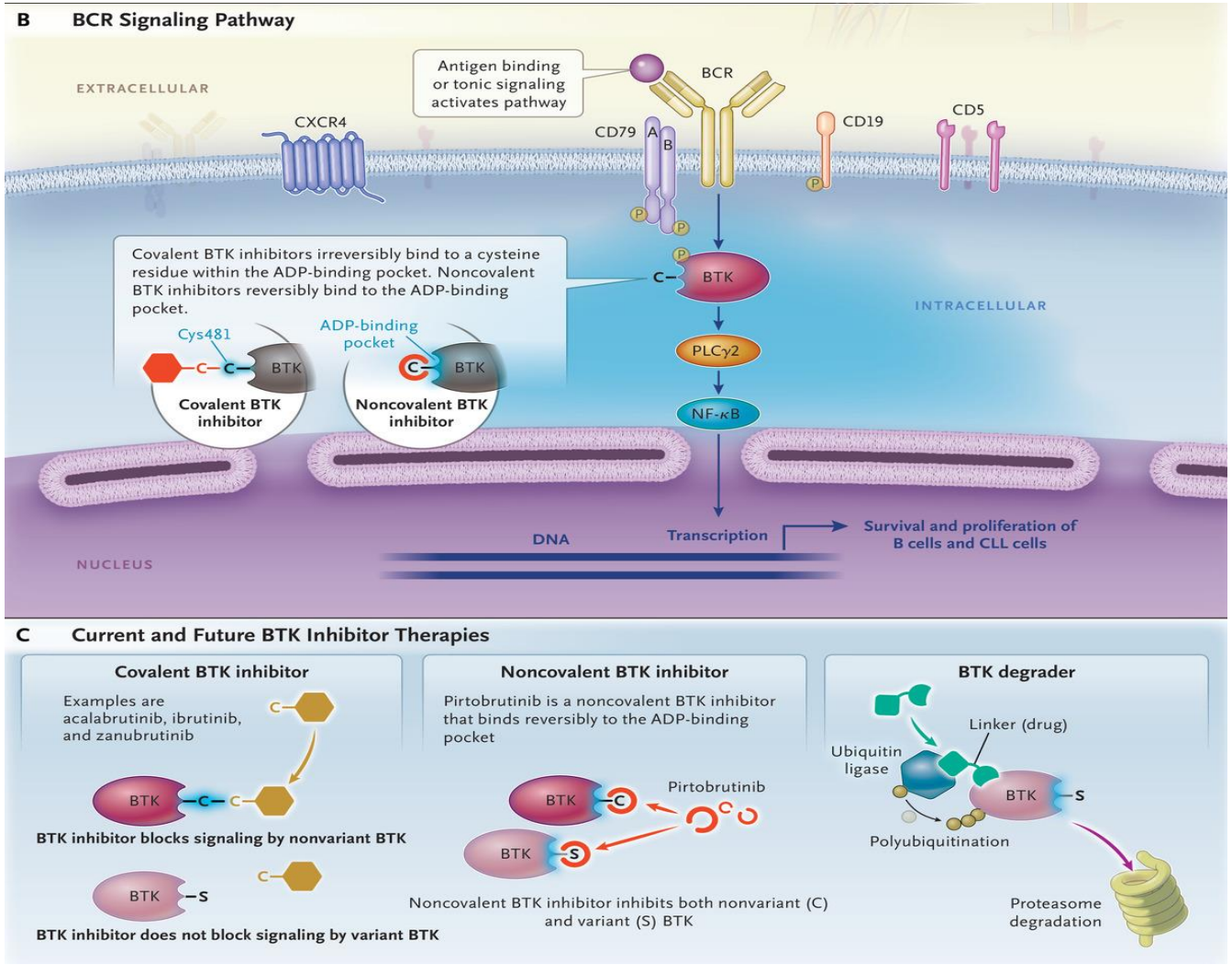
Anthony R. Mato, et al NEJM 2023

phase 1–2 trial in which patients with relapsed or refractory B-cell cancers received pirtobrutinib.

Here, we report efficacy results among patients with CLL or SLL who had previously received a BTK inhibitor as well as safety results among all the patients with CLL or SLL.

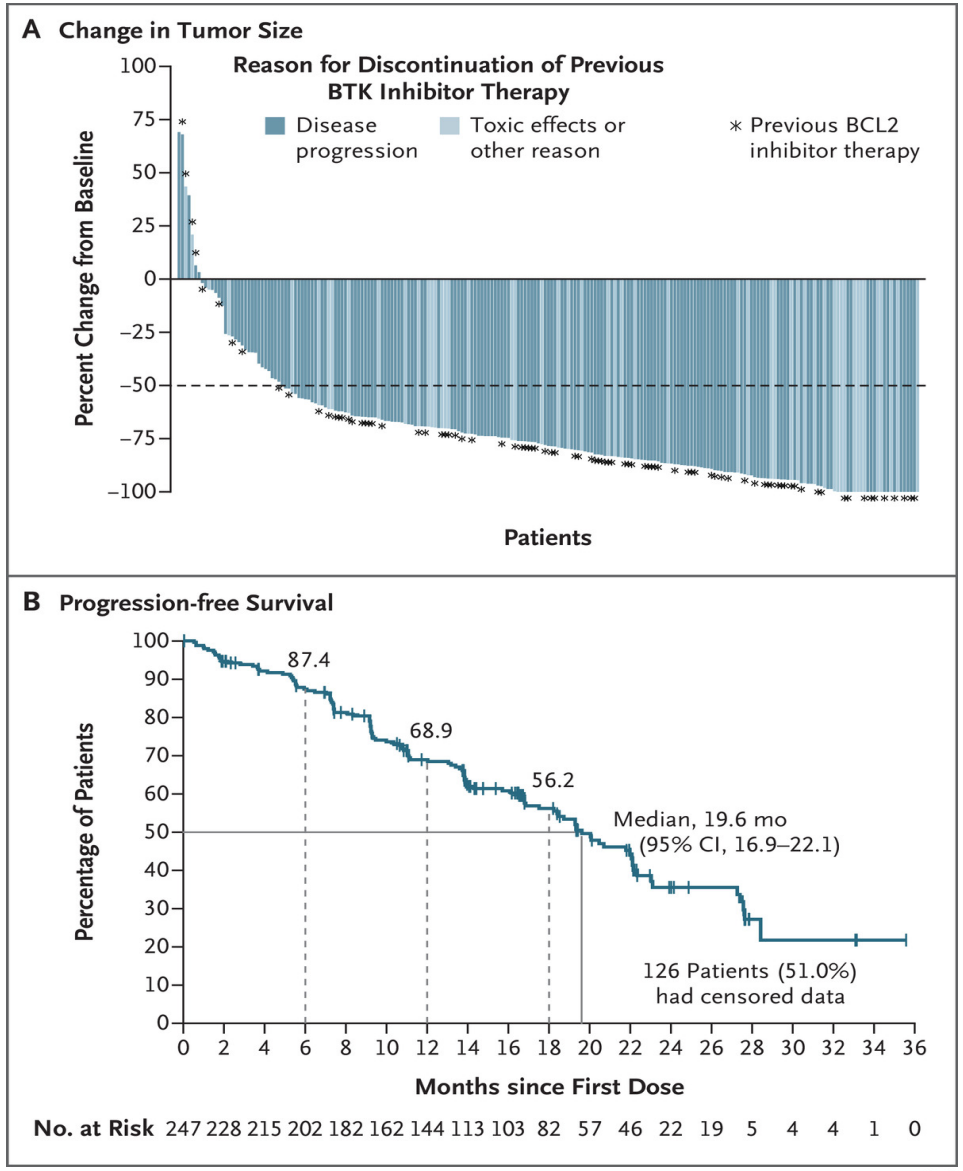
The primary end point was an overall response (partial response or better) as assessed by independent review.

Secondary end points included progression-free survival and safety.



AP Kater, B Eichhorst. N Engl J Med 2023;389:83-86.

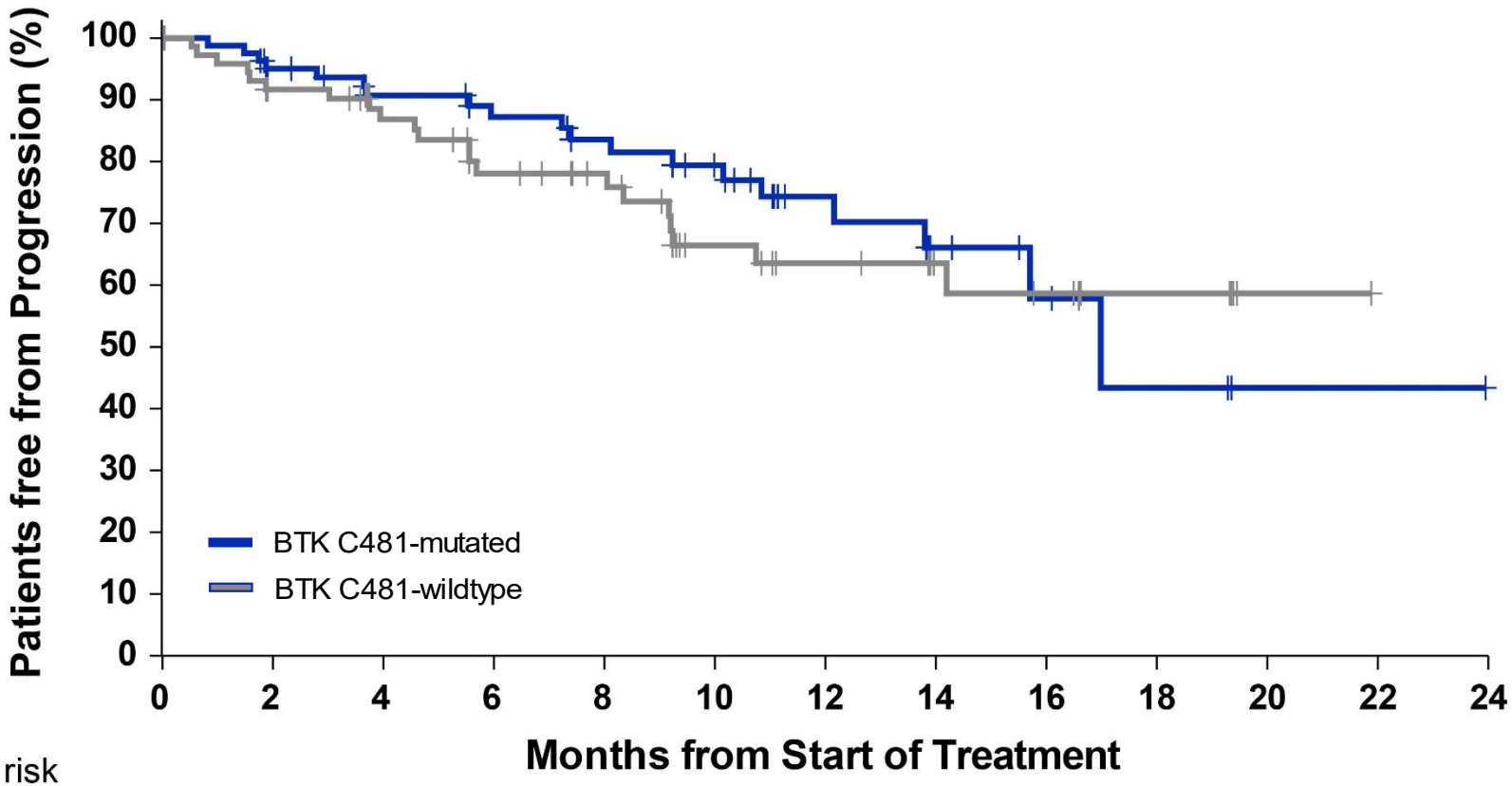
Change in Tumor Size and Progression-free Survival.



AR Mato et al. N Engl J Med 2023;389:33-44.

BTK C481 Mutation Status is not Predictive of Pirtobrutinib Benefit

Progression-free survival by BTK C481 mutation status in CLL/SLL patients with progression on a prior BTK inhibitor



Number at risk													
BTK C481-mutated	84	68	54	49	40	33	18	10	7	3	1	1	0
BTK C481-wildtype	74	62	52	40	35	23	19	13	11	5	1	0	

Non-C481 *BTK* mutations block drug binding to BTK

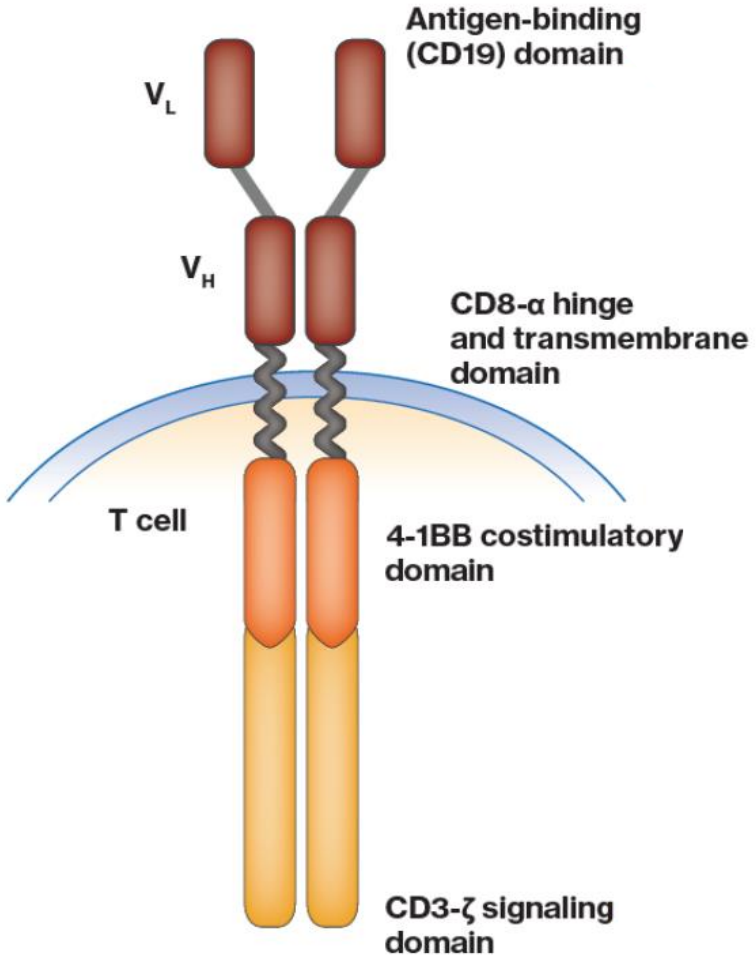
	Noncovalent inhibitors (K_D in nM)				Covalent inhibitors (Kinact/KI, in μM^{-1} sec^{-1}; except where indicated)		
BTK Protein	Pirtobrutinib	ARQ531	Vecabrutinib	Fenebrutinib	Ibrutinib	Acalabrutinib	Zanubrutinib
WT BTK	0.9	87	0.8	0.2	0.044	0.005	0.052
A428D	No binding detected	2300	No binding detected	No binding detected	No binding detected	No binding detected	No binding detected
M437R	71	29	1.2	159	0.088	<0.001	0.050
T474I	14	8000	14	2.1	0.015	<0.001	<0.001
L528W	No binding detected	No binding detected	24	1.5	No binding detected	<0.001	No binding detected
C481S	2.6	79	2.5	5.1	29 nM	358 nM	69 nM

A428D T474I M437R BTK

≥10X reduced binding

Wang, Mi, Thompson, et al. NEJM 2022

CAR-T and Bispecifics



1. Milone MC, et al. *Mol Ther*. 2009;17:1453-1464. 2. Zhang H, et al. *J Immunol*. 2007;179:4910-4918.
3. Kalos M, et al. *Sci Transl Med*. 2011;3:95ra73.

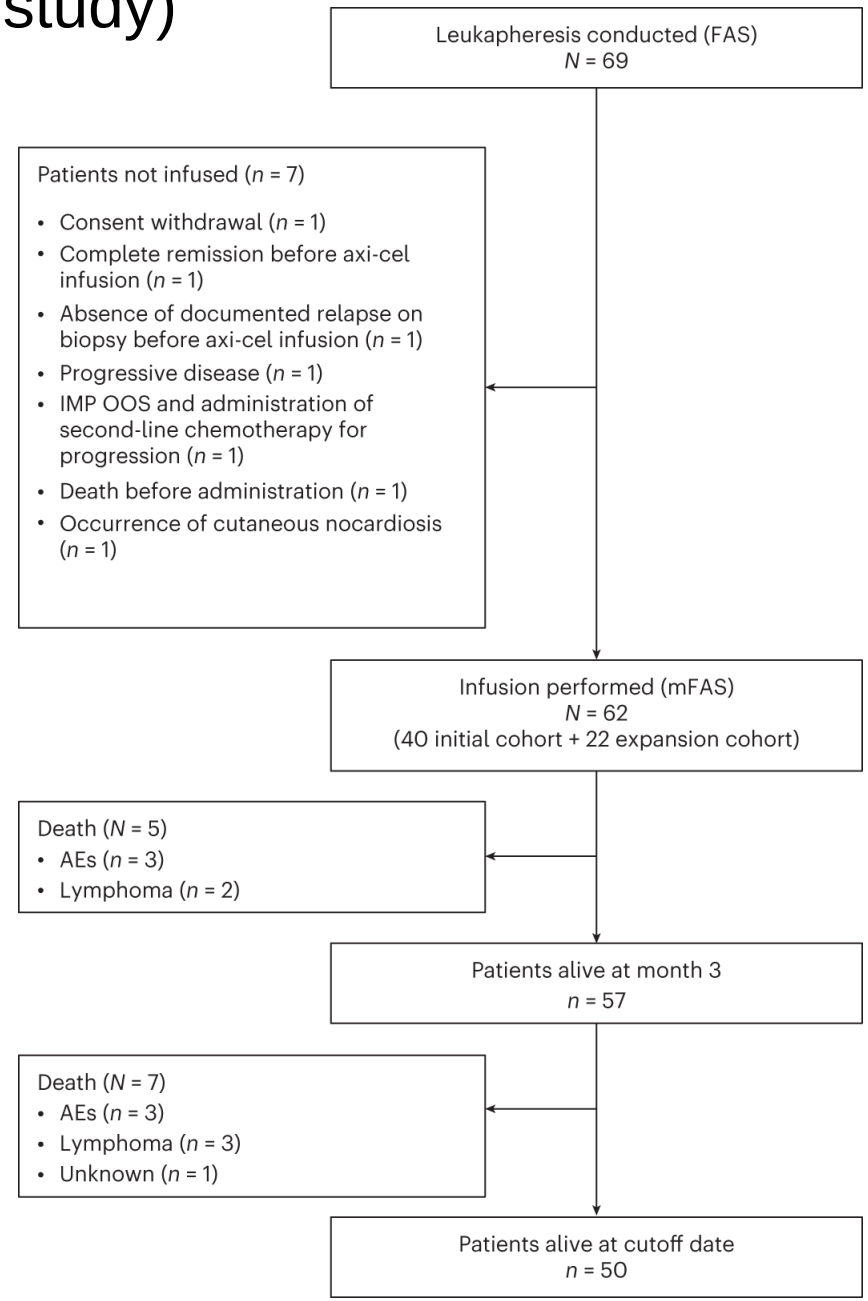
nature medicine

Article

https://doi.org/10.1038/s41591-023-02572-5

Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial

Consort (Phase II study)

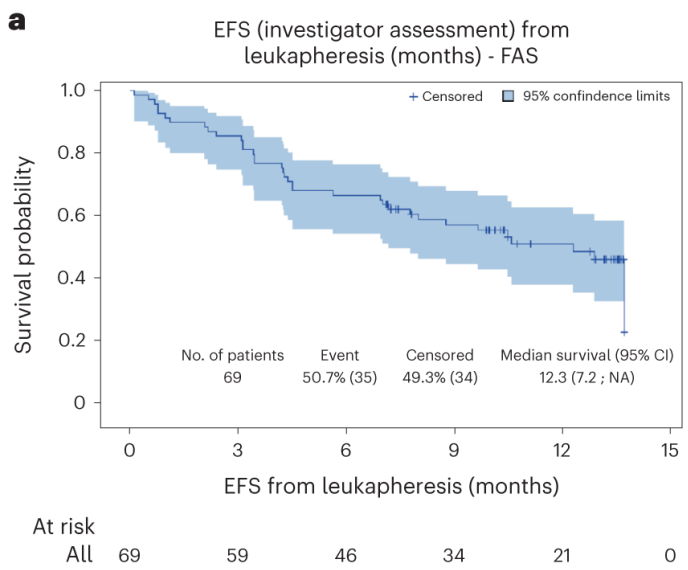


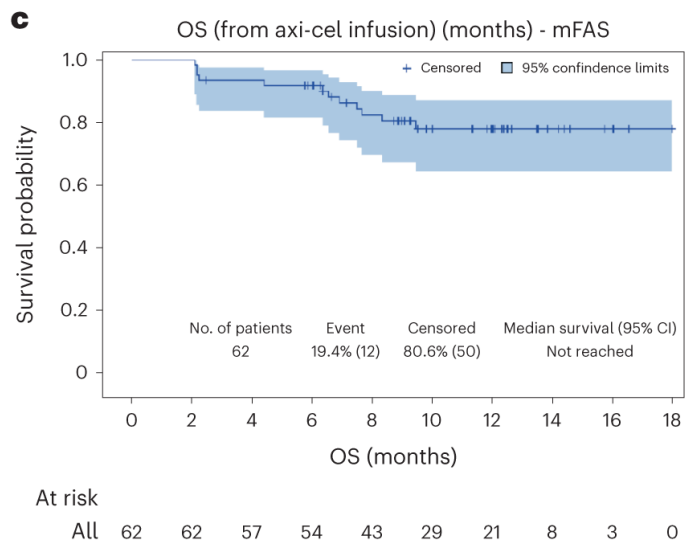
nature medicine

Article

https://doi.org/10.1038/s41591-023-02572-5

Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial





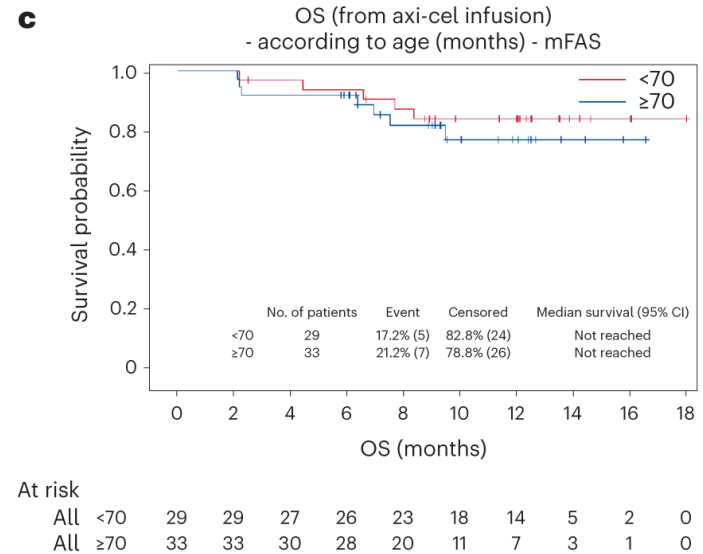


Table 3 | Adverse events of special interest in the modified full analysis set (*N*=62)

	Patients who received axi-cel (*N*=62)
CRS, *n* (%)	
Any	58 (93.5)
Grade 1–2	53 (85.5)
Grade 3–4	5 (8.1)
Median time to onset (Q1–Q3), days	1.5 (1.0–3.0)
Median duration (Q1–Q3), days	5.0 (4.0–9.0)
ICANS, *n* (%)	
Any	32 (51.6)
Grade 1–2	23 (37.1)
Grade 3–4	9 (14.5)
Median time to onset (Q1–Q3), days	6.0 (5.0–8.0)
Median duration (Q1–Q3), days	5.0 (3.0–8.0)
Grade ≥ 3 prolonged cytopenia[a], *n* (%)	23 (37.1)
Grade ≥3 prolonged neutropenia	15 (24.2)
Grade ≥3 prolonged anemia	14 (22.6)
Grade ≥3 prolonged thrombocytopenia	14 (22.6)
Use of tocilizumab to manage CAR-T cell toxicities, *n* (%)	48 (77.4)
Use of corticosteroids to manage CAR-T cell toxicities, *n* (%)	40 (64.5)
ICU transfer due to CAR-T cell toxicities, *n* (%)	16 (25.8)
Infections, *n* (%)	
Any	33 (53.2)

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

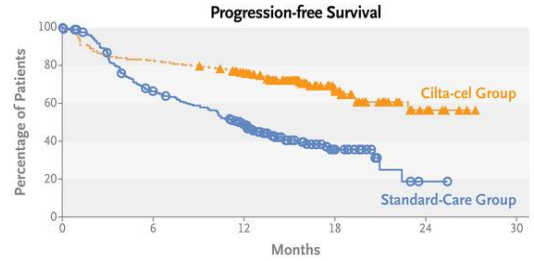
Efficacy: At the 12-month follow-up in the intention-to-treat population, progression-free survival was 75.9% in the cilta-cel group and 48.6% in the standard-care group.

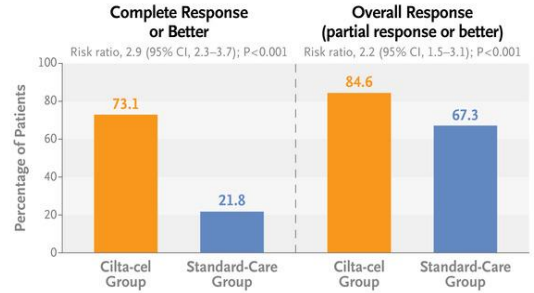
Safety: Three quarters of cilta-cel recipients had cytokine release syndrome, mostly of grade 1 or 2 severity.

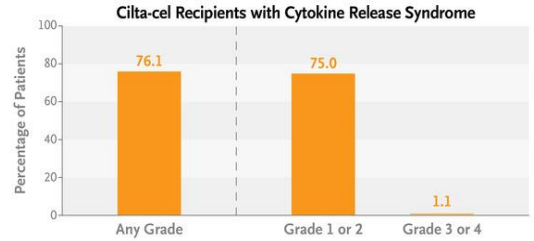
LIMITATIONS AND REMAINING QUESTIONS

- 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.

nature medicine

Article

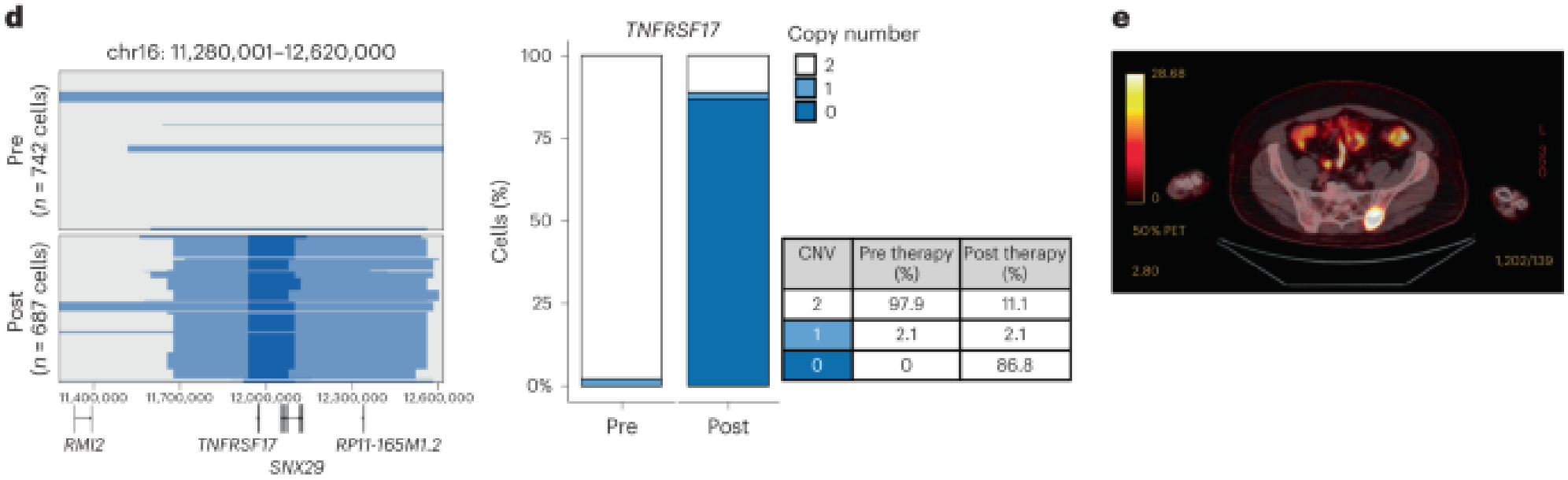
https://doi.org/10.1038/s41591-023-02491-5

Mechanisms of antigen escape from BCMA- or GPRC5D-targeted immunotherapies in multiple myeloma

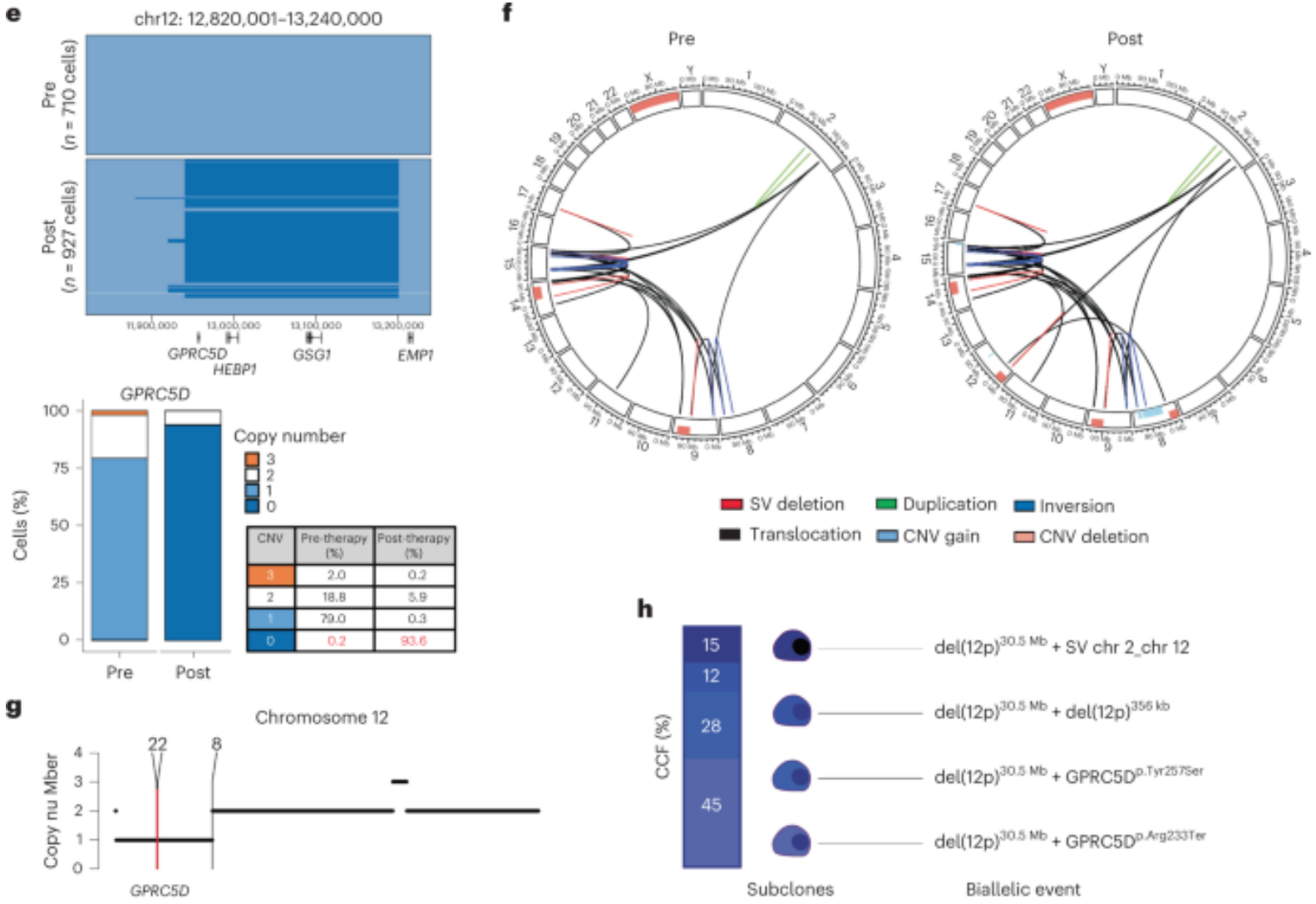
Lee et al

biallelic *TNFRSF17* loss

nontruncating, missense mutations or in-frame deletions in the extracellular domain of BCMA negated the efficacies of anti-BCMA TCE therapies, despite detectable surface BCMA protein



MM relapse with **biallelic mutations of *GPRC5D*** after anti-GPRC5D TCE therapy, including two cases with **convergent evolution** where multiple subclones lost *GPRC5D* through somatic events.

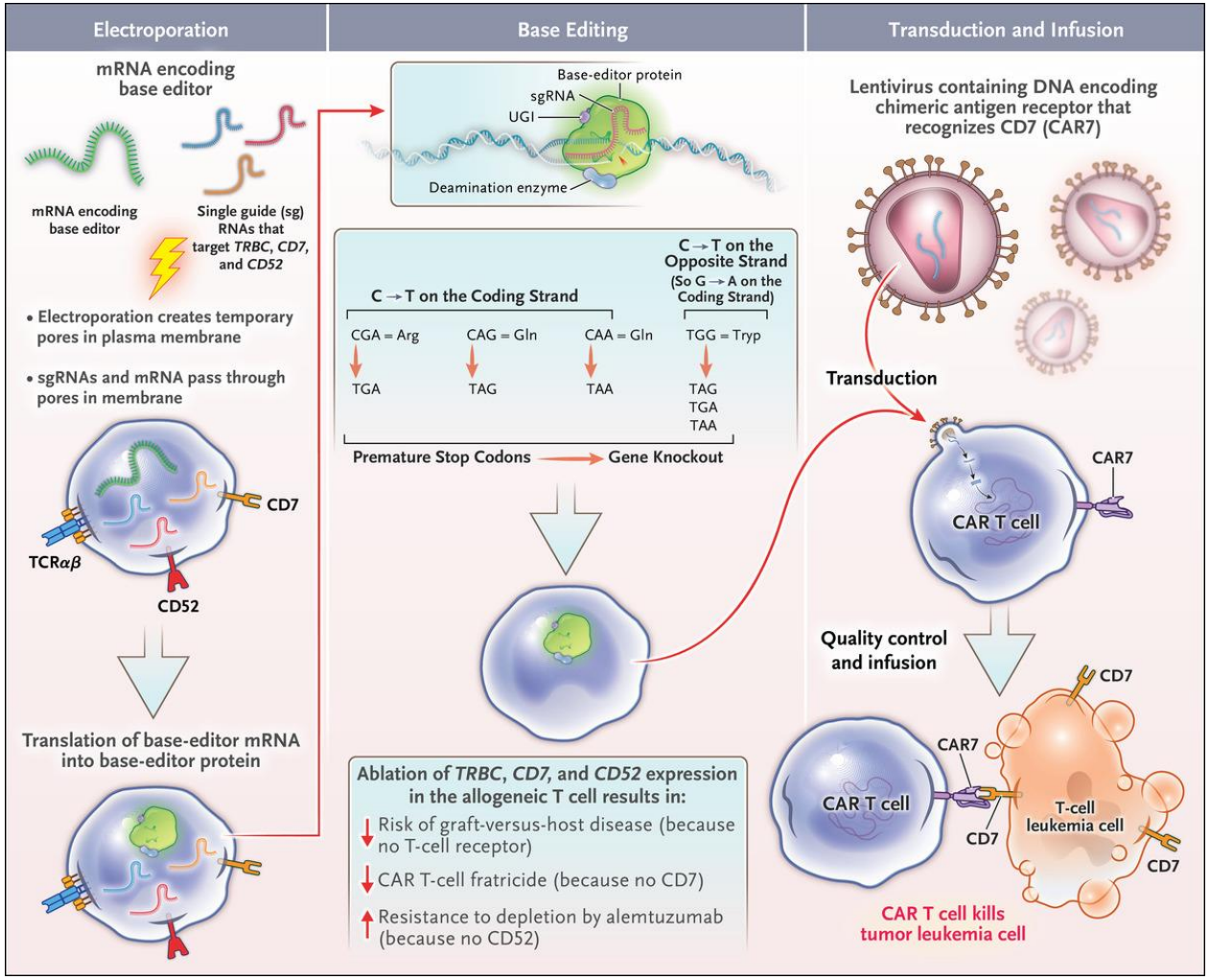


ORIGINAL ARTICLE

Base-Edited CAR7 T Cells for Relapsed T-Cell Acute Lymphoblastic Leukemia

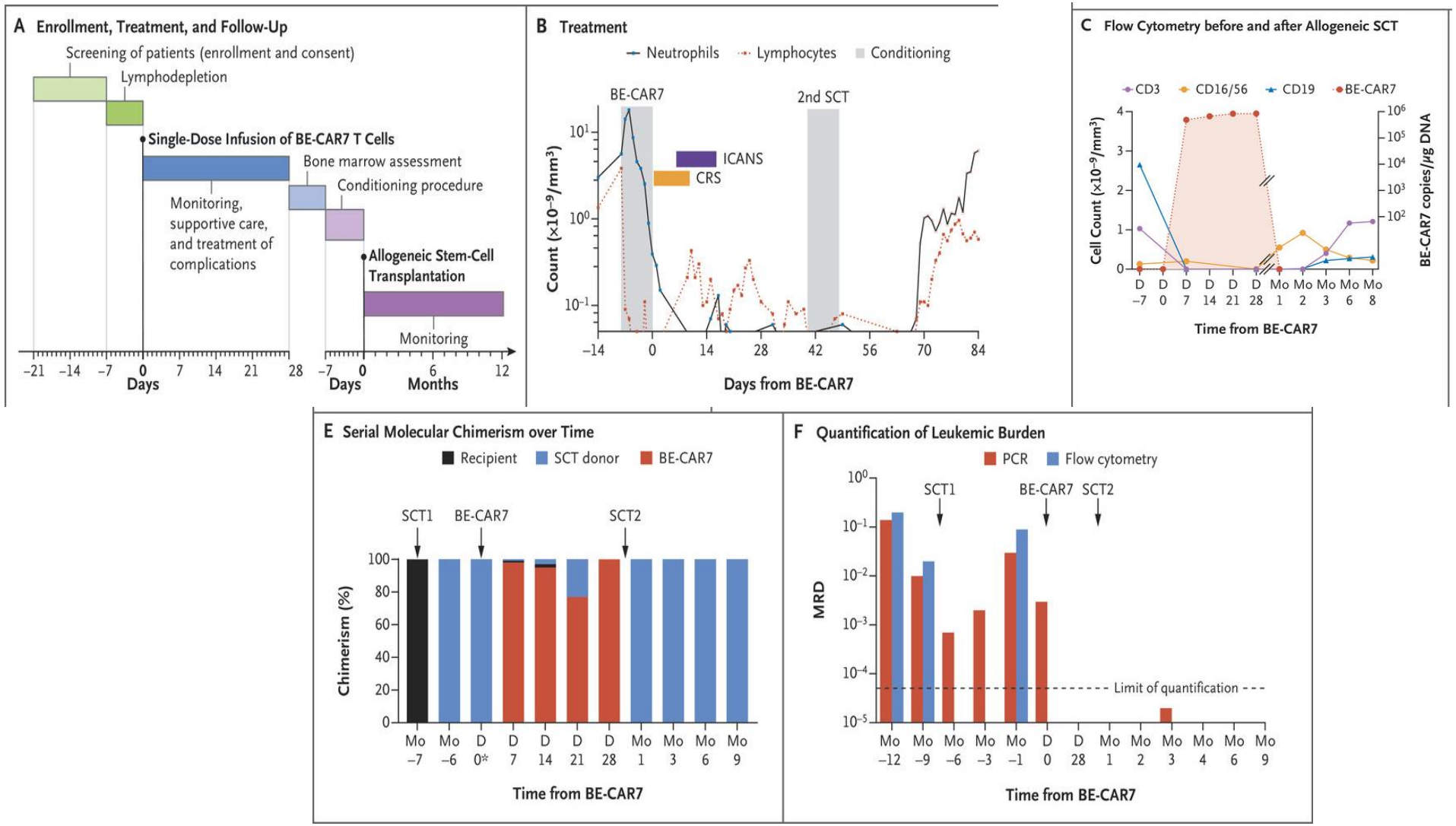
Robert Chiesa, M.D., Christos Georgiadis, Ph.D., Farhatullah Syed, Ph.D., Hong Zhan, Ph.D., Annie Etuk, Ph.D., Soragia Athina Gkazi, Ph.D., Roland Preece, Ph.D., Giorgio Ottaviano, M.D., Toni Braybrook, M.Bio., Jan Chu, M.Sc., Agnieszka Kubat, B.Sc., Stuart Adams, Ph.D., Rebecca Thomas, Ph.D., Kimberly Gilmour, Ph.D., David O'Connor, M.B., Ch.B., Ajay Vora, M.B., B.S., and Waseem Qasim, M.B., B.S., Ph.D., for the Base-Edited CAR T Group*

Base-Editing Donor T Cells to Target T-Cell Leukemia.



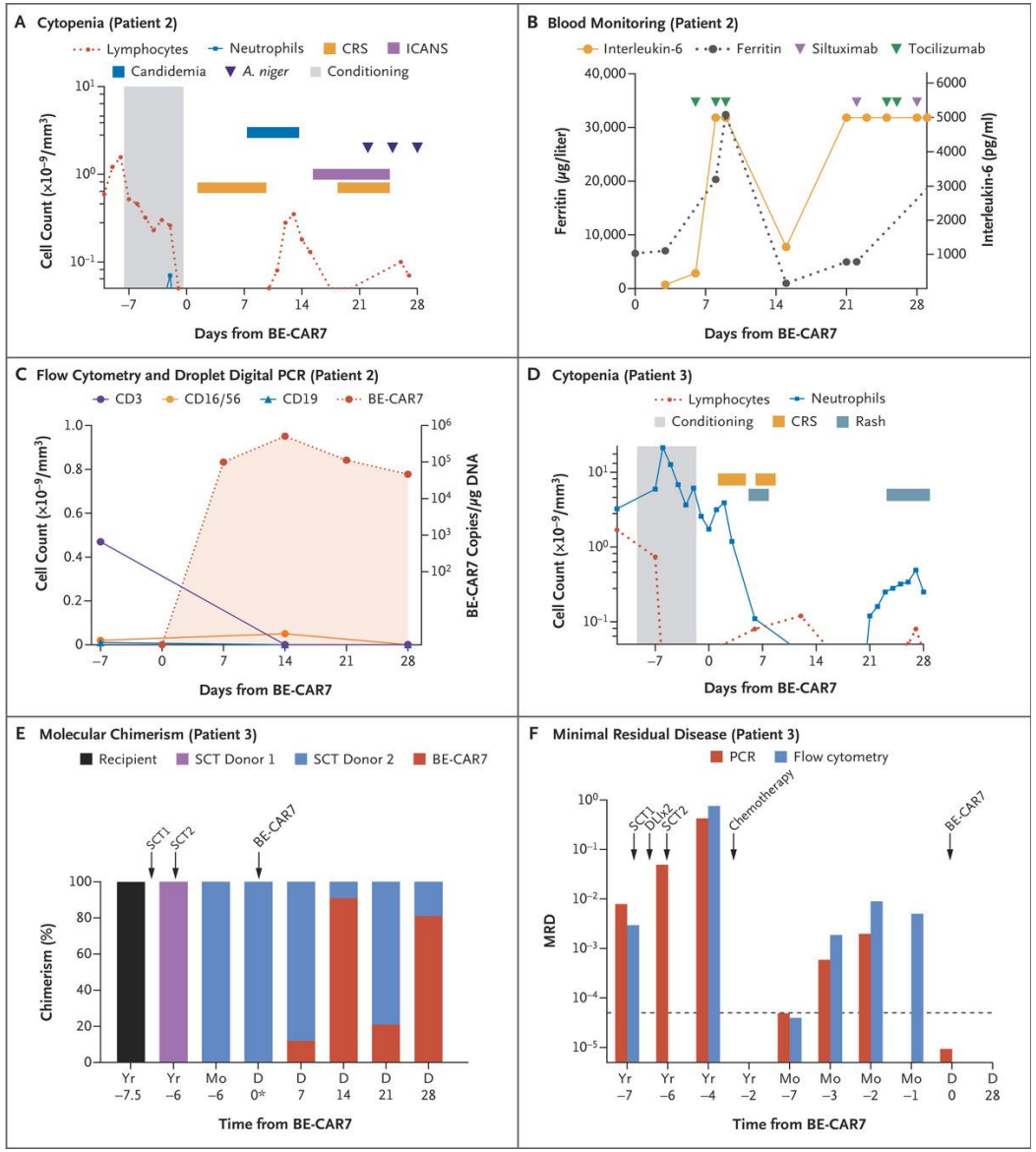
R Chiesa et al. N Engl J Med 2023;389:899-910.

Treatment and Outcomes, Patient 1.



R Chiesa et al. N Engl J Med 2023;389:899-910.

Treatment and Outcomes, Patients 2 and 3.

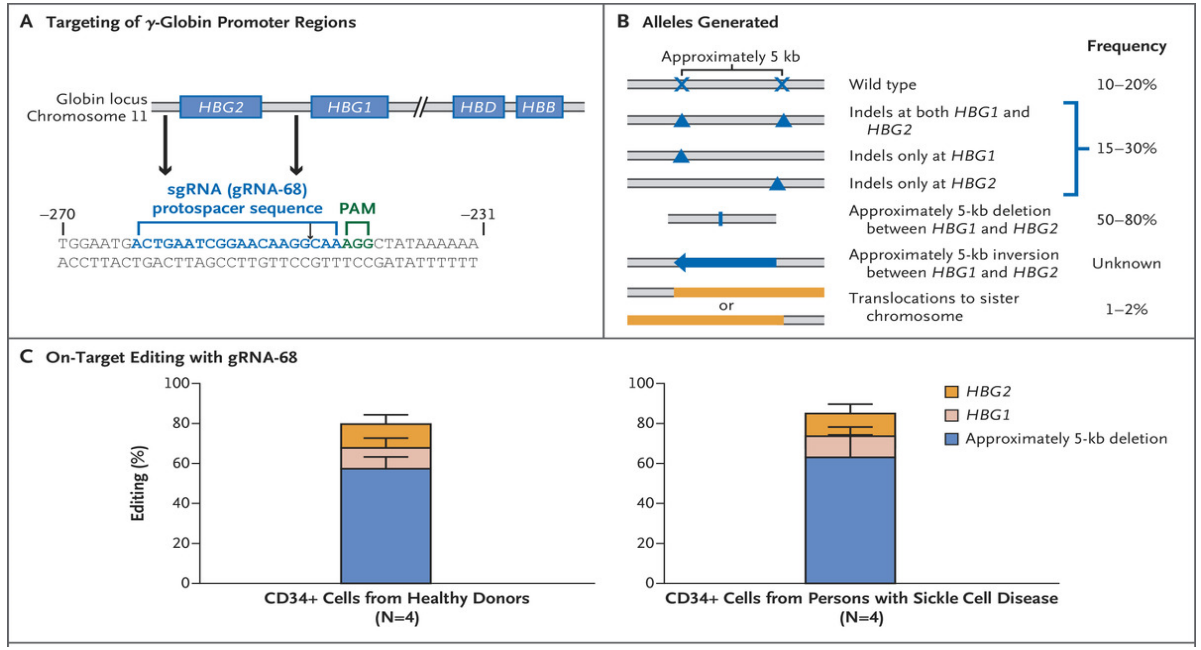


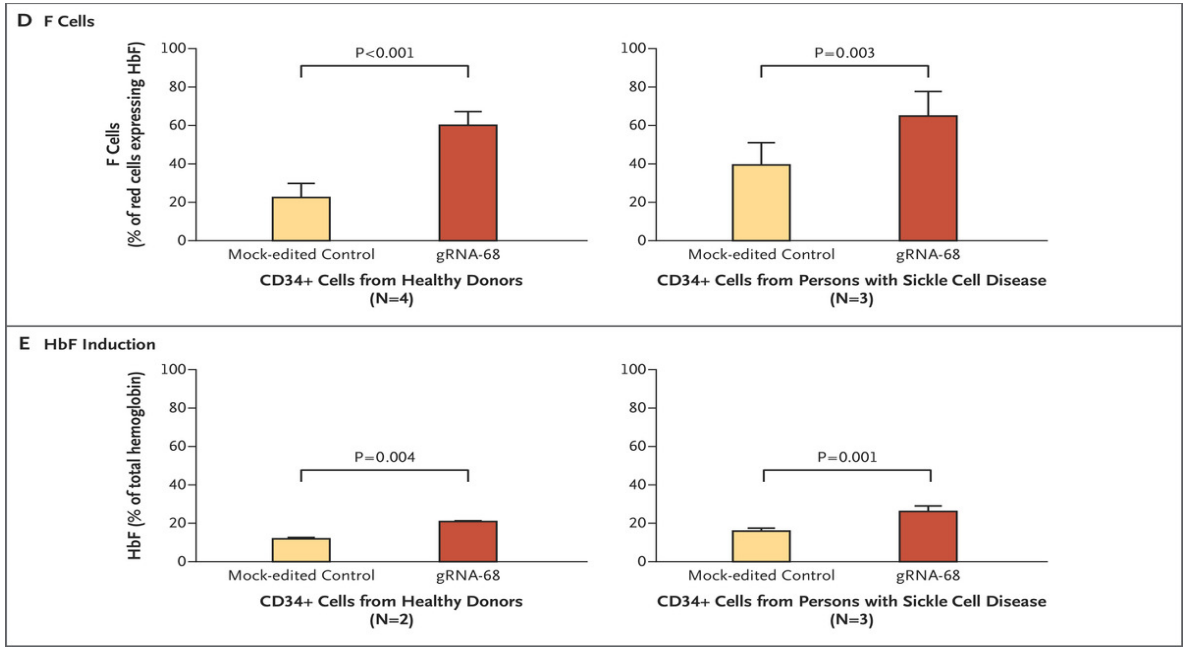
R Chiesa et al. N Engl J Med 2023;389:899-910.

Summary

CHIP
CLL
CAR-T Lymphoma/ Myeloma
Novel Resistance Mechanisms
allog. CAR-T for T-ALL

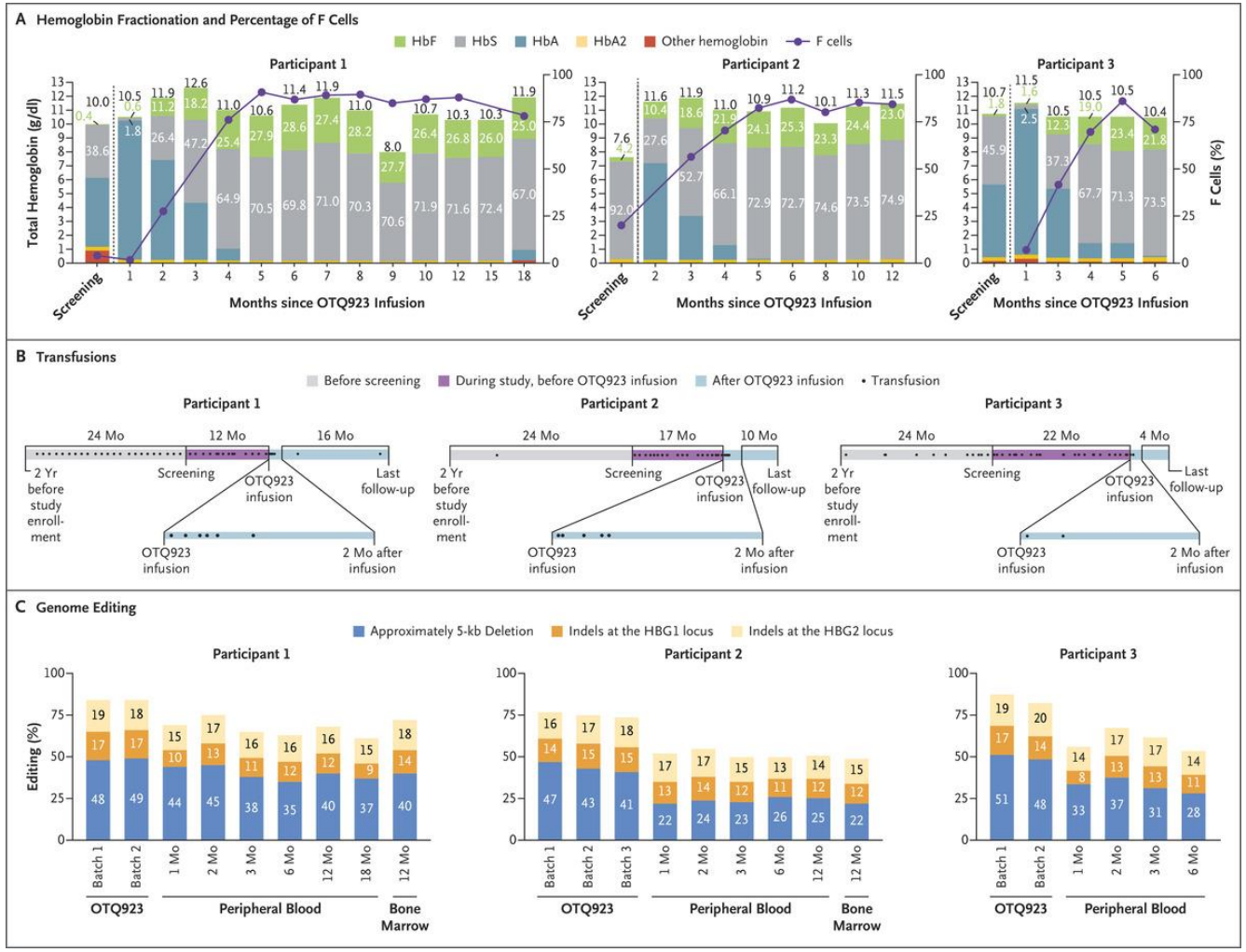
Molecular Approach and Preclinical Characterization of Guide RNA-68 (gRNA-68)–Edited Hematopoietic Stem Cells.





A Sharma et al. N Engl J Med 2023;389:820-832.

Total Hemoglobin and Its Fractions, Percentage of F Cells, and Tracking of Edited Alleles in Three Participants.



A Sharma et al. N Engl J Med 2023;389:820-832.