

CART versus stem cell transplant for patients with relapsed diffuse large B cell lymphoma

Great Debate Sea Island 2022

The Debators

The “Kid”



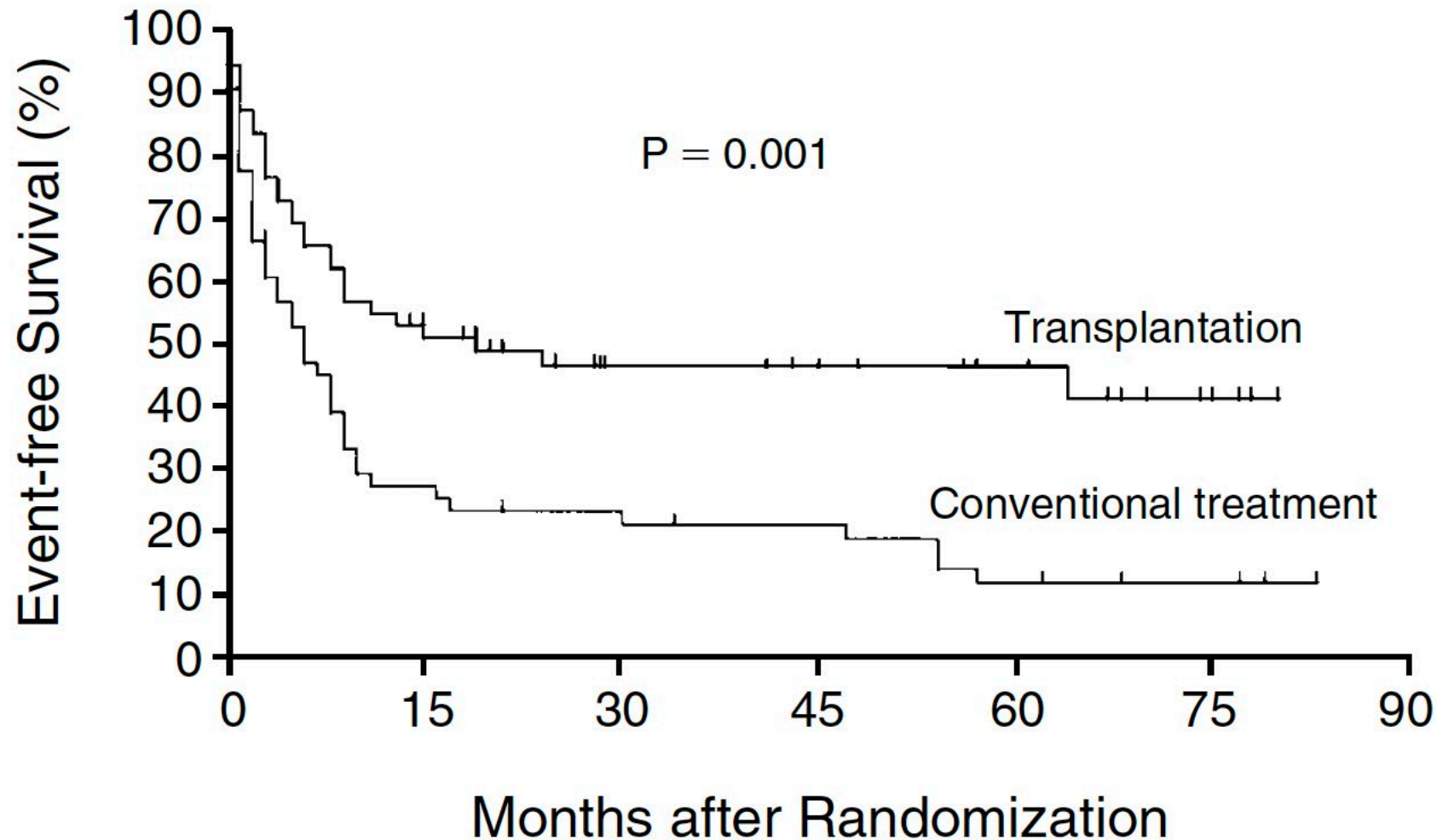
The “Old Geezer”



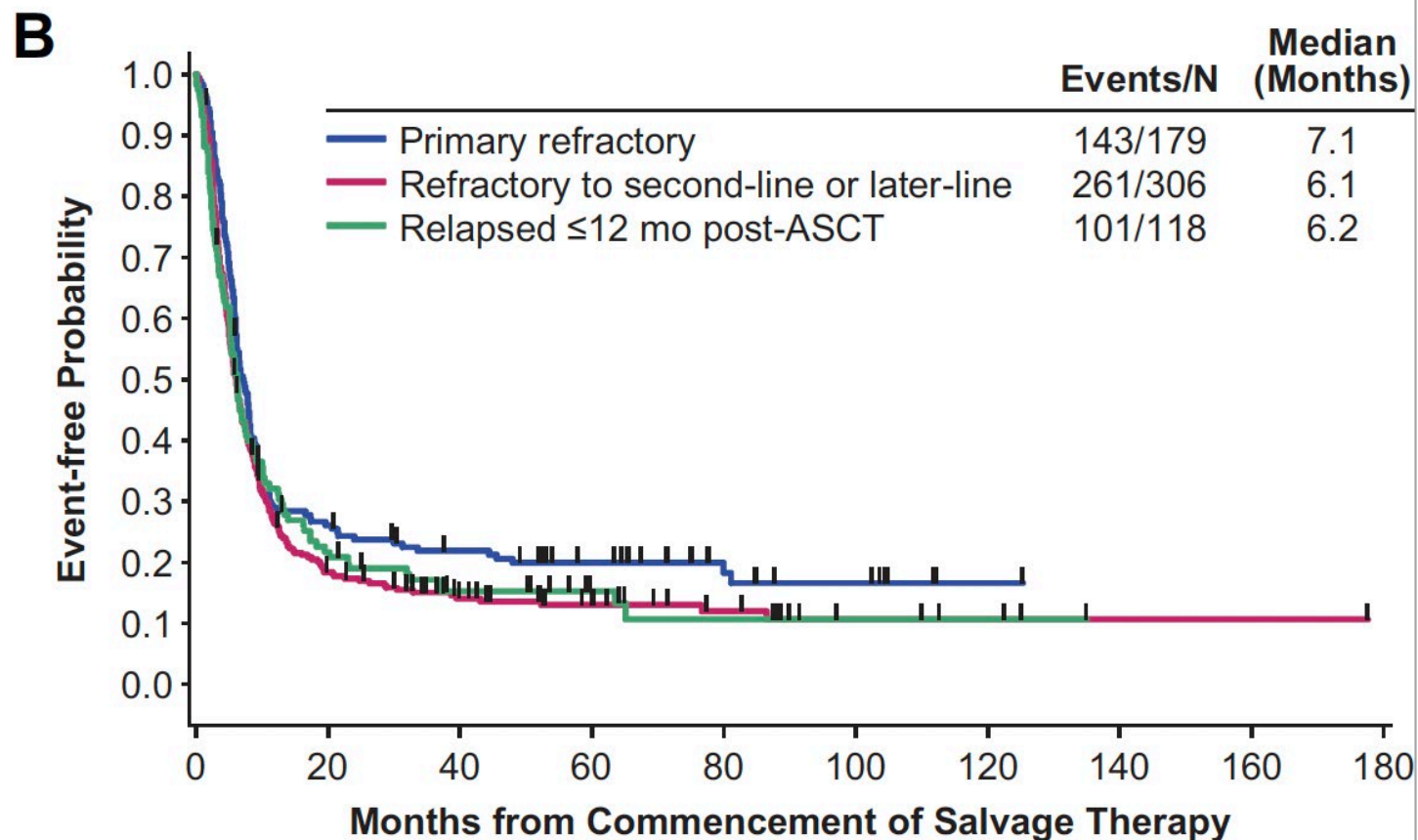
A question of old versus new....

Anti-CD19 directed CART are more effective in achieving Progression-free survival for patients with relapsed refractory DLBCL than high-dose BEAM chemotherapy and autologous stem cell transplantation

Transplants became enshrined as SOC for r/r DLBCL in the pre-Rituximab era



Outcomes in the modern era for relapsed refractory DLBCL are poor



Observational cohort of 165 r/r DLBCL and TFL patients at MDACC for second-line therapy

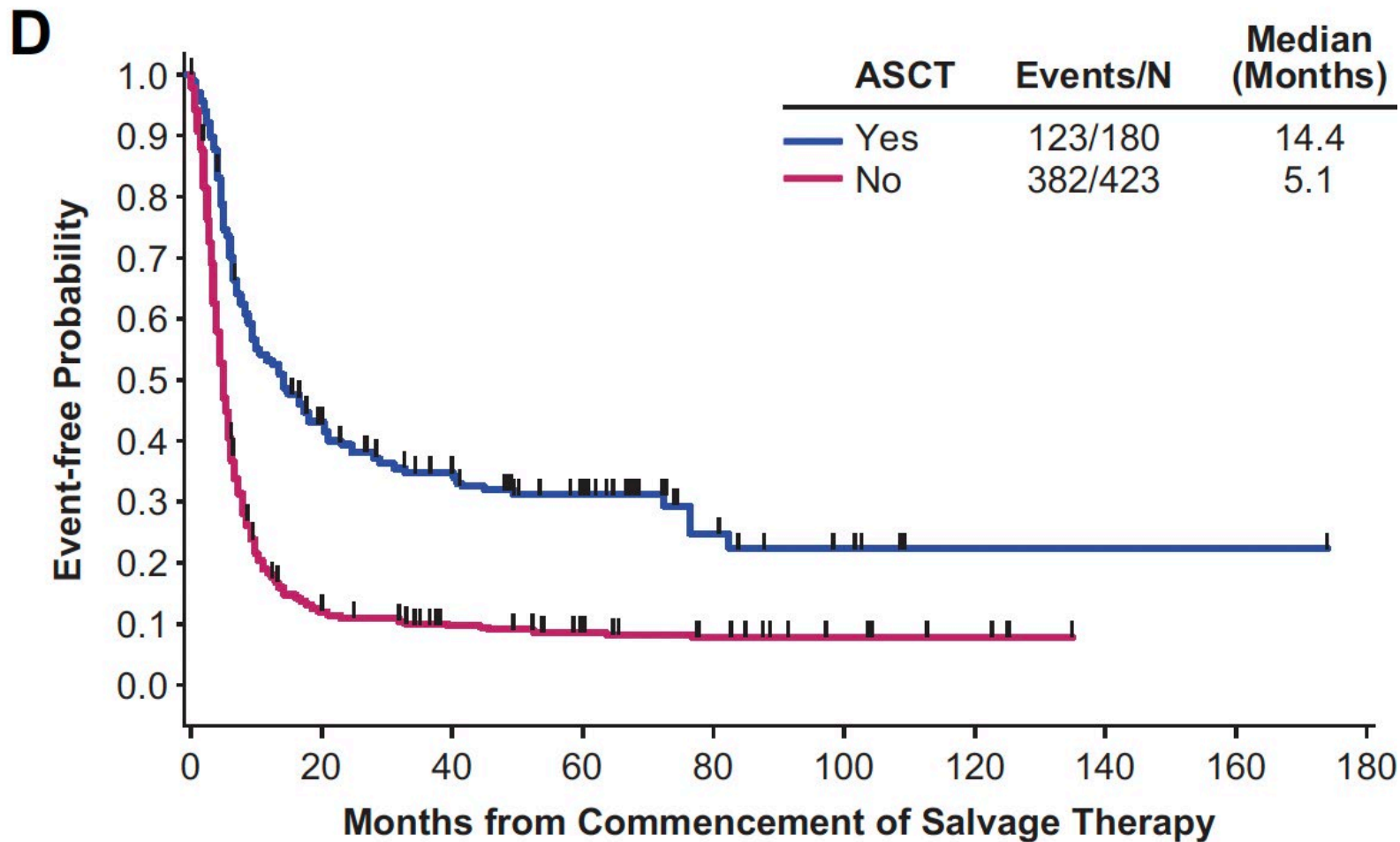
IA/MC US observational cohort with 82 r/r DLBCL patients

LY1.2 included 219 r/r DLBCL patients from 4 countries

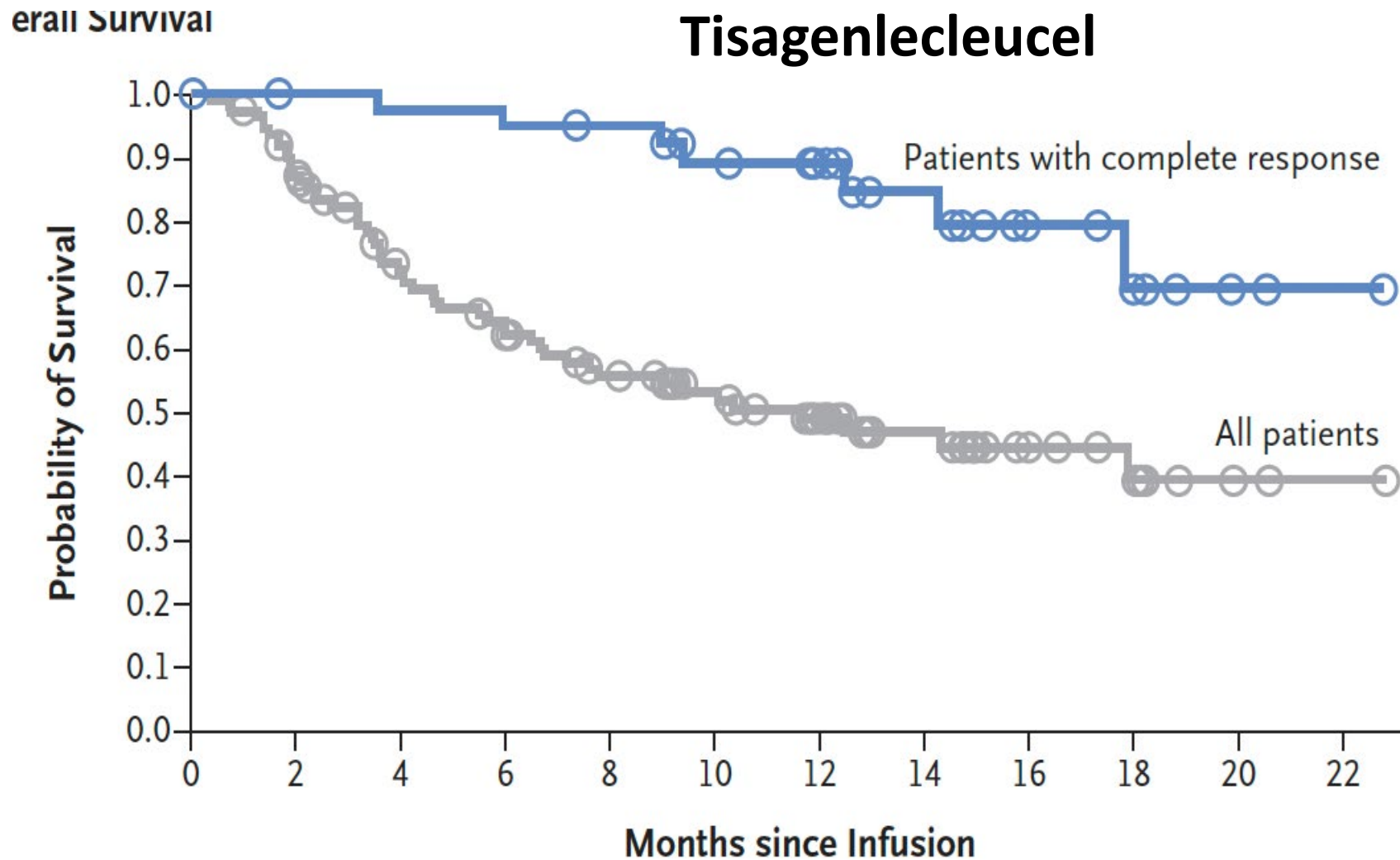
CORAL study included 219 r/r DLBCL patients from 11 countries

Auto-transplant,
when it is performed
in the 30% of r/r
DLBCL patients who
achieve remission,
is effective in only
25% of patients

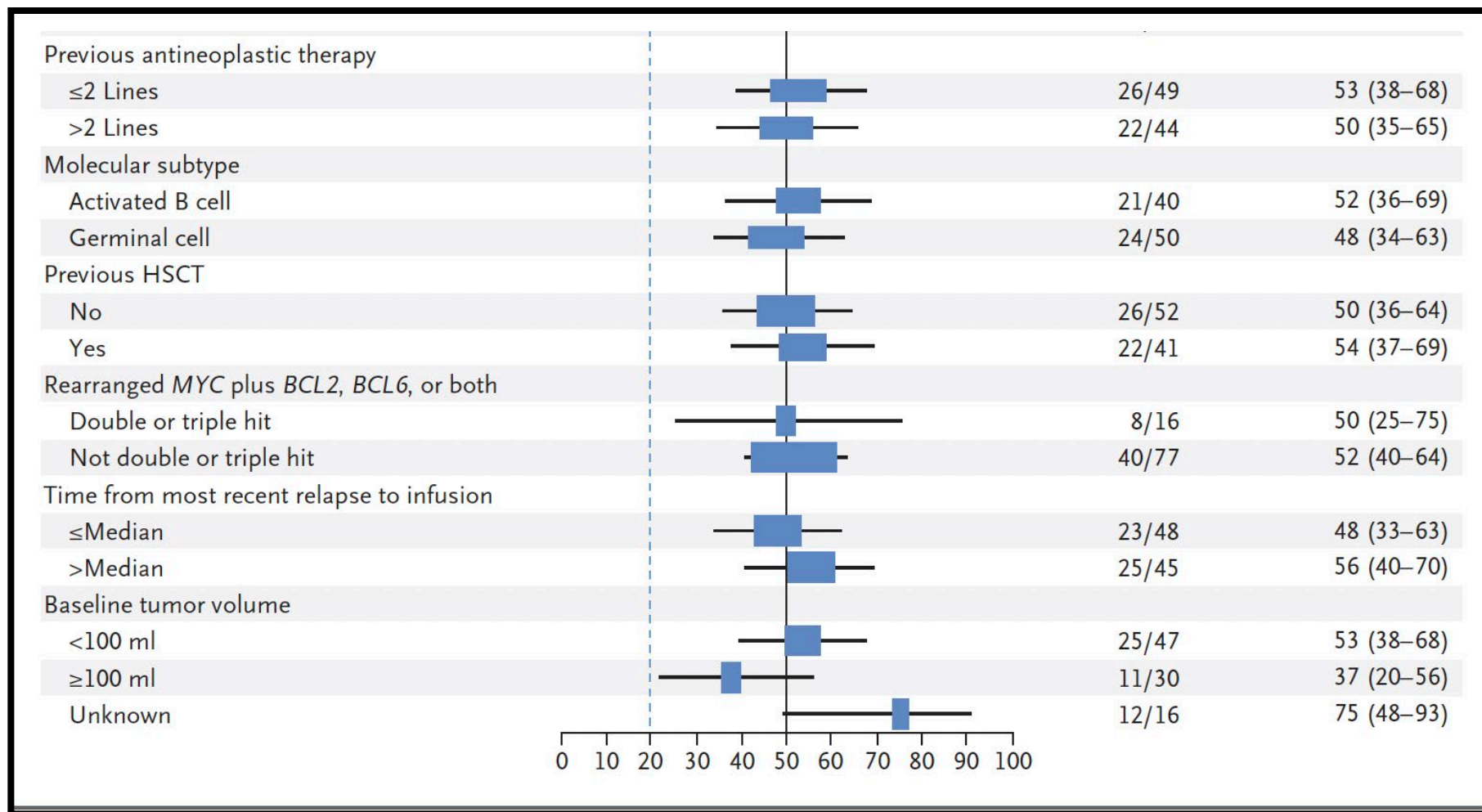
Crump Blood 2017



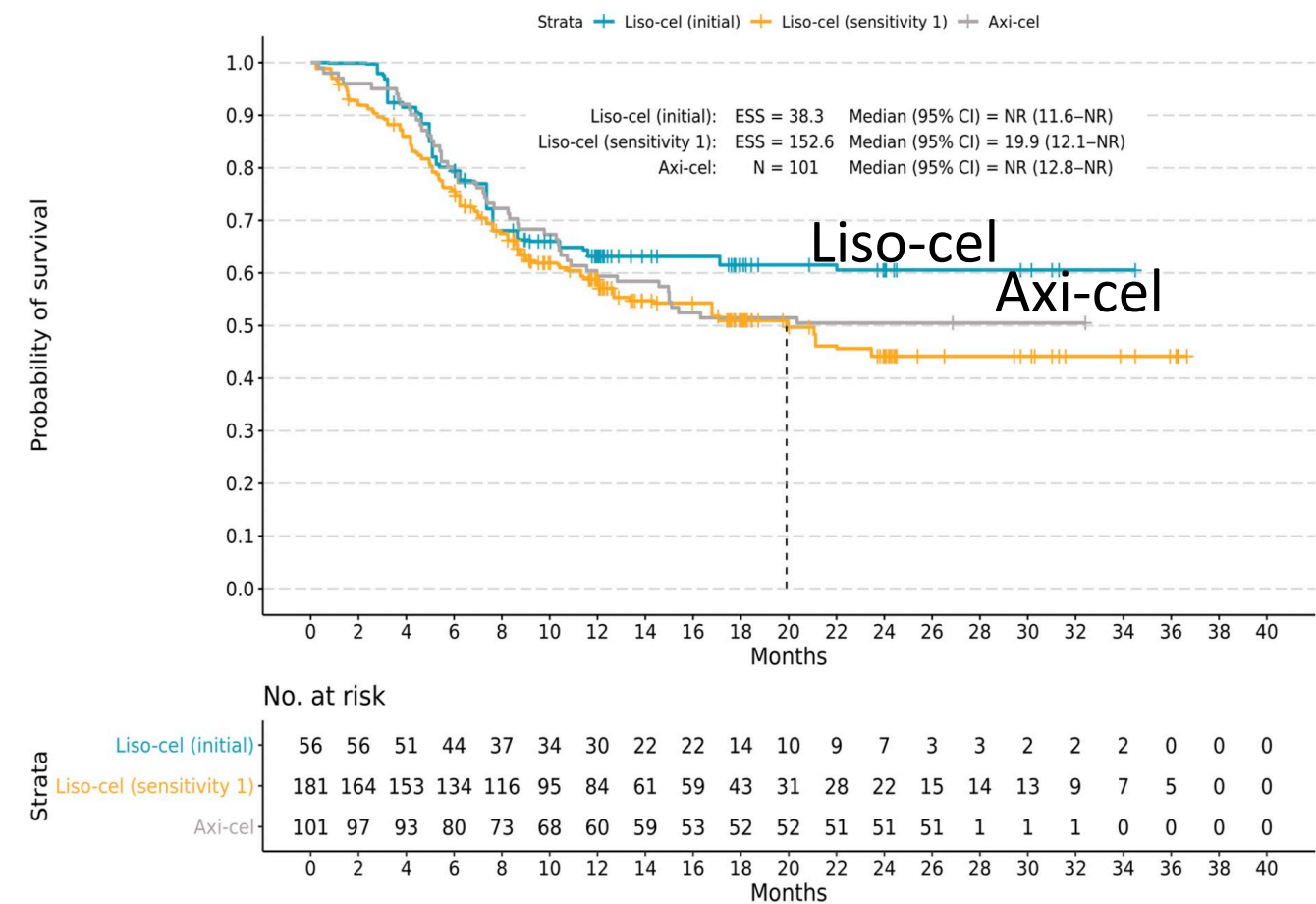
CART produced durable remissions patients with r/r DLBCL



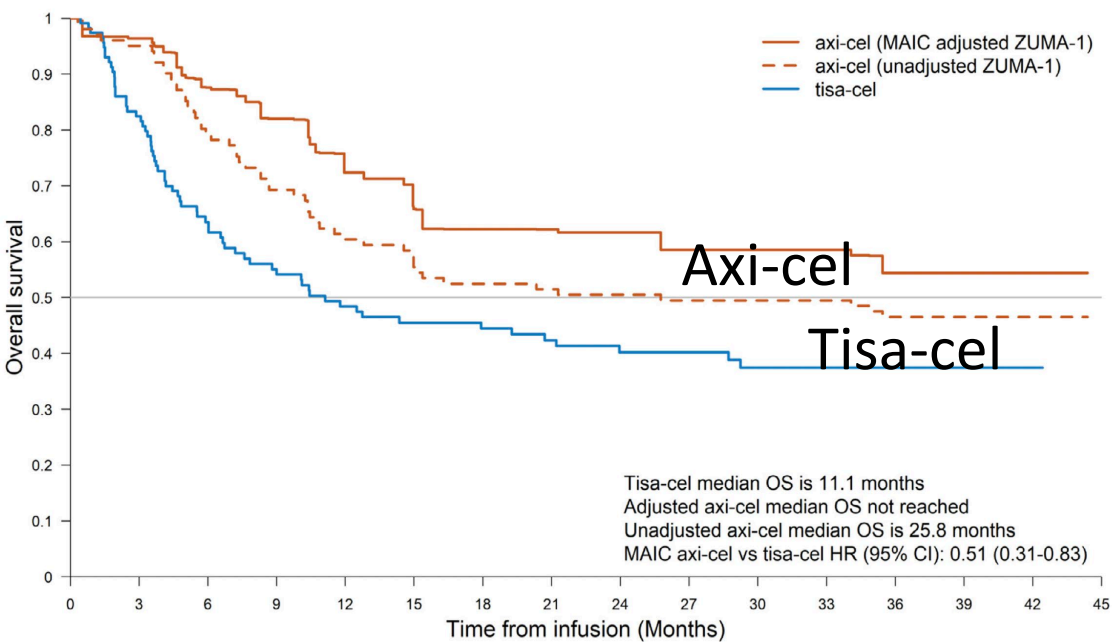
CART are effective in all subsets of r/r DLBCL patients



Different CART brands have similar activities in DLBCL patients



Maloney Hematology and Oncology (2021)

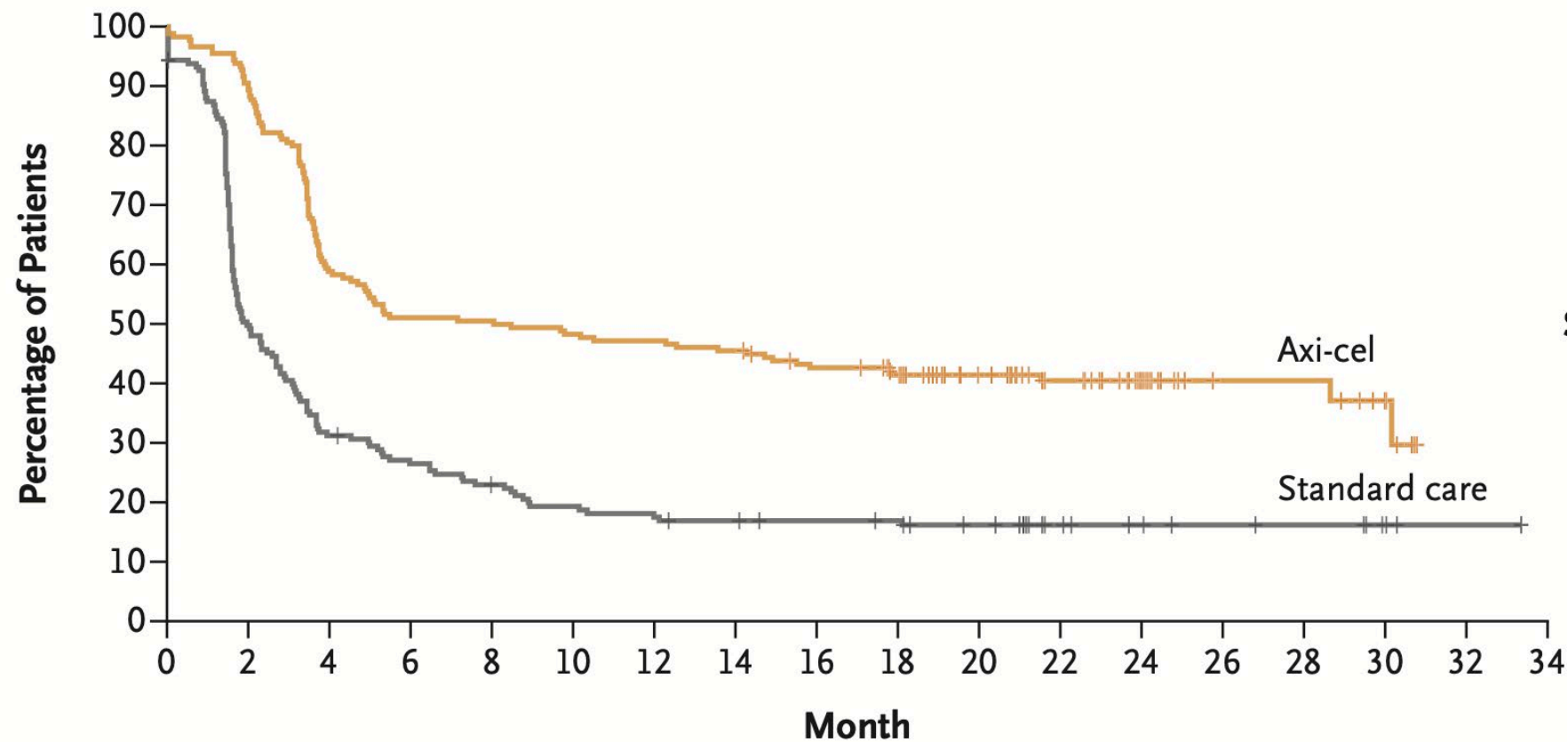


Oluwole et al. Biol Blood Marrow Transplant (2020)

Results from 3 randomized studies comparing
CART and autologous stem cell transplant as
second line therapy for relapsed DLBCL

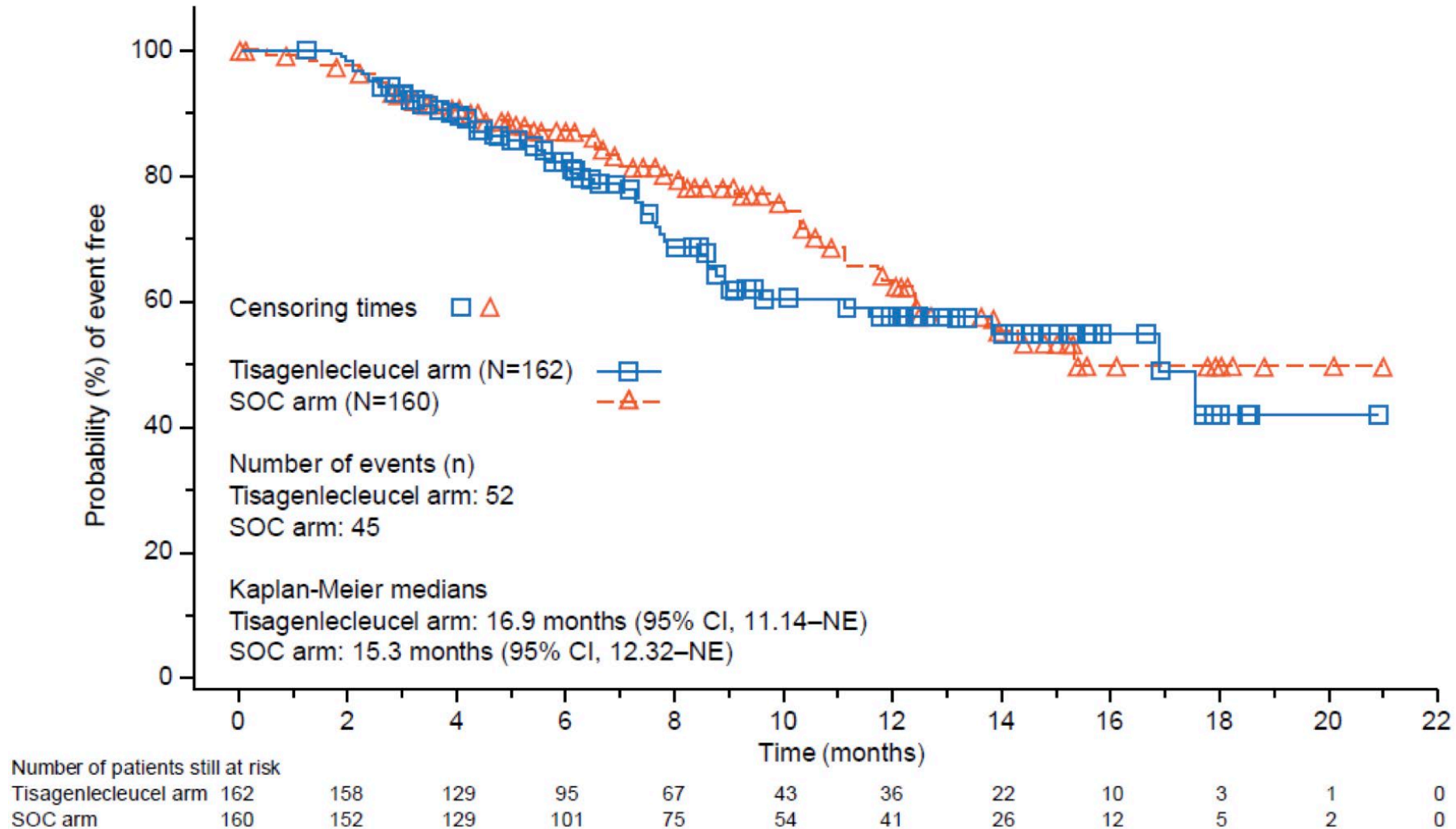
Axi-cel met the primary end-point of superior EFS compared to auto-transplant in phase 3 trial of DLBCL patients

A Event-free Survival

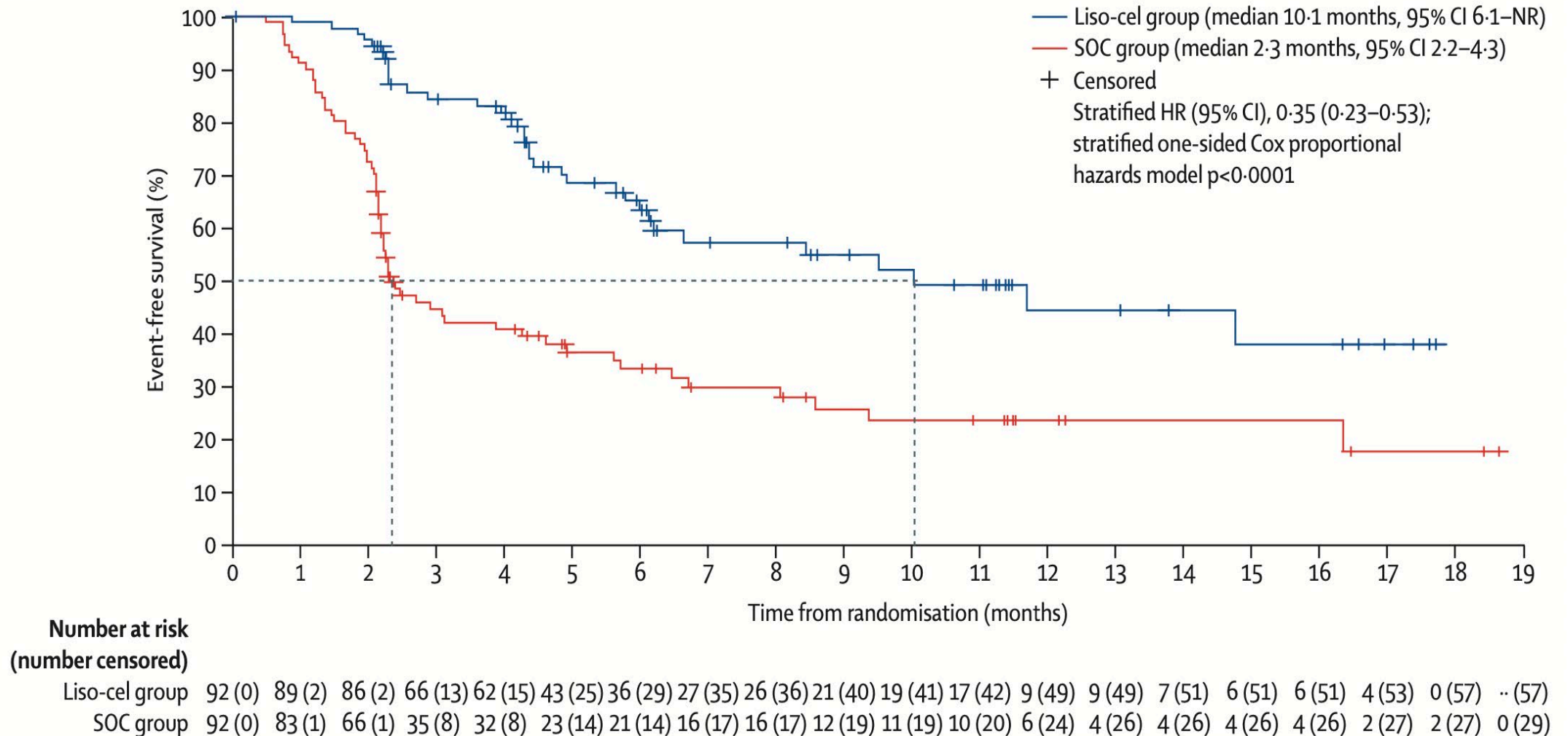


No. at Risk																			
Locke NEJM 2021	Axi-cel	180	163	106	92	91	87	85	82	74	67	52	40	26	12	12	6		
	Standard care	179	86	54	45	38	32	29	27	25	24	20	12	9	7	6	3	1	0

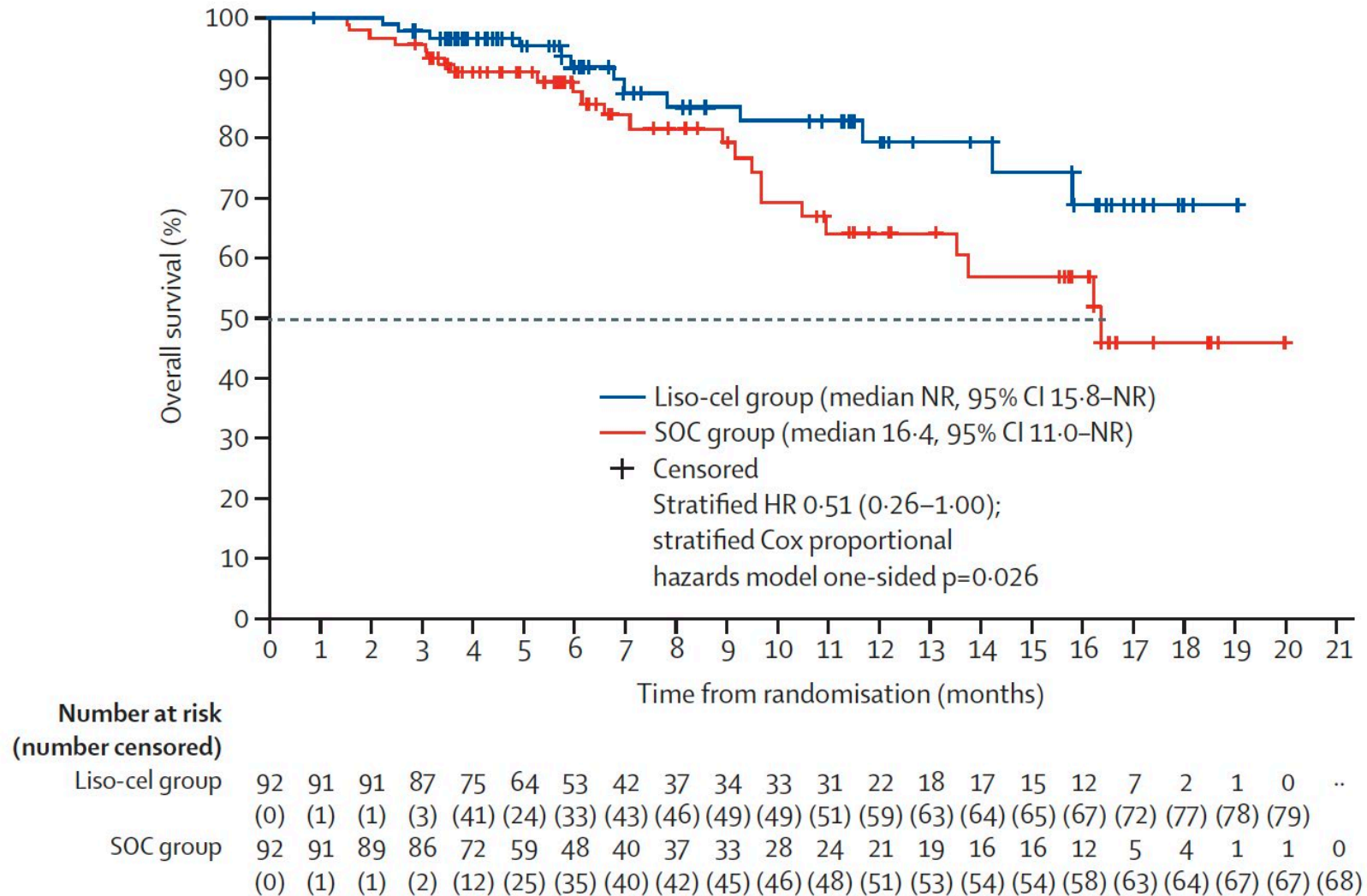
Patients randomized to Tisa-cel had equivalent OS compared to SOC/auto-transplant



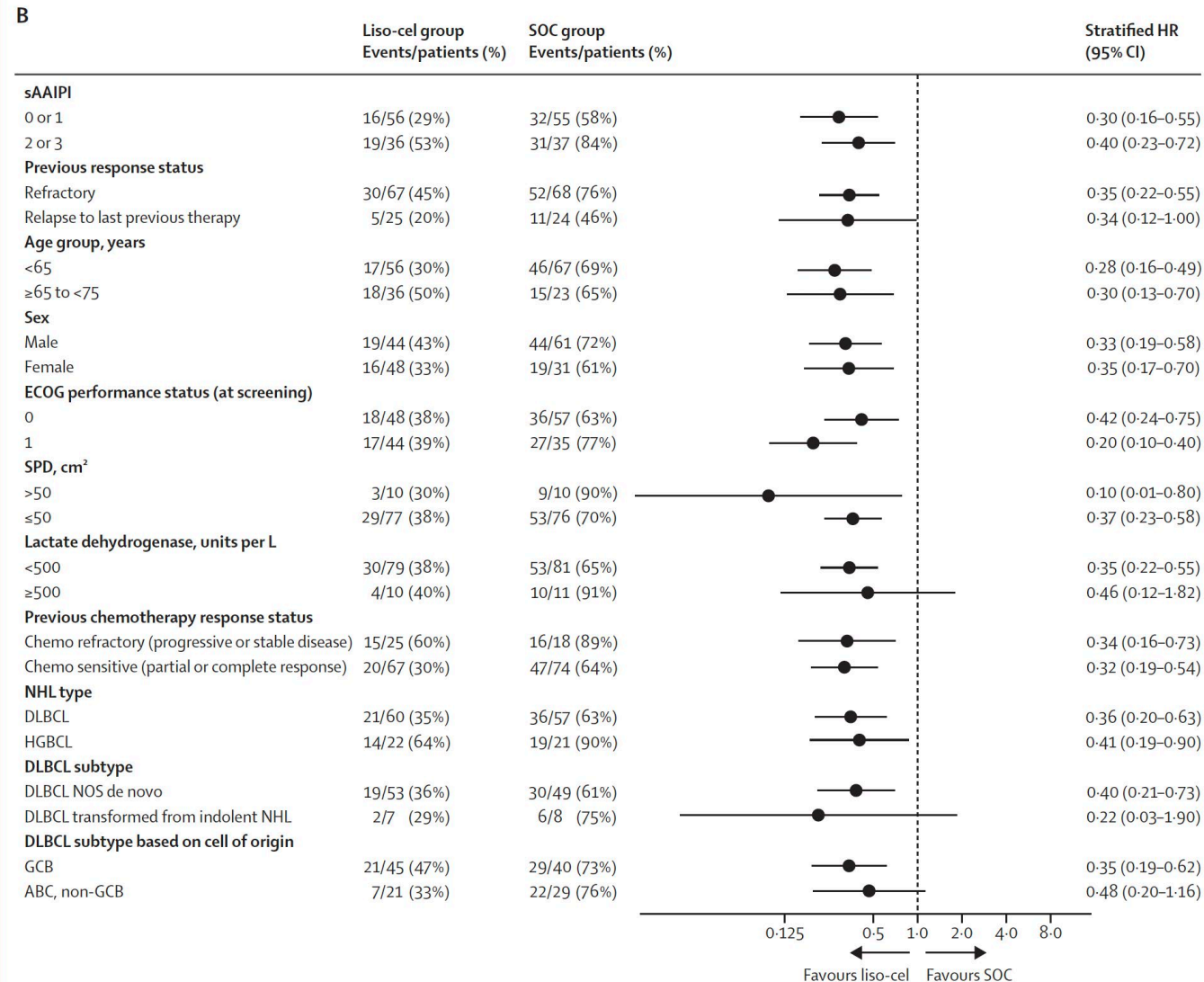
Improved EFS among DLBCL patients randomized to Liso-cel versus SOC/auto-transplant



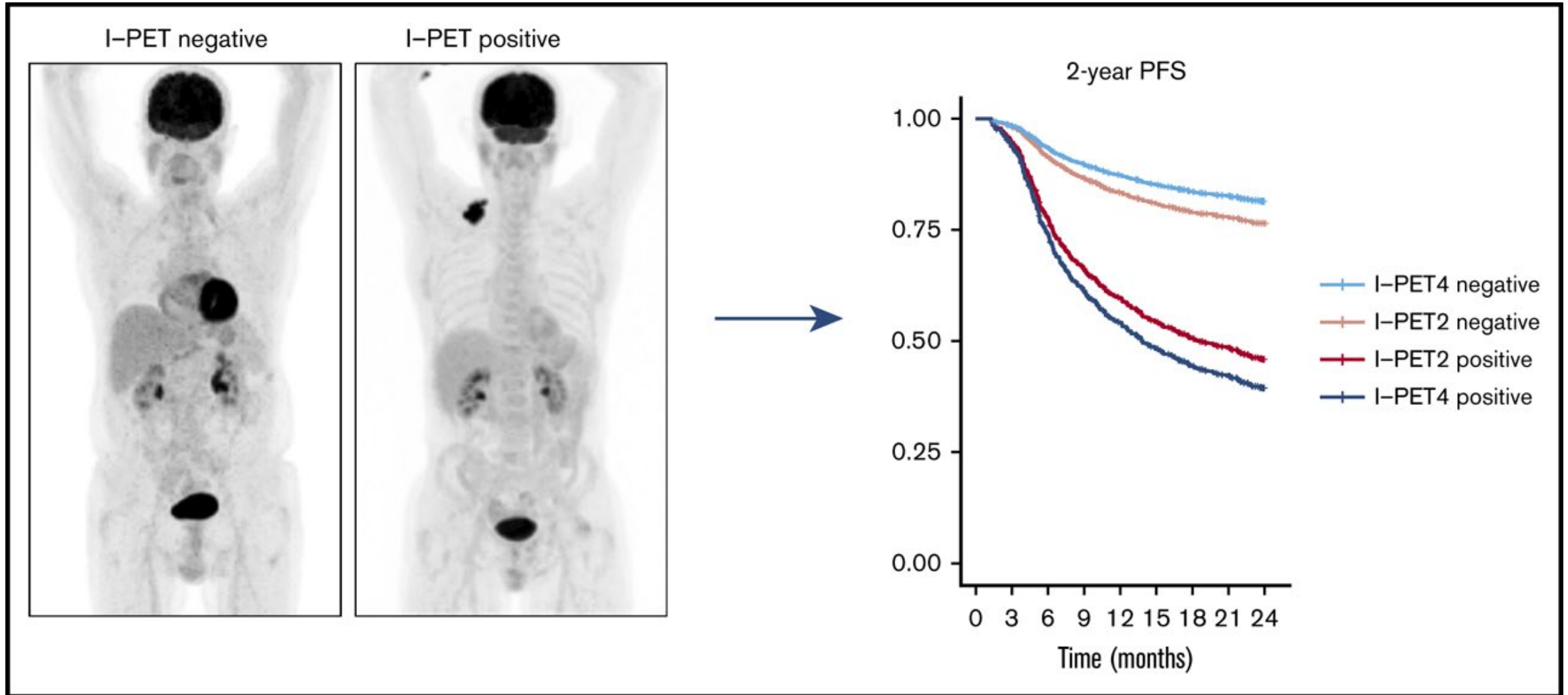
Better OS among DLBCL patients randomized to liso-cel CART



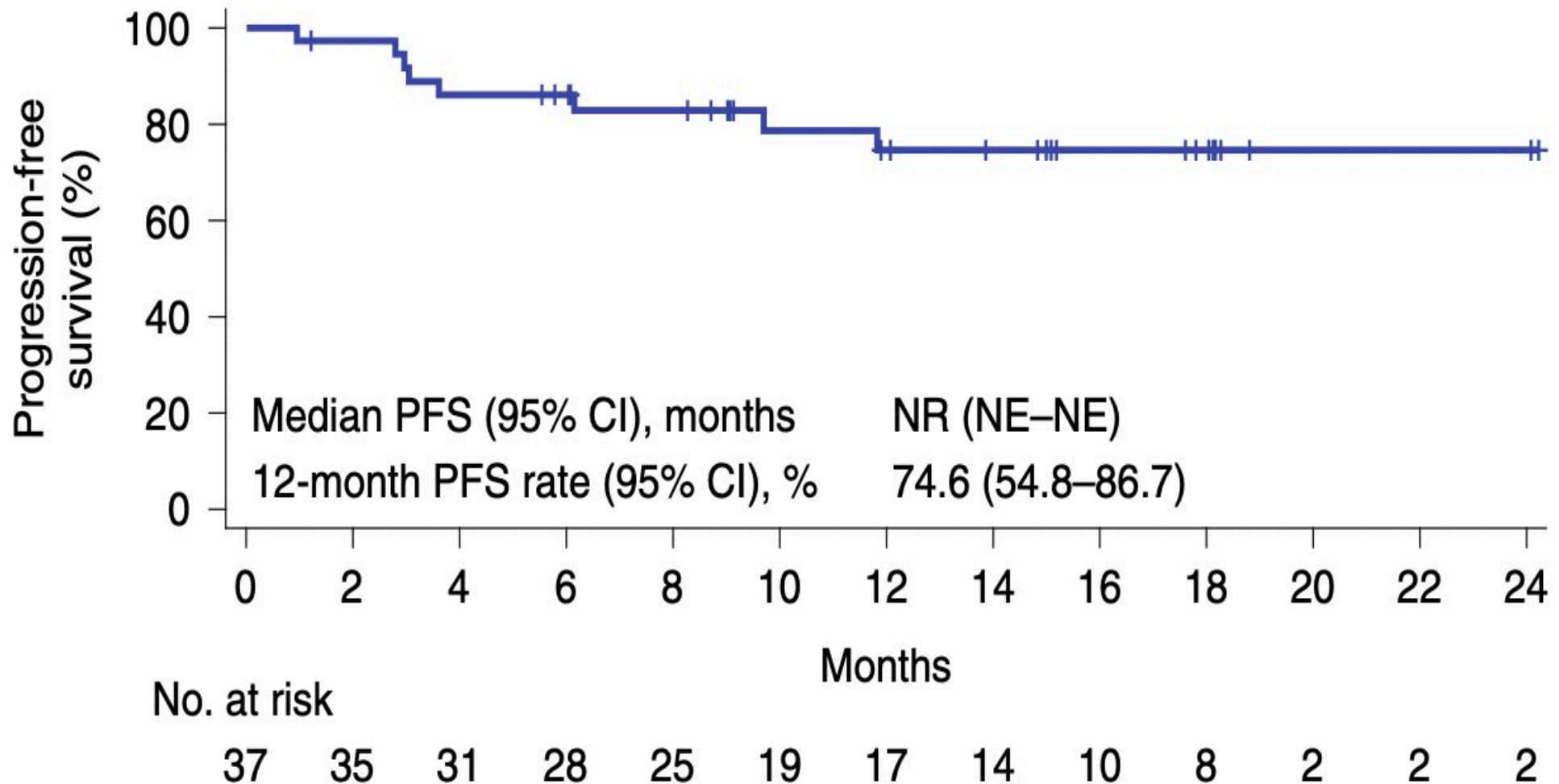
All DLBCL patient subsets benefited from liso-cel over SOC/Auto-transplant



Poor results among I-PET2+ DLBCL patients after 2 cycles of R-CHOP



Phase 2 study shows >75% 2 –year PFS among I-PET2+ DLBCL patients treated pre-emptively with Axi-cel



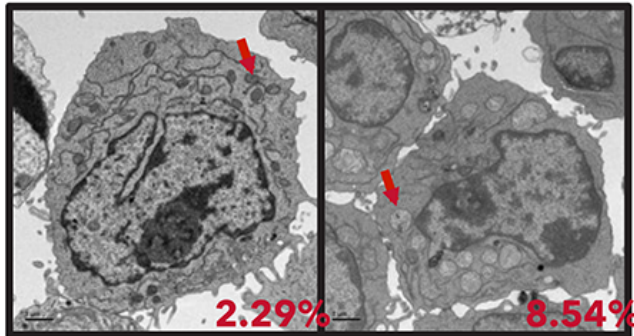
Strategies to enhance efficacy of CART against CD19+ targets

The PI3K δ/γ dual-inhibitor duvelisib enhances CART cell phenotype and function

CART cells

0.1% DMSO

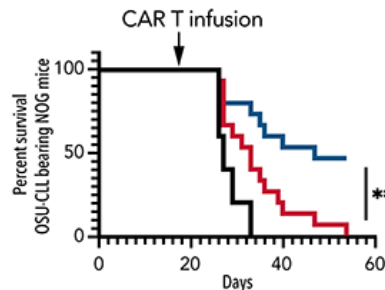
300nM duvelisib



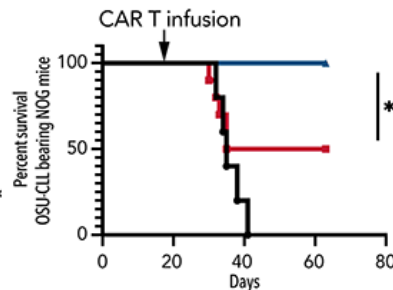
PI3K δ/γ blockade promotes:

- Formation of CD8+ T_{SCM} and CD8+CD27+CD45RO-memory CART cells
- Reductions in immune checkpoint expression
- Increases in CART cell mitochondrial fusion (red arrows) with representative preservation in mitochondrial cross-sectional area despite decreased cytoplasmic size

CD28/CD19 CART



41BB/CD19 CART

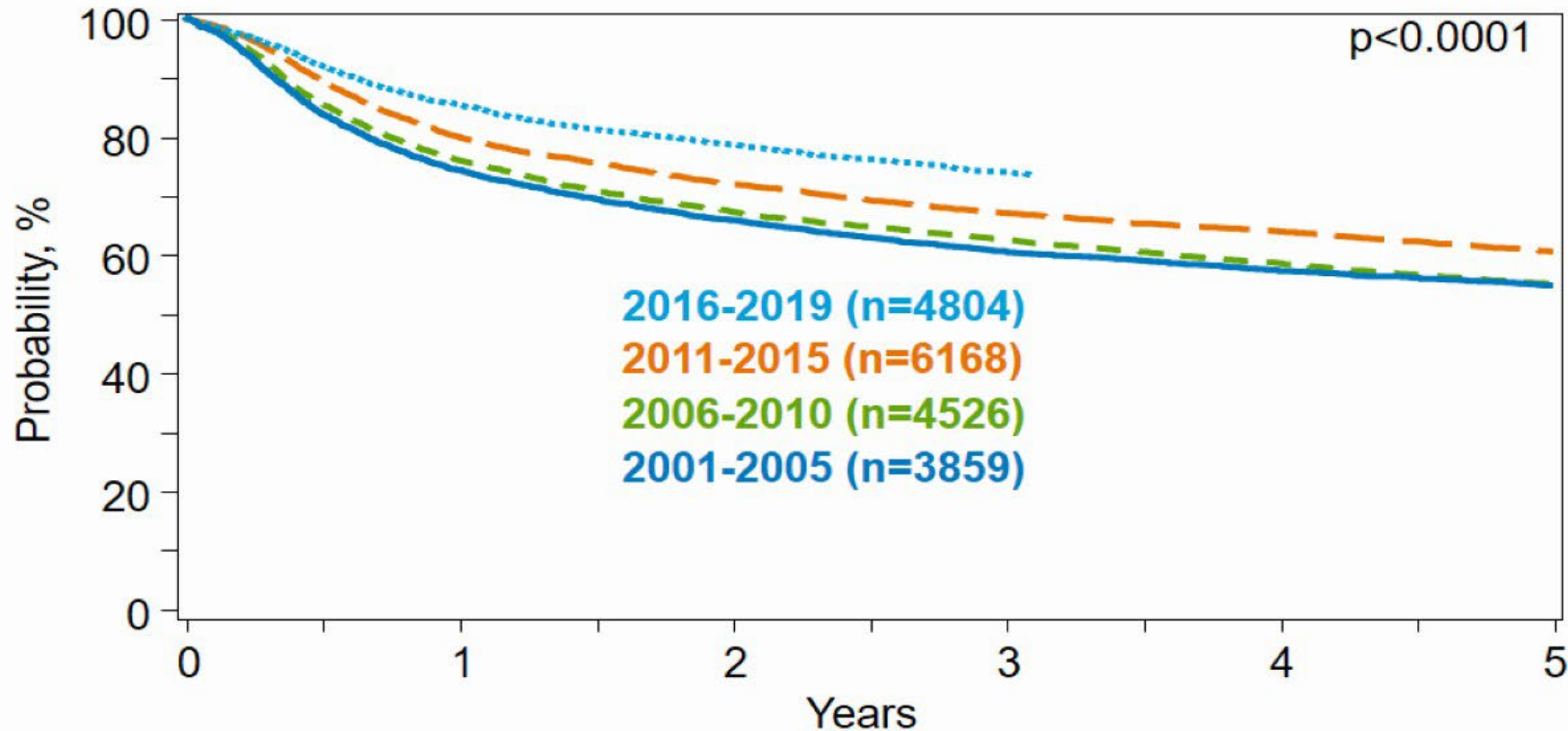


Duvelisib improves CART cell function:

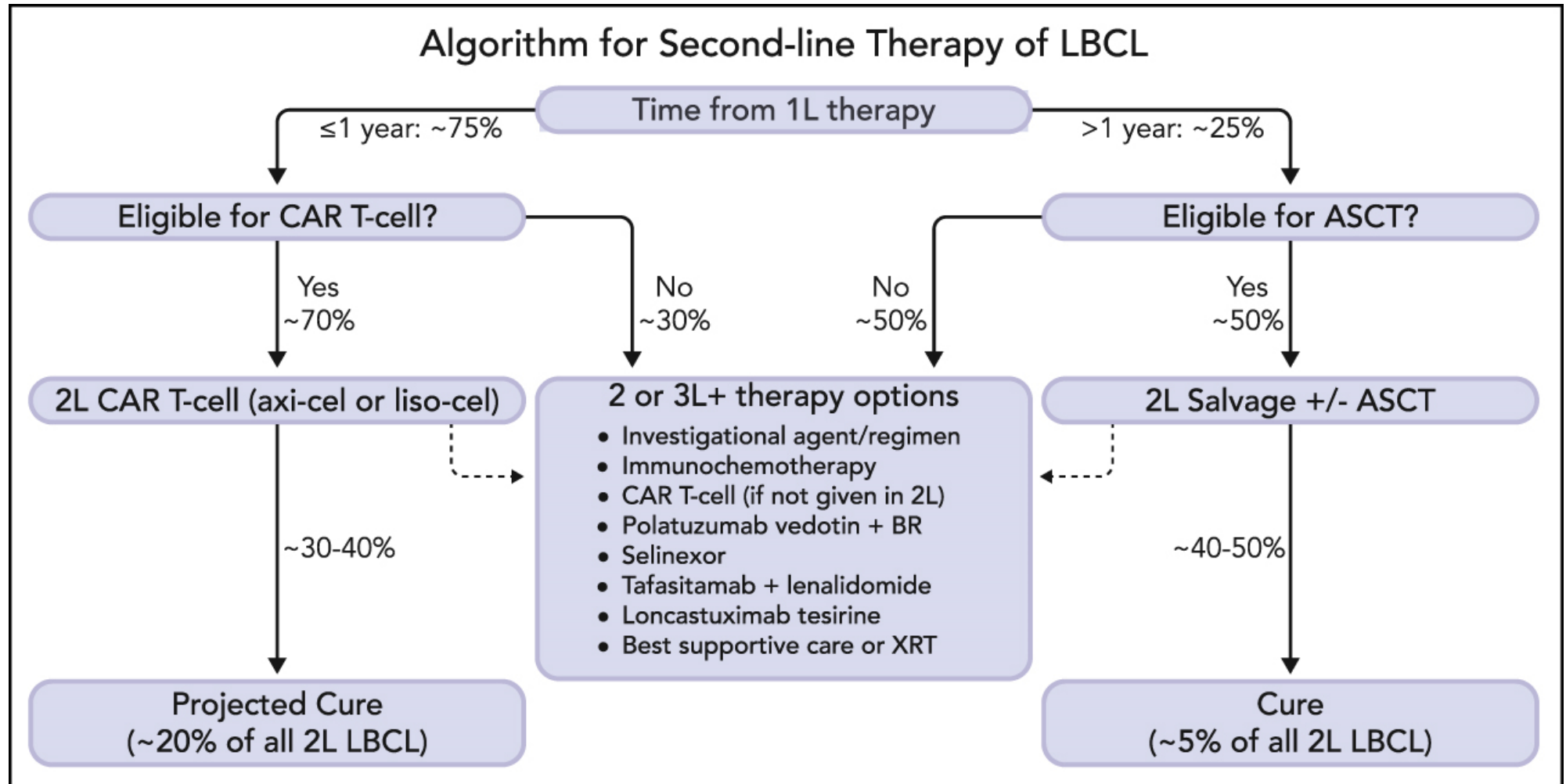
- Duv-CART cells exhibit greater proliferation and persistence of CD8+ and CD4+ CART cells with CD28 or 41BB costimulatory domain
 - Duv-CART show altered epigenetic regulation after ex vivo duvelisib exposure
- Duv-CART cells enhanced survival of NOG mice engrafted with the human CLL line OSU-CLL

Auto-transplant for DLBCL might be considered effective...

Trends in Survival after Autologous HCTs for Diffuse Large B-Cell Lymphoma (DLBCL), in the US, 2001-2019



Auto-transplant as a second-line therapy for DLBCL cures only 5% of DLBCL patients versus 20% cured by CART



In conclusion....

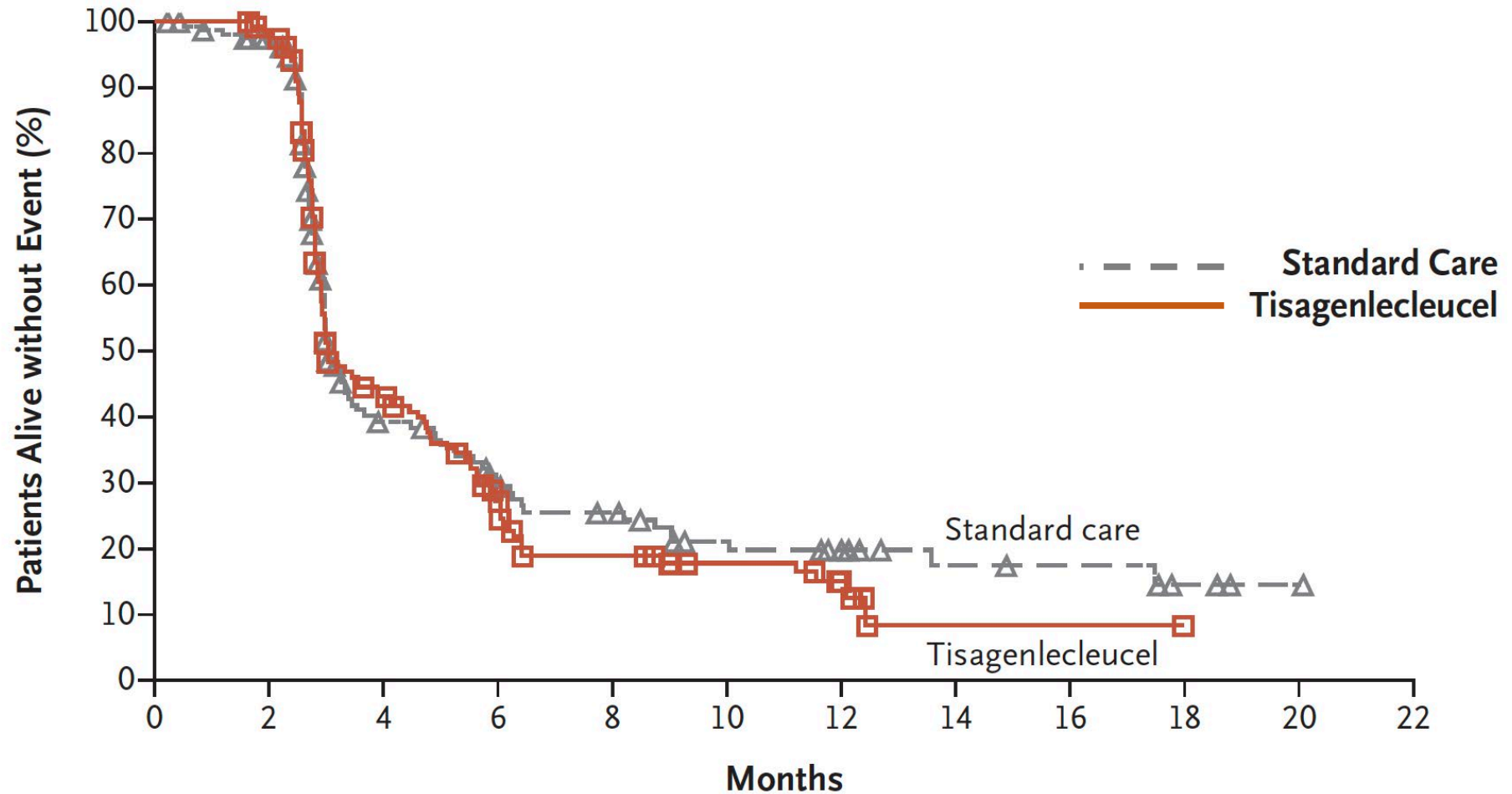
Select the FDA approved therapy for relapsed/refractory DLBCL:

- Tisa-cell, Axi-cell or Liso-cell for third line therapy, transplant ineligible
- Axi-cell or Liso-cell for second line therapy
- Better EFS, better OS with liso-cel
- Autologous stem cell transplant has never been FDA approved!

Questions?



Patients randomized to Tisa-cel had equivalent EFS compared to SOC/auto-transplant



No. at Risk

Standard care	160	148	45	31	25	17	12	7	6	3	1	0
Tisagenlecleucel	162	156	57	32	19	13	6	1	1	0	0	0

Patients randomized to Axi-cel trended towards better OS compared to SOC/auto-transplant patients

