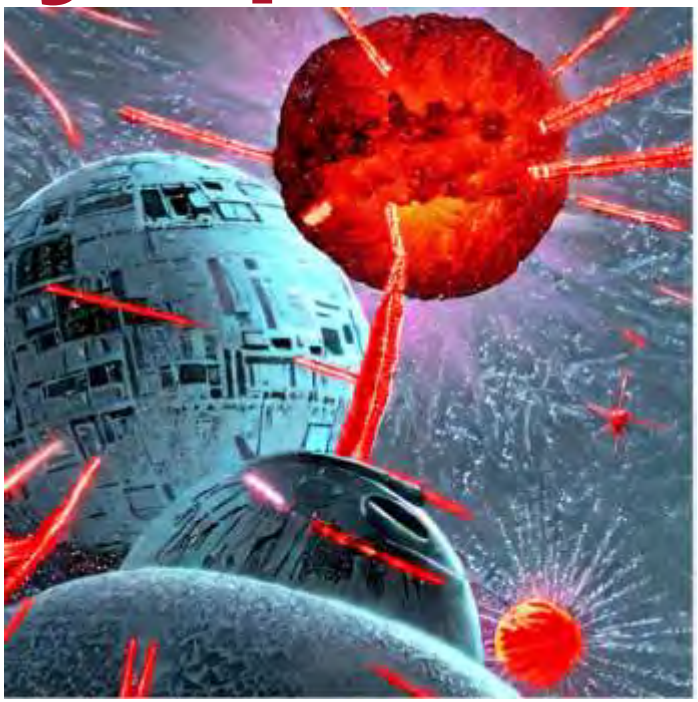
ASH 2022 Highlights Lymphoma



Christopher D'Angelo, MD
Assistant Professor, Hematology/Oncology
University of Nebraska Medical Center
2/2023

University of Nebraska Medical Center

Outline

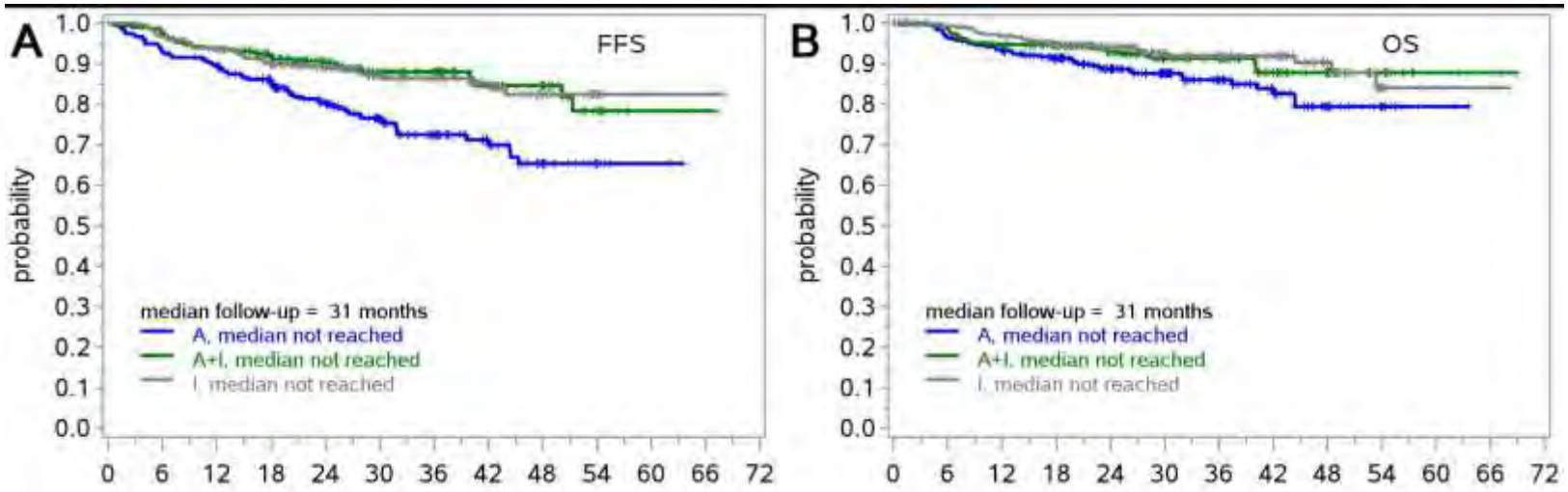
- Mantle Cell Lymphoma
  - Triangle: ibr + chemo +/- ASCT
  - glofitamab
- Follicular Lymphoma
  - Watch and wait trial update
  - mosunetuzumab
- Cellular/Immune Therapy
  - Bispecific antibody therapy
  - Updated liso-cel 2L analysis

Disclosures

- Advisory: BMS, Abbvie, Ono Pharma, Seagen
- Research: BMS, Beigene, Fate Therapeutics

Mantle Cell Lymphoma

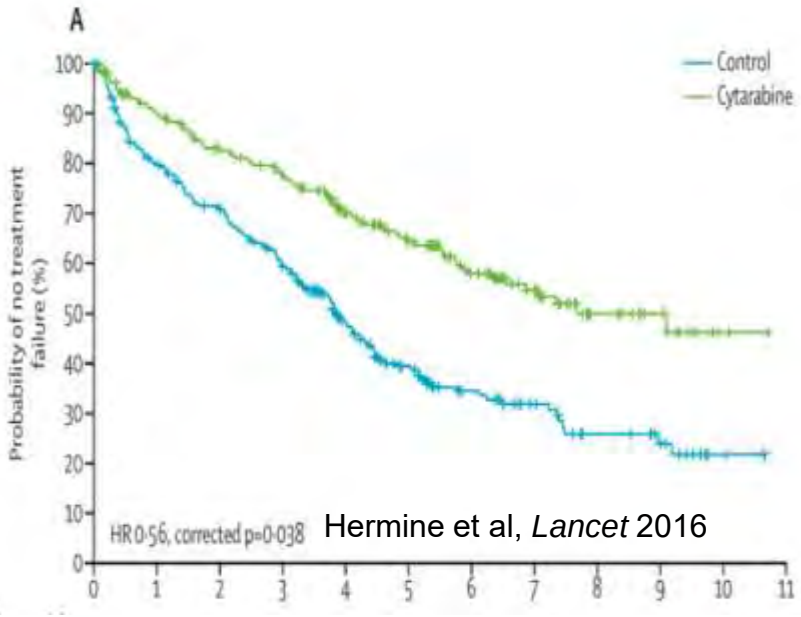
- Triangle study: chemo + ASCT +/- ibrutinib



Dreyling et al, Abstract 1, 12/11/22

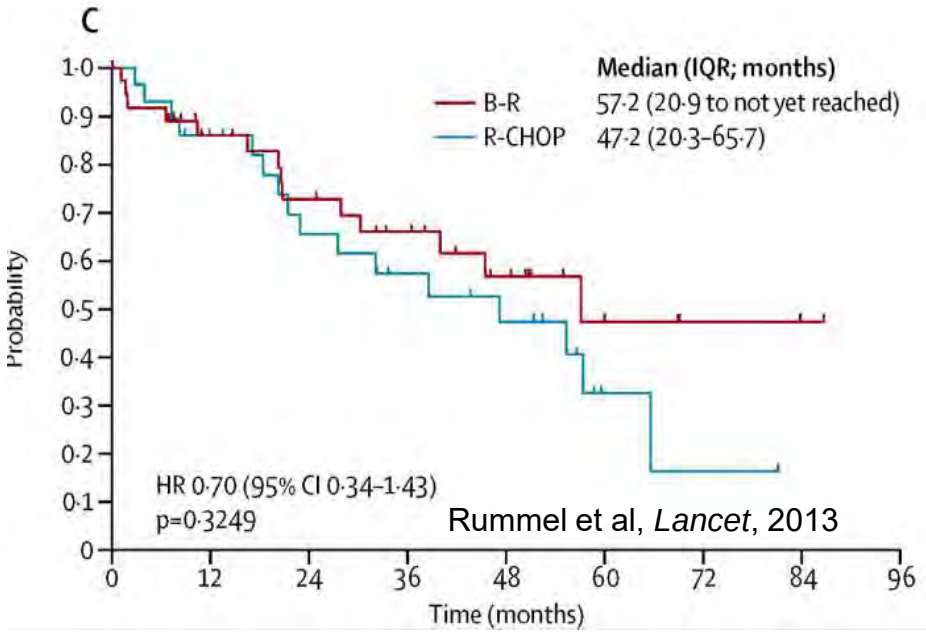
ASCT in Mantle Cell Lymphoma

R-CHOP/DHAP vs R-CHOP -> ASCT



Hermine et al, *Lancet* 2016

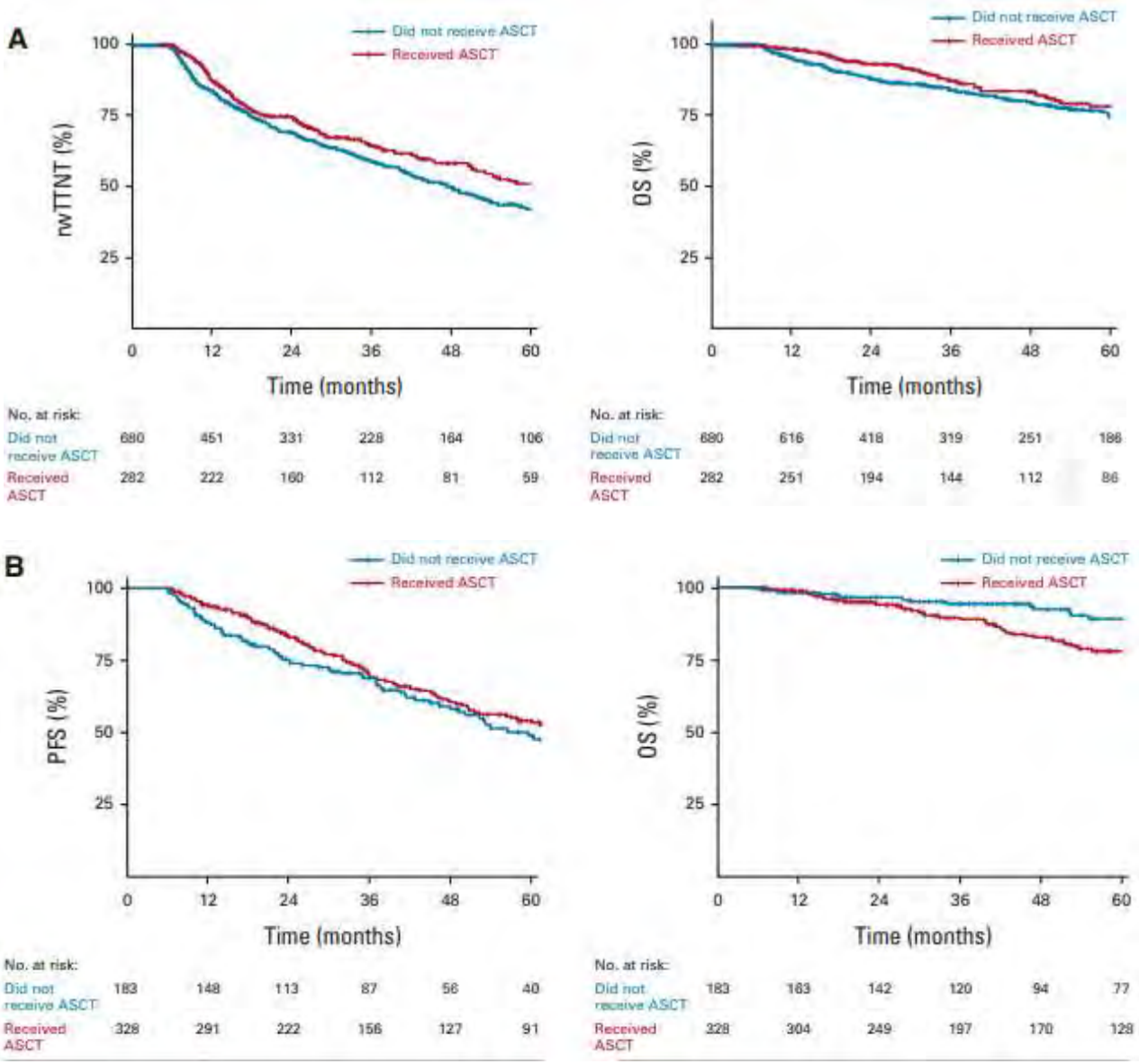
BR vs R-CHOP no ASCT



Rummel et al, *Lancet*, 2013

- Historically, clinical trials have separated into ASCT-eligible and ineligible
- Overall best outcomes observed in transplant-containing groups
  - Reserved for the most fit patients

Recent ? For ASCT in MCL

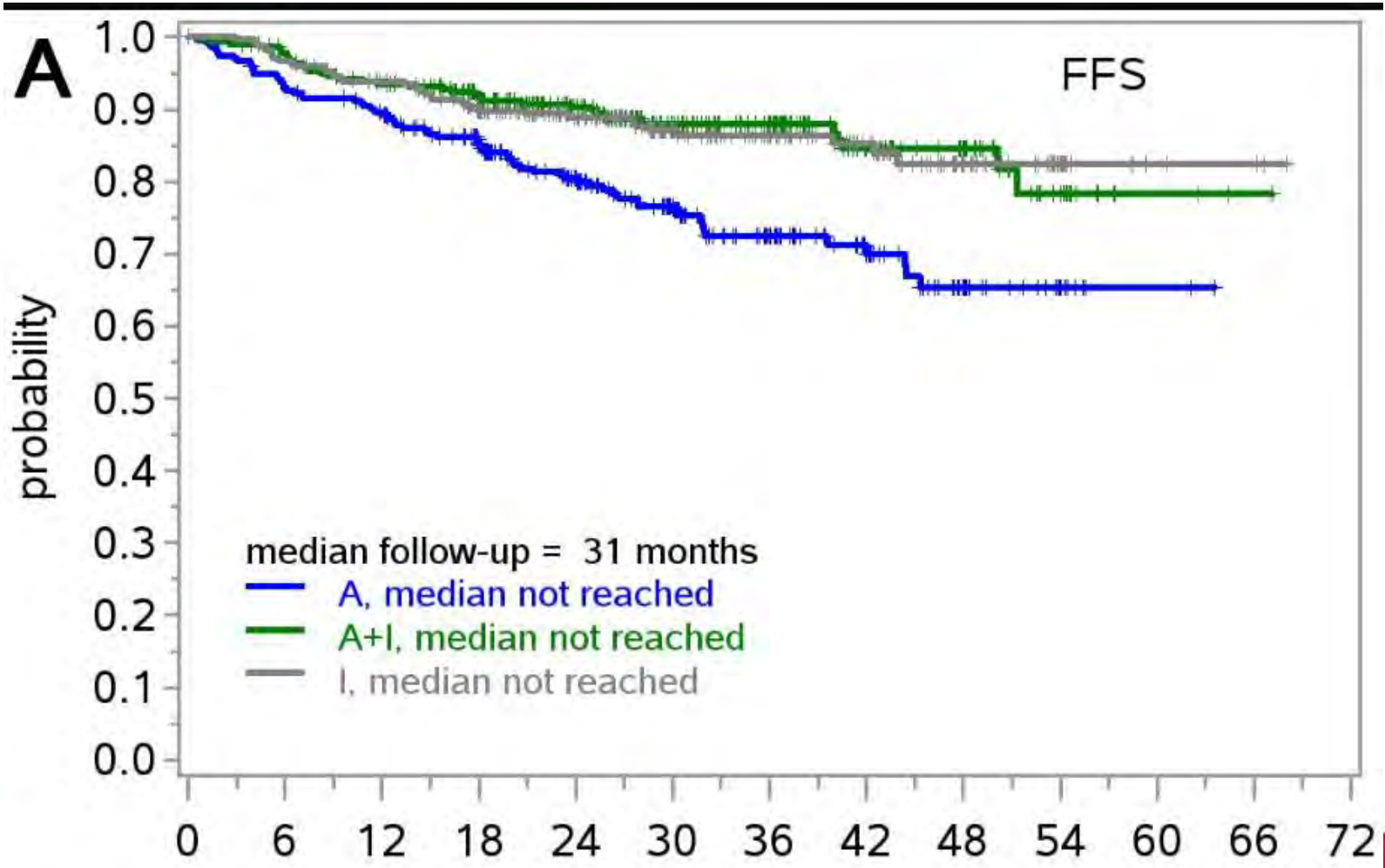


Martin et al, JCO 2022

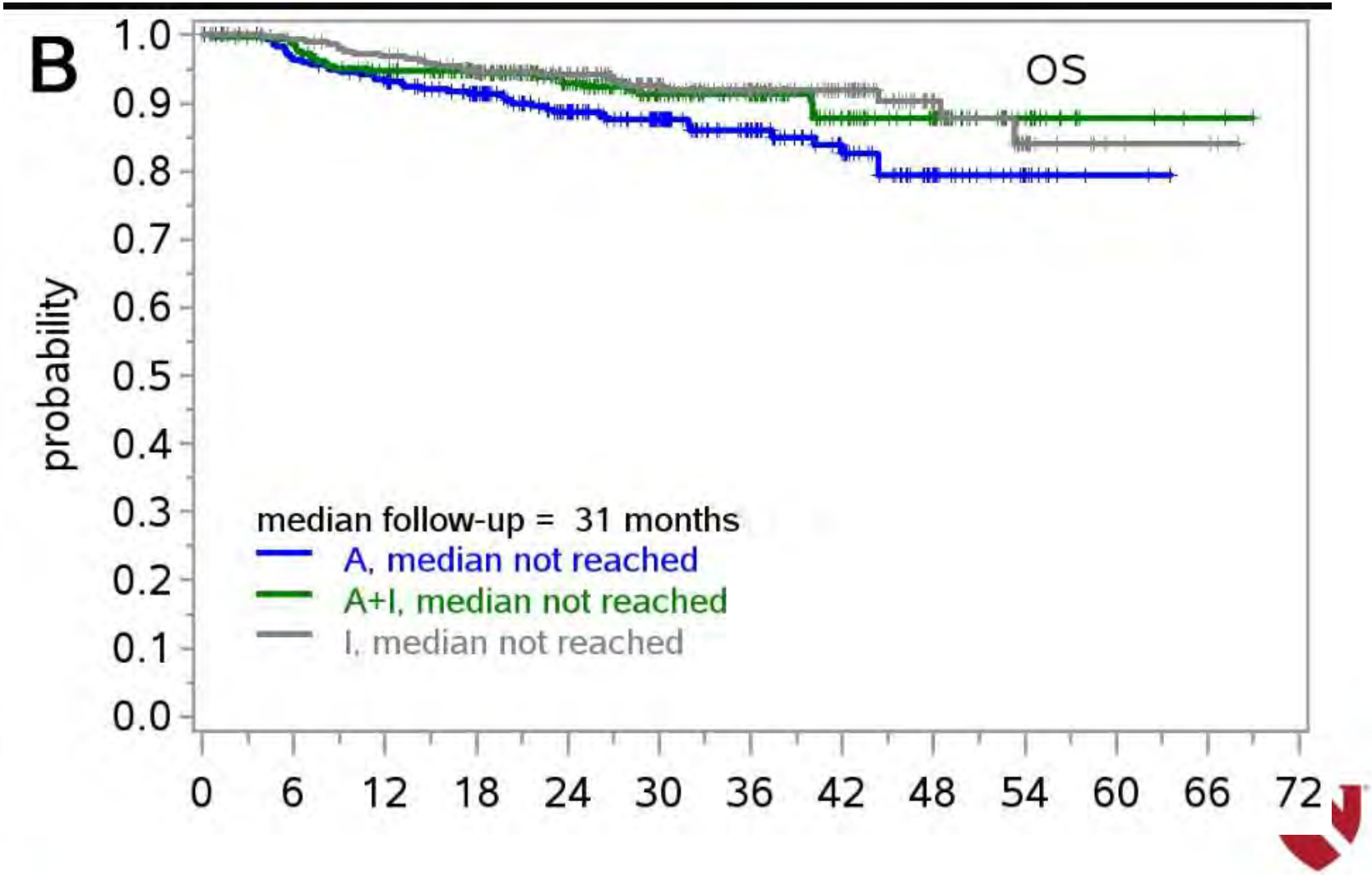
Triangle Study

- RCT 1:1:1 3 arms transplant eligible <65
  - R-CHOP-I/DHAP -> Ibrutinib 2yr
  - R-CHOP-I/R-DHAP -> ASCT-> Ibrutinib 2y
  - R-CHOP/R-DHAP -> ASCT
- Powered for Failure-free survival
  - Progression, death, SD post induction events
- Maintenance rituximab per guidelines
- N= 282 in each group

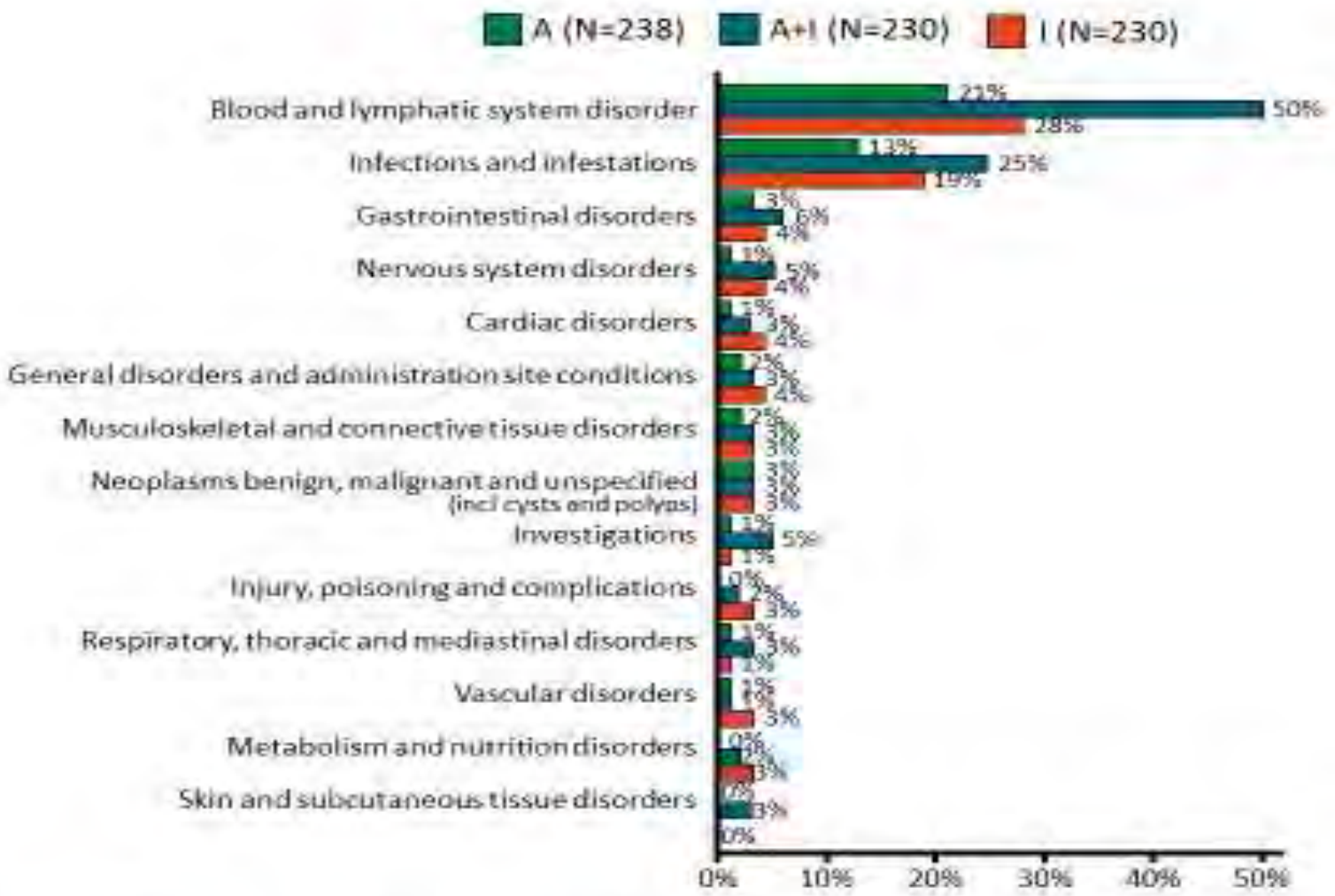
Triangle 1L MCL



Triangle 1L MCL



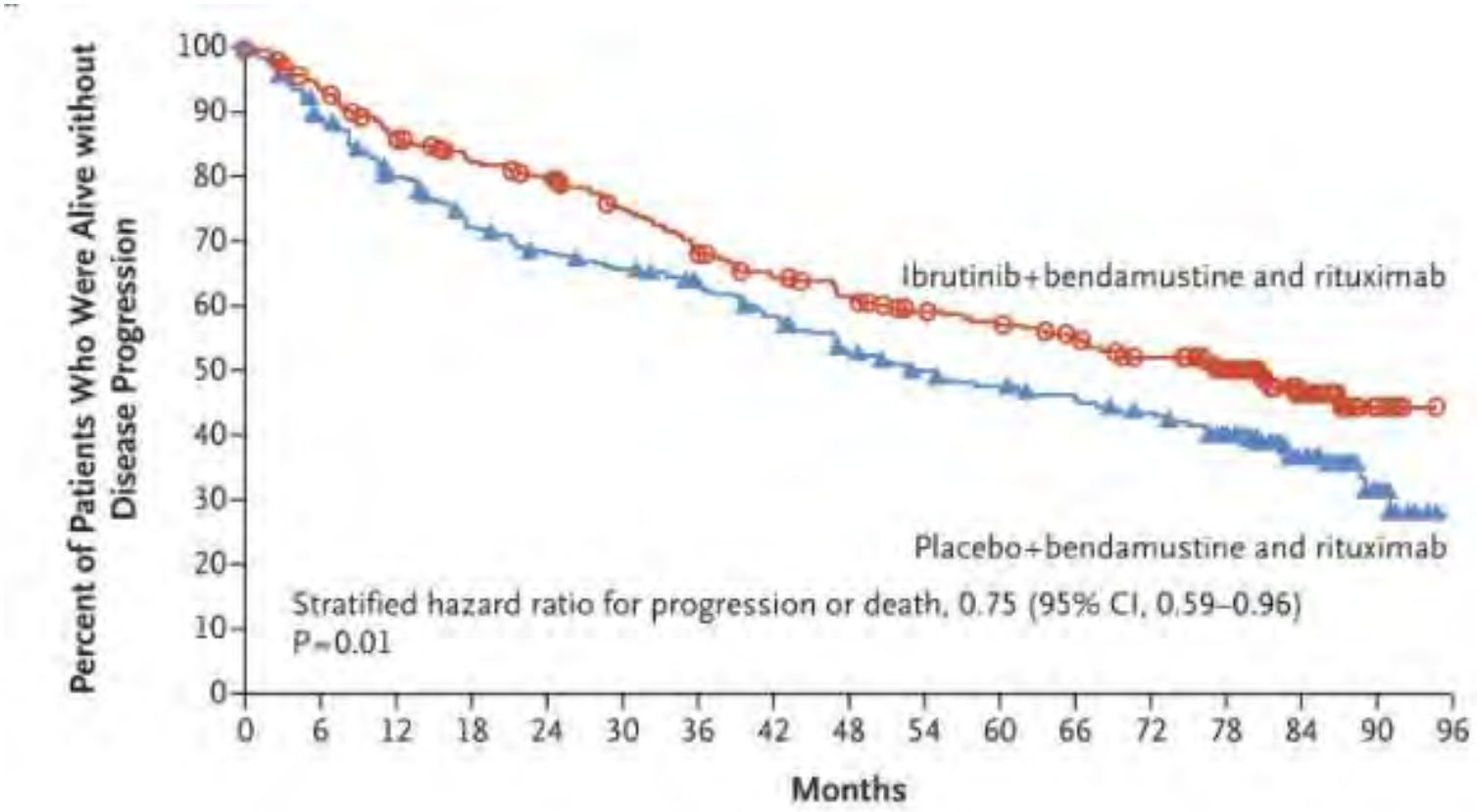
Triangle Safety



Dreyling, ASH 2022. Abstr 1. Reproduced with permission

Slide credit: clinicaloptions.com

Comparisons: SHINE



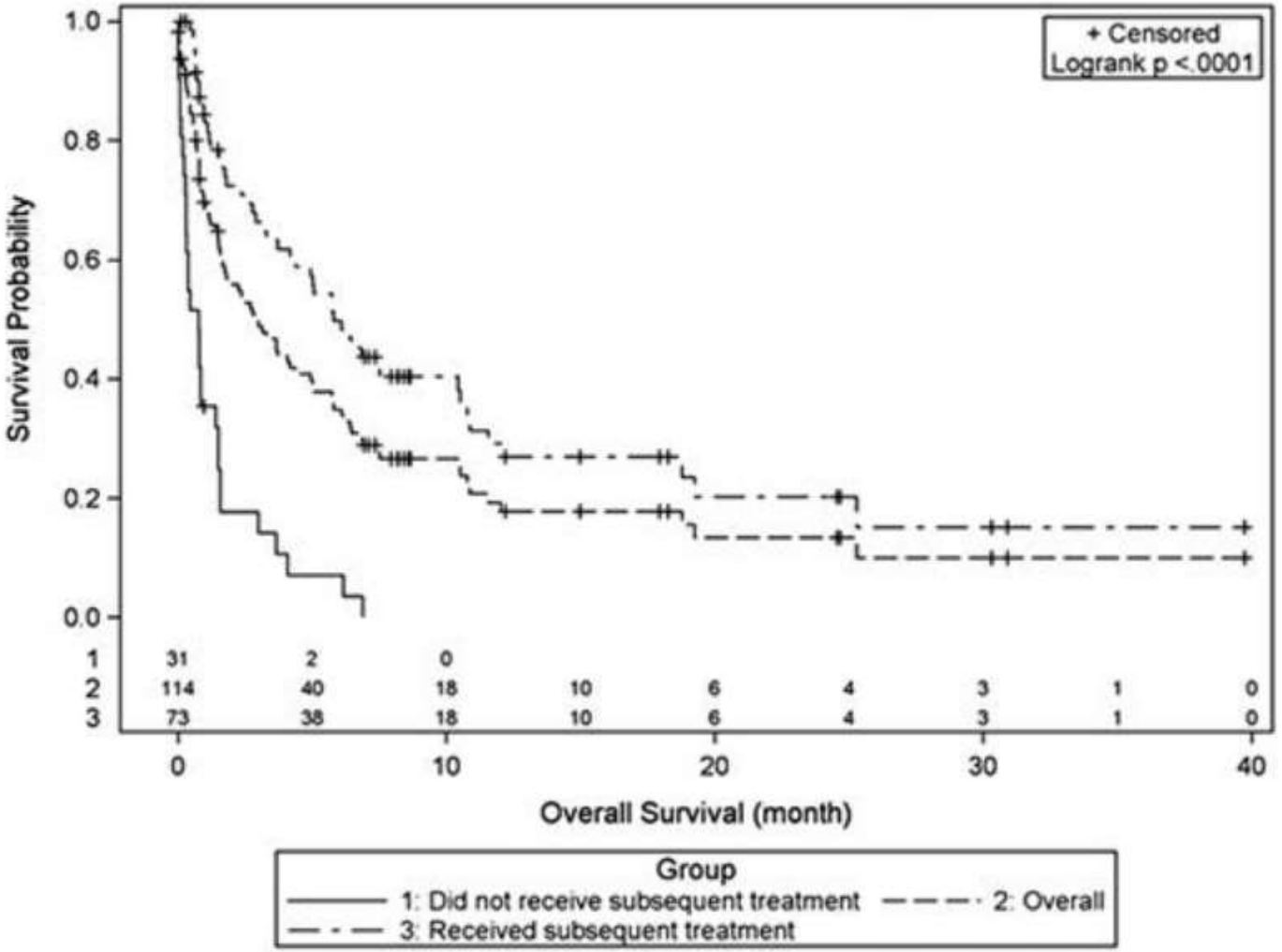
- Transplant ineligible
- BR +/- Ibrutinib (given continuously)
- Median f/u ~80 months
- No OS benefit

Triangle conclusions/Future

- Data support Ibrutinib-RCHOP/DHAP for 1L in young
  - Over R-CHOP/DHAP + ASCT
  - Kudos for a study in 1L TE patients with a non-ASCT arm
- Accumulating evidence ? Role of ASCT
  - At least not for everyone eligible, esp if BTK-eligible
  - Need to determine who benefits (MRD?)
- 1L acala/len/R excellent PFS, 100% ORR
  - Ruan et al *Blood* (2022) 140 (Supplement 1): 175–177.
- E4151 assessing MR vs ASCT in MRD- MCL
- For now:
  - Considering ibrutinib for 1L
  - Discussing this data with TE patients

Relapsed Mantle Cell Lymphoma

- Poor survival post BTKi failure



Maddocks et al, *Blood* 2016

Mantle Cell Lymphoma

- Glofitamab: CD20 xCD3 bispecific, IV
- Obinutuzumab pre-treatment
  - Depletes target CRS source from blood/tissue
  - May reduce dependence on step-up dosing

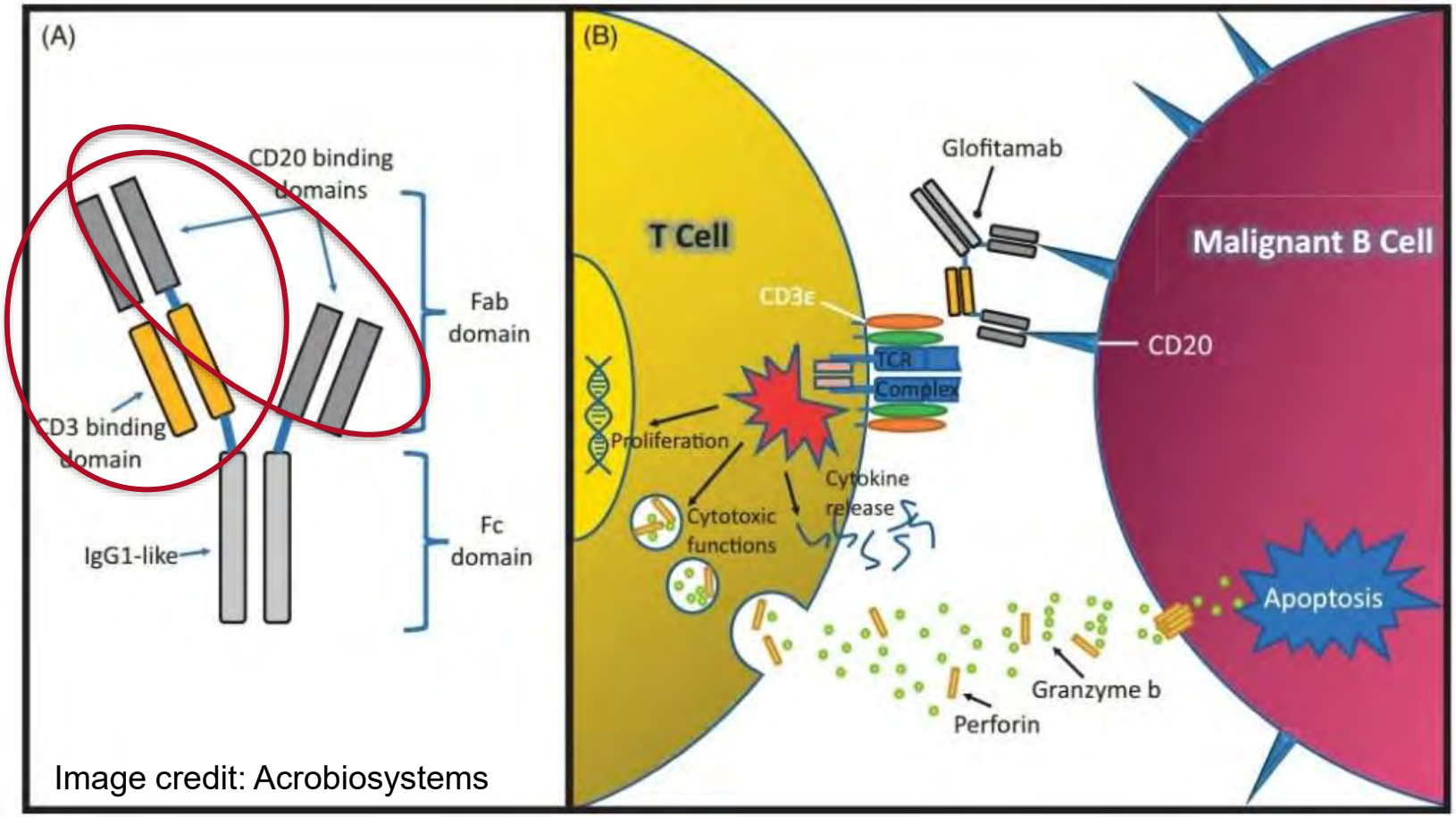
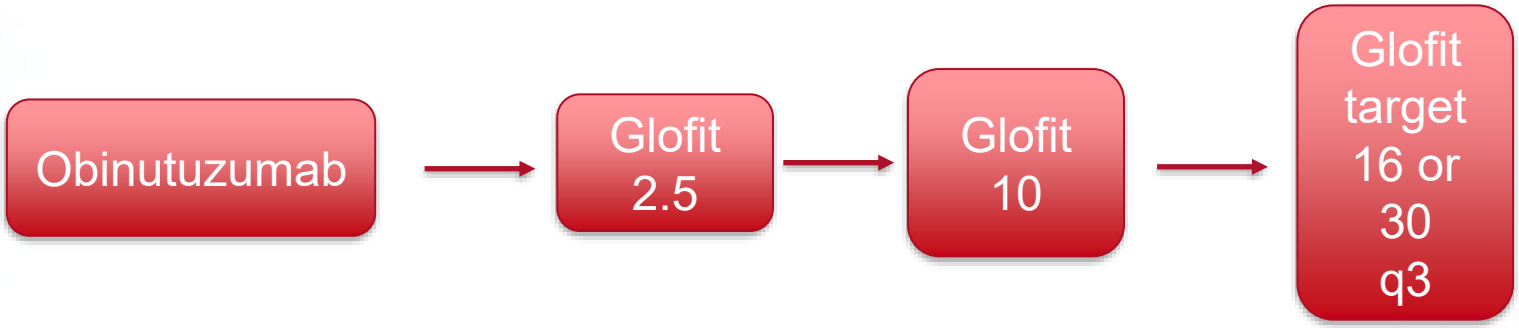


Image credit: Acrobiosystems

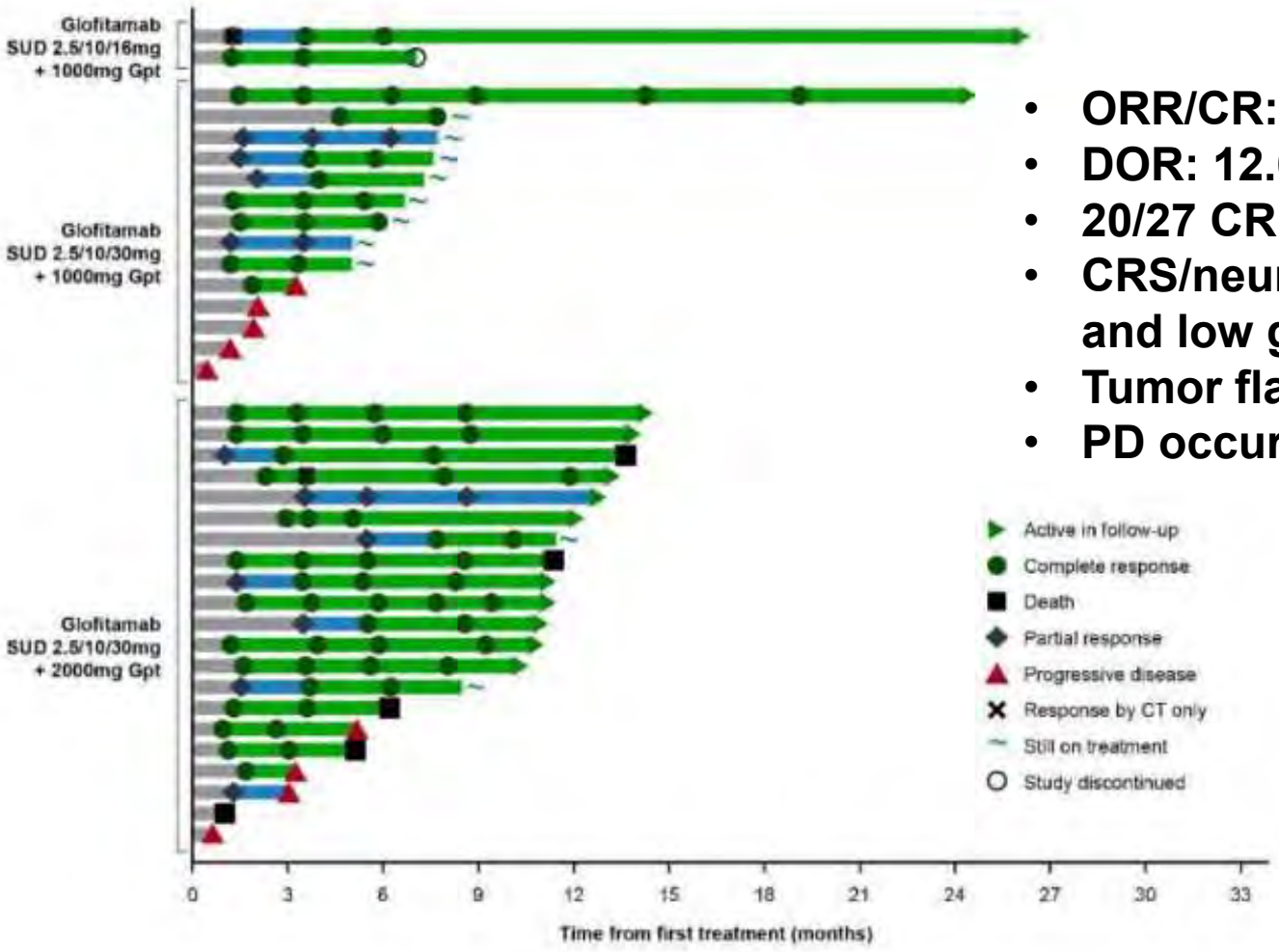
Mantle Cell Lymphoma r/r

- Glofitamab: CD20 xCD3 bispecific, IV
- Obinutuzumab pre-treatment, step-up
- 37 pts, med f/u 8 mo
  - 64% prior BTKi
  - Med prior lines 3
- Fixed duration: q3w Received up to 12 cycles
  - 9 months of therapy



Phillips et al, Abstract #74, 12/10/22

Mantle Cell Lymphoma

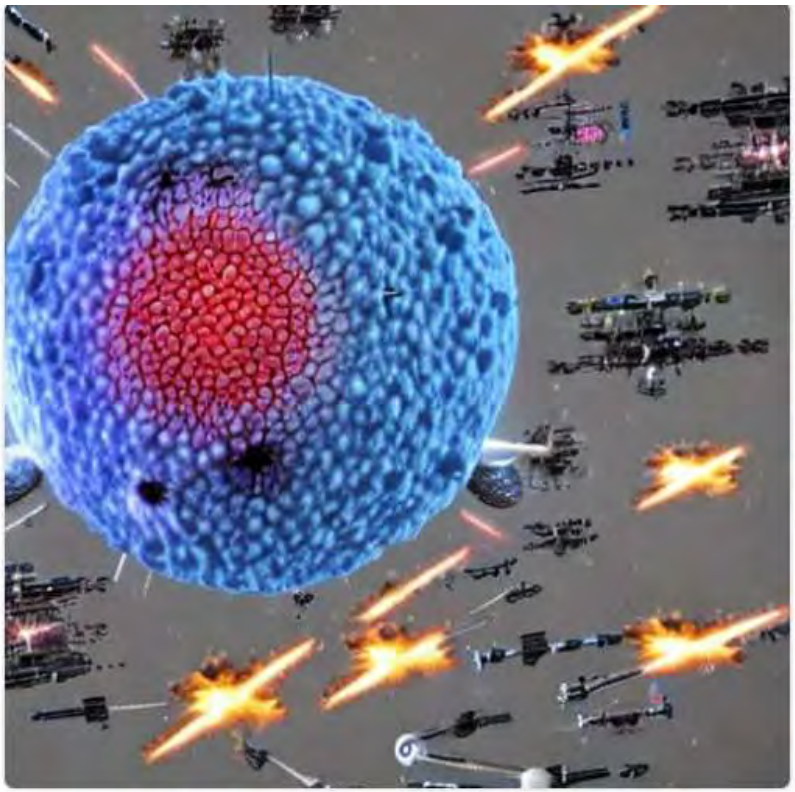


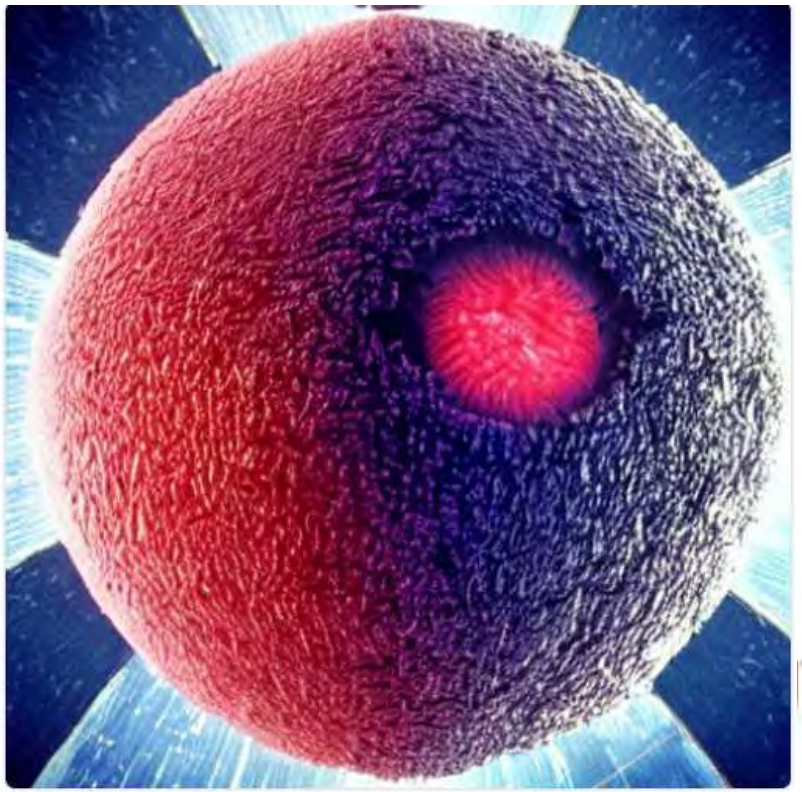
- **ORR/CR: 83/73%**
- **DOR: 12.6mo,**
- **20/27 CR's ongoing**
- **CRS/neuro common and low grade**
- **Tumor flare in 13%**
- **PD occurs <6, often <3**

Phillips et al, Abstract #74, 12/10/22

Follicular Lymphoma

- Mosunetuzumab
- Watch and wait trial



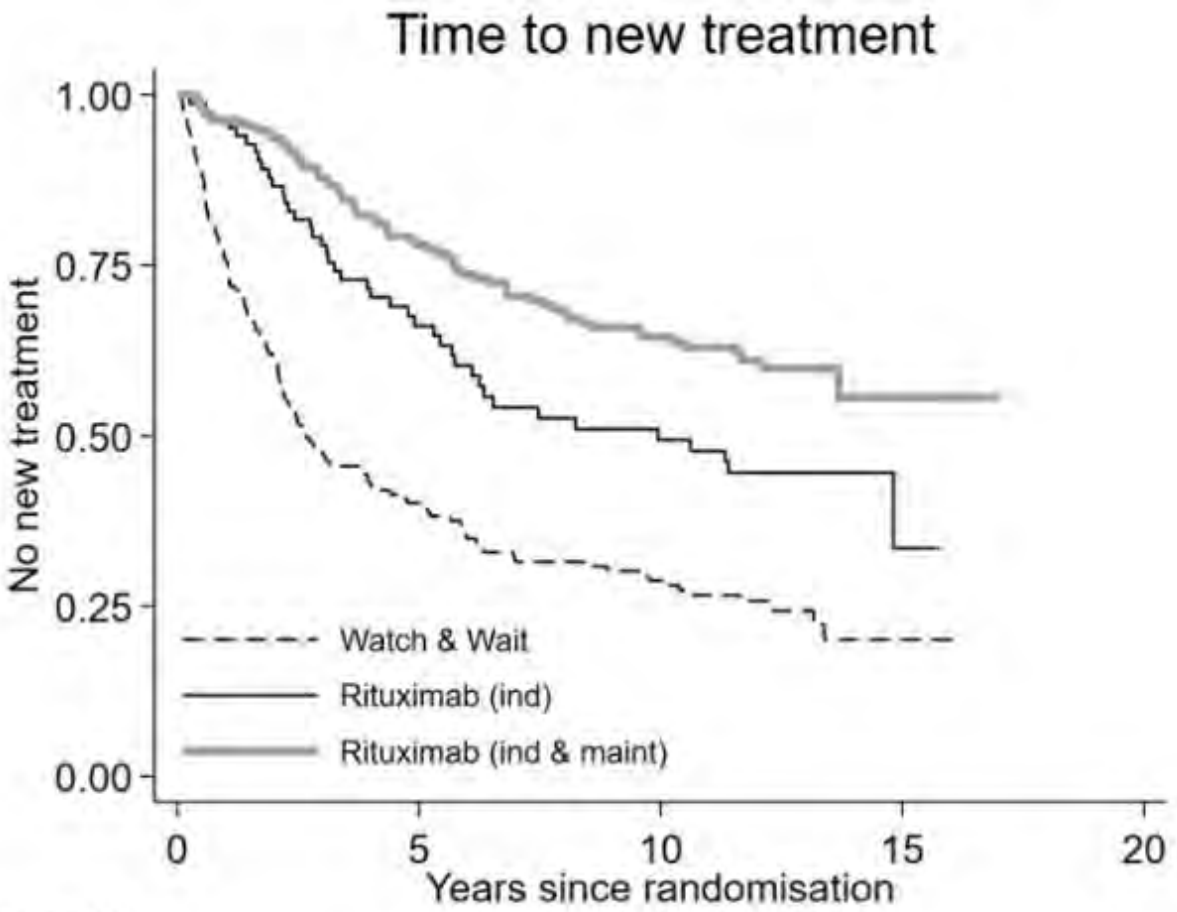


Watch and Wait Update

- Watch/wait: Ph3 1:1:1 obs vs ritux x4 dose, vs R + R maintenance 2y
- Low tumor burden FL
- 463 pts, median followup 12.3 years
- Primary endpoint: time to next treatment

Northend et al, abs #607, 12/11/2022

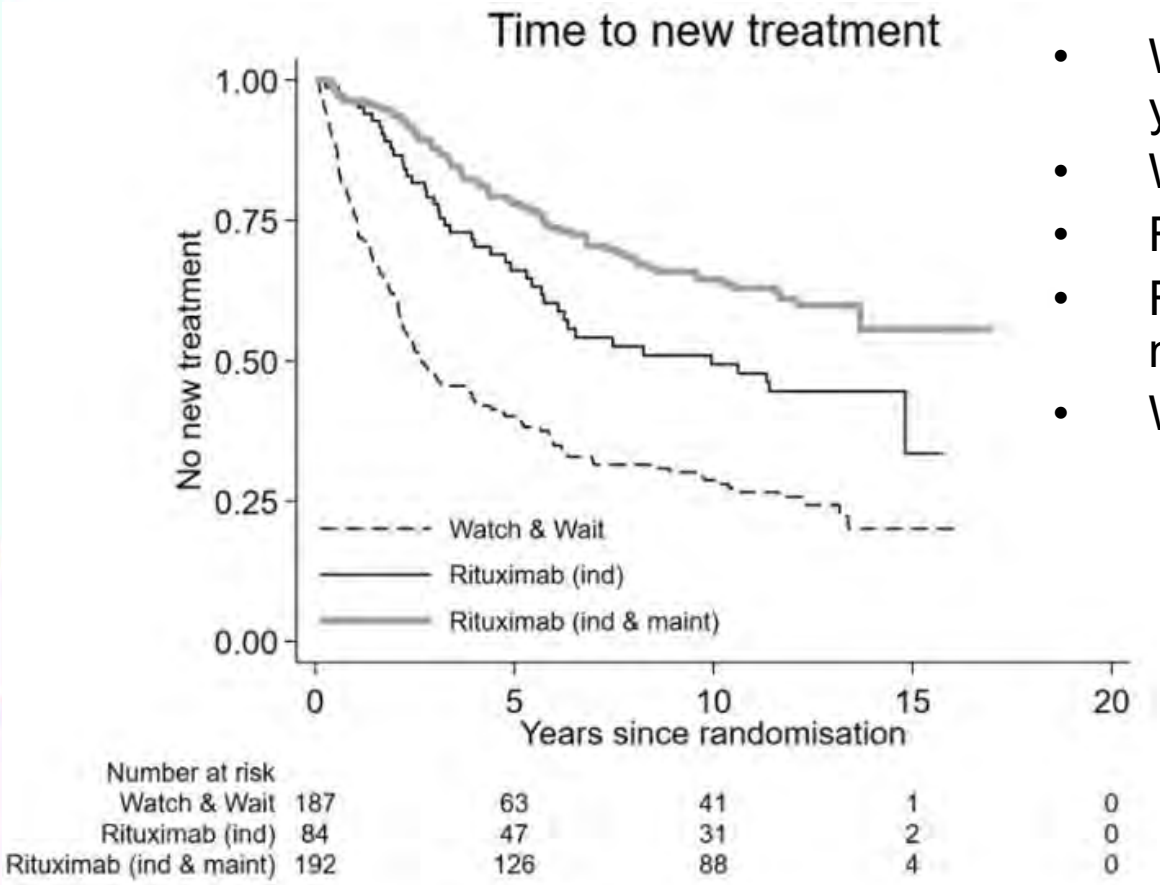
Watch and Wait Update



Number at risk					
Watch & Wait	187	63	41	1	0
Rituximab (ind)	84	47	31	2	0
Rituximab (ind & maint)	192	126	88	4	0

Northend et al, abs #607, 12/11/2022

Watch and Wait Update

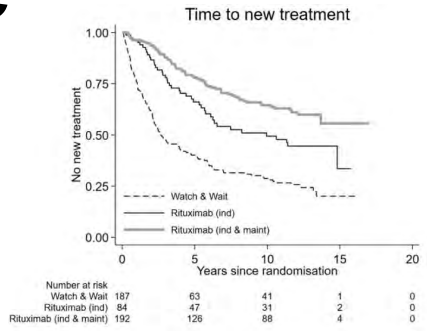


- W/W: most events by 5 years
- W/W: TTNT: 2.7 yrs
- Rituximab: 9.9 yrs
- Rituximab + maintenance: not reached
- W/W:
  - Spontaneous regression 19% - most recur
  - ~25% on W/W still off treatment 10yrs out

Northend et al, abs #607, 12/11/2022

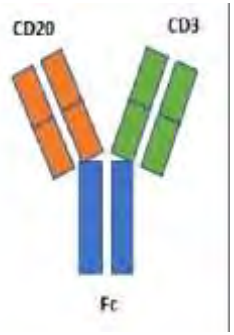
Watch and Wait: interpretation

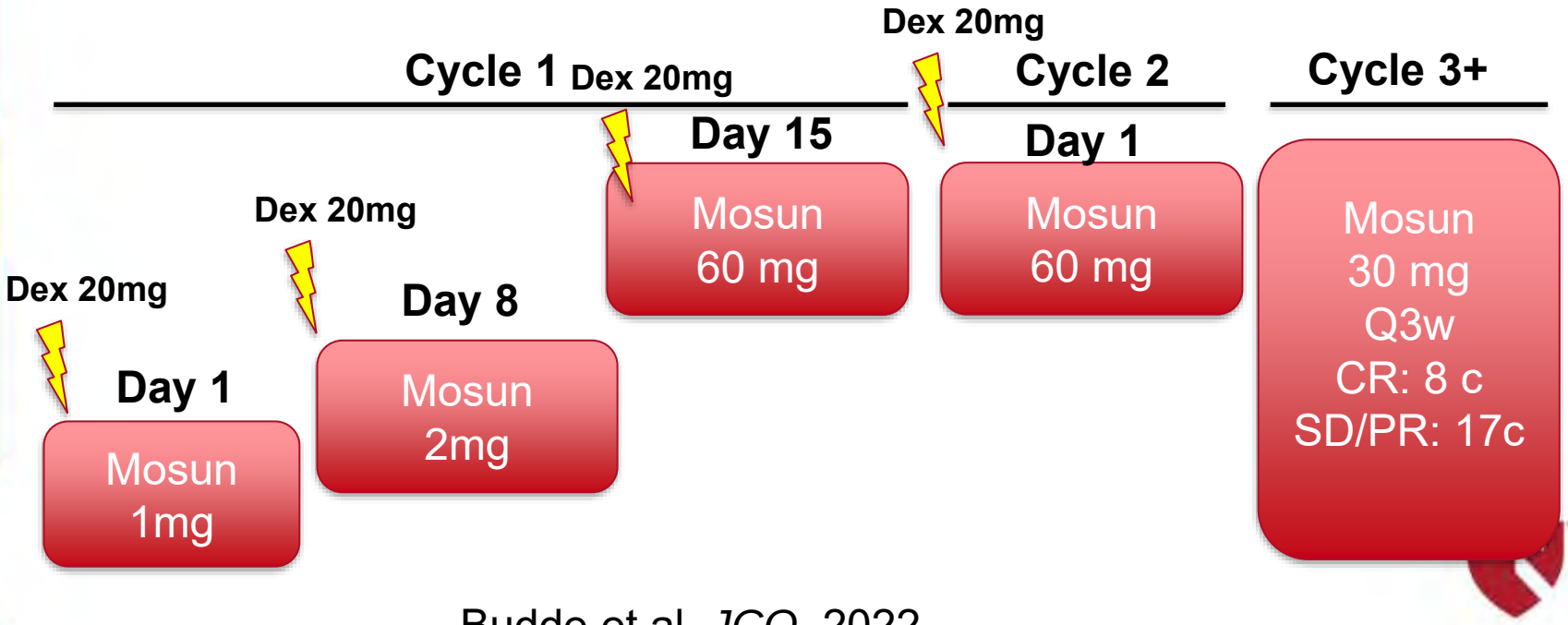
- Depends on how we interpret risk
- Allows greater choice for patients
  - W/W: 25% treatment free at 10 years!
  - Rituximab: median TTNT **10 years**
- Considerations for
  - Frail
  - Young with low tumor burden
  - On fence with chemoimmunotherapy
- I’m discussing this with pts more



Follicular Lymphoma

- Mosunetuzumab: CD3-CD20 bispecific Ab
- Ph2 n=90, fixed duration q3w
- FL G1-3a, rr to ≥2L
- 50% POD24



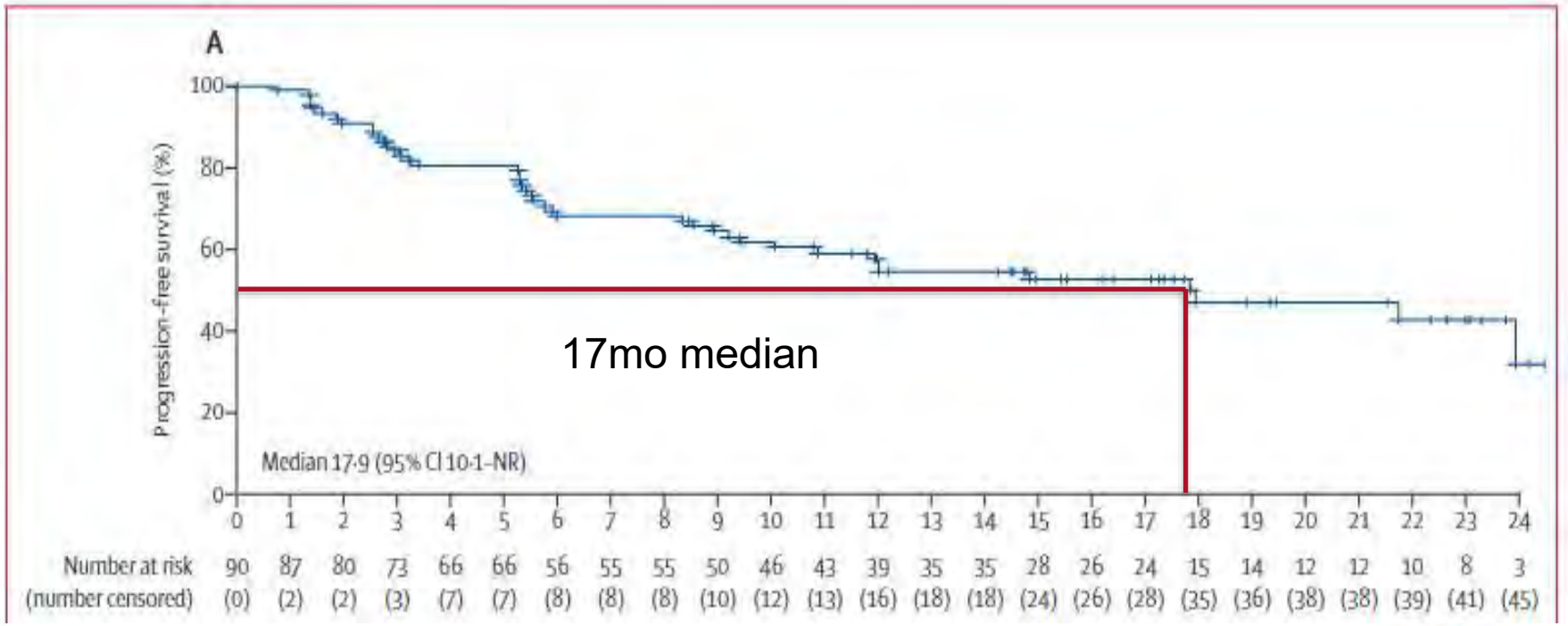


Budde et al, *JCO*, 2022

Mosun: efficacy

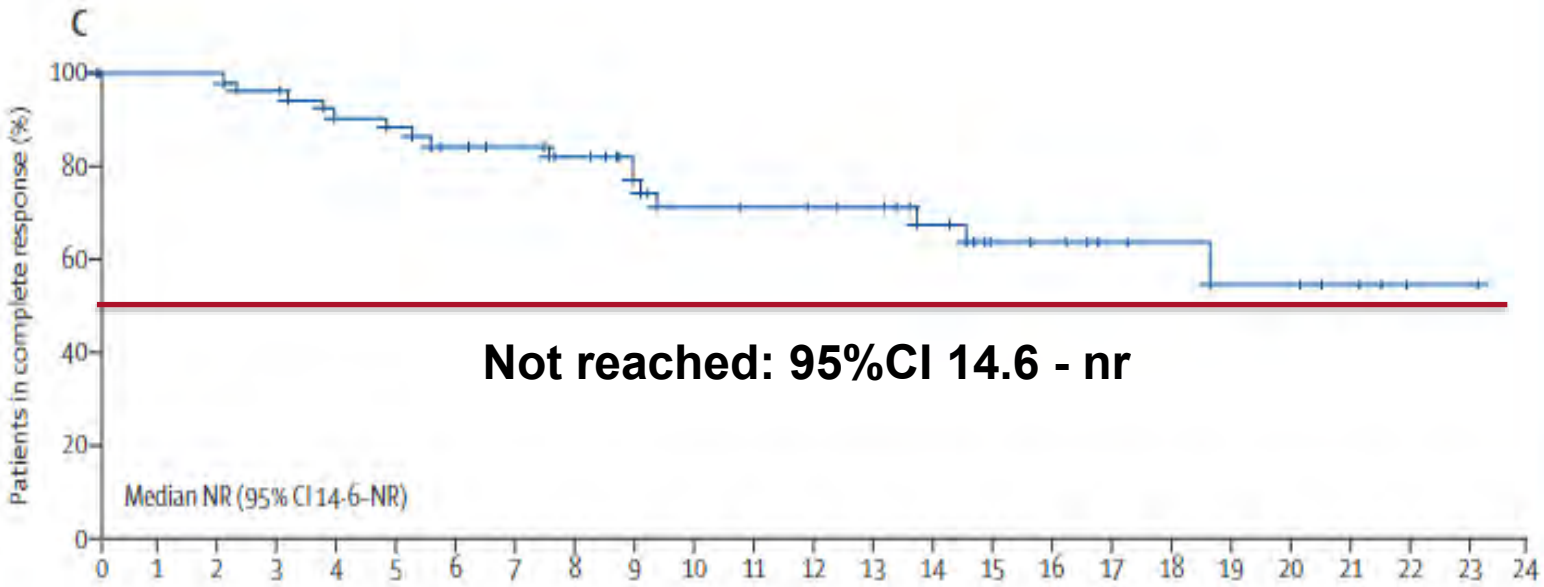
- ORR: 80%CR: 60%
- Med f/u: 18mo
- First response: 1.4 mo

Progression-Free Survival



Mosun: efficacy

Duration of Complete response: 60% population
*** 24weeks (8cycles) of treatment**



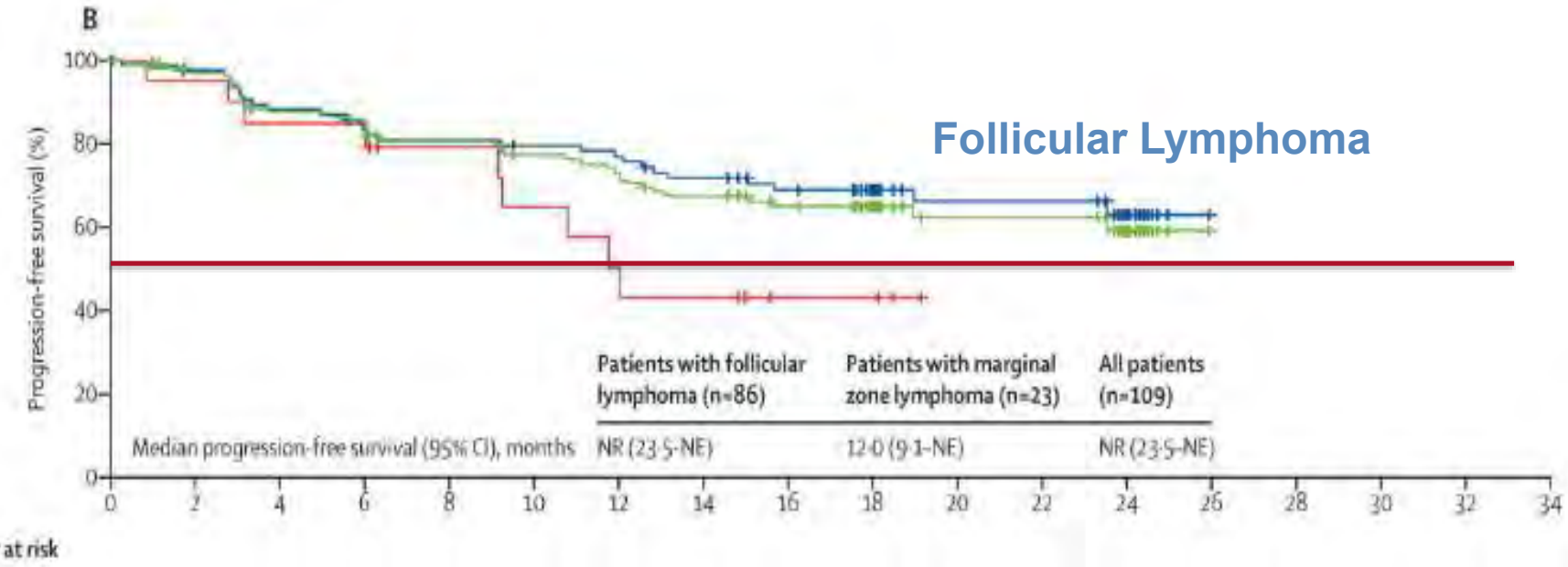
Not reached: 95%CI 14.6 - nr

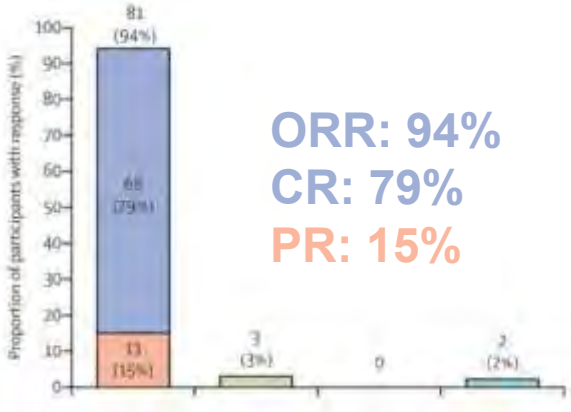
Duration of complete response	
Patients with event	16/54 (30%)
Median, months (95% CI)	NR (14·6–NR)
12-month event-free rate	71·4% (57·9–84·9)
18-month event-free rate	63·7% (48·0–79·4)

Mosun: toxicity

- CRS: ~42% G1/2, 2% G3/4
  - 8% required toci
  - 15% steroids
  - 10% both
  - ~1/2 admitted with G1/2 CRS
- Neurotoxicity: 5/90, all G1 all resolved
- Tumor flare in 3/90 patients

Comparison: CAR-T for FL





ORR: 94%
CR: 79%
PR: 15%

Axi-cel: zuma-5: similar trial population to mosun
Axi-cel: med PFS not reached
Mosun: med PFS 17.9mo
More toxicity with axi-cel

Jacobsen et al, *Lancet Oncology,* 2022

Conclusions

- Mosunetuzumab exciting option for FL
- FDA approved 12/2022
- Excellent durability in response
  - Re-treatment?
- Advantages over CAR-T
  - Access
  - Minimal toxicity
- Disadvantages
  - May be less efficacious/durable
  - Multiple-dosing

DLBCL

- CD19 directed therapies
- Cellular Therapies
- Bispecific antibody Trials

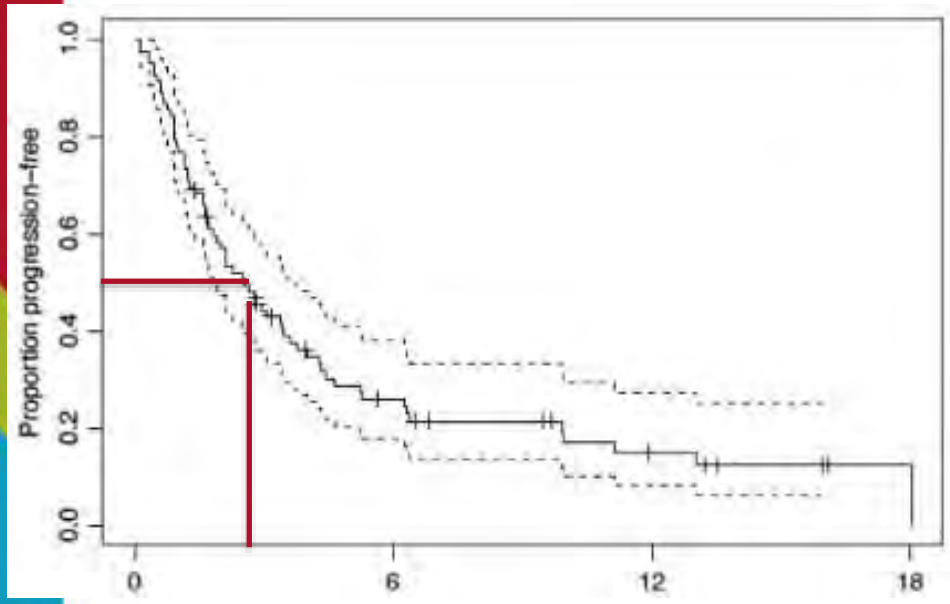
DLBCL: Tafasitamab + lenalidomide

- Real world outcomes with tafa/len
  - Tafasitamab CD19 mAb
  - Busy cycle 1 dosing
- 9 centers
- N=82, 91% ineligible for L-MIND
- L-mind
  - 1-3 prior lines
  - ECOG 0-2
  - Ineligible for ASCT (ie >70)
  - Not primary refractory
  - Med time from Dx: 27mo
- Real world cohort
  - 0-11 lines (median 2)
  - 46% primary refractory
  - 70% refractory to last line (~40% in L-mind)
  - 21% prior CAR_T

Tafa-len

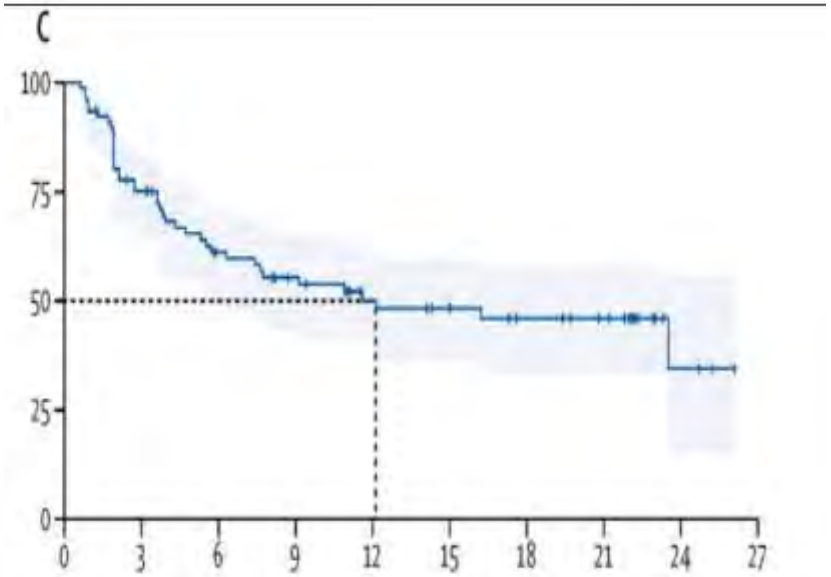
Progression-Free Survival

RW Retrospective cohort



Median PFS: 2.8mo
ORR/CR: 27/17%

L-Mind Trial

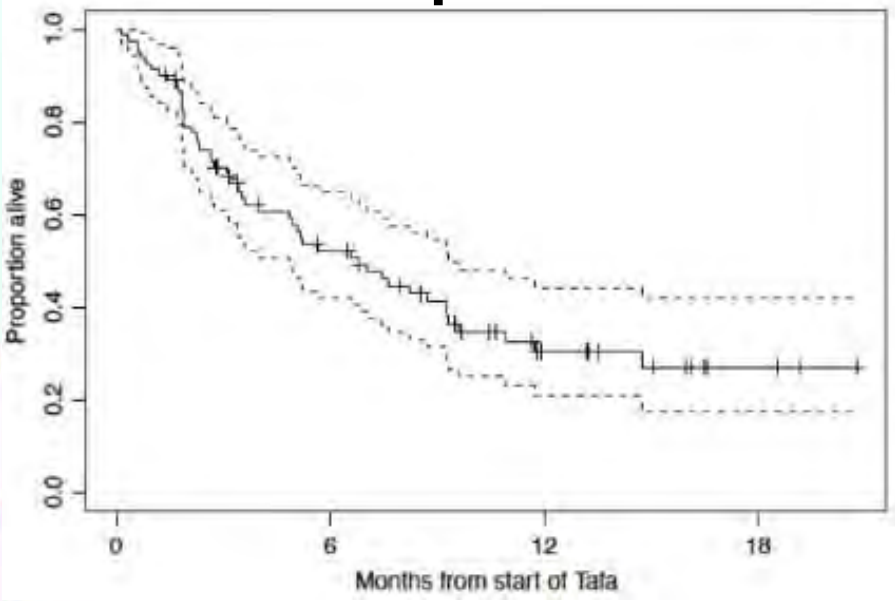


Median PFS: ~12mo
ORR: 60/43%

Tafa-Len

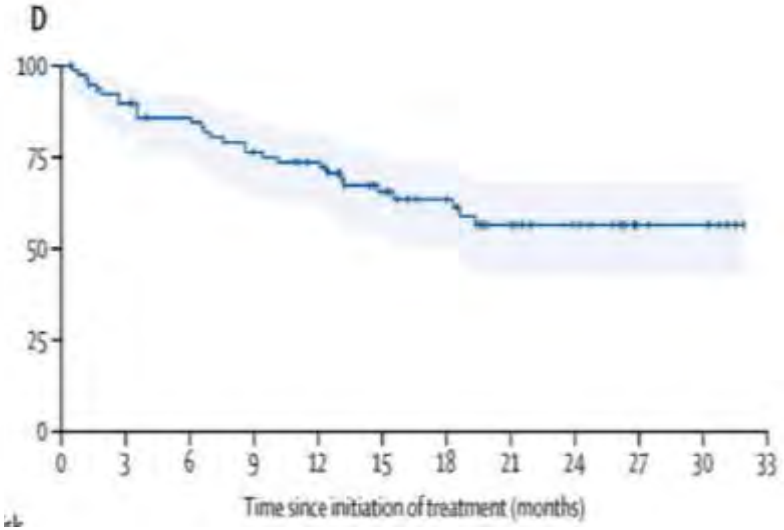
Overall Survival

RW Retrospective cohort



Median OS: 6.8 mo

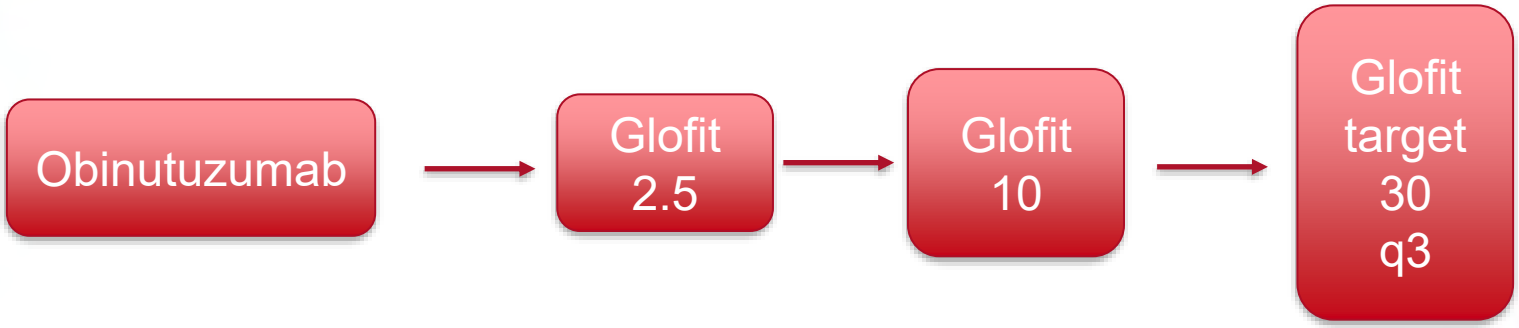
L-Mind Trial



Median OS: not reached

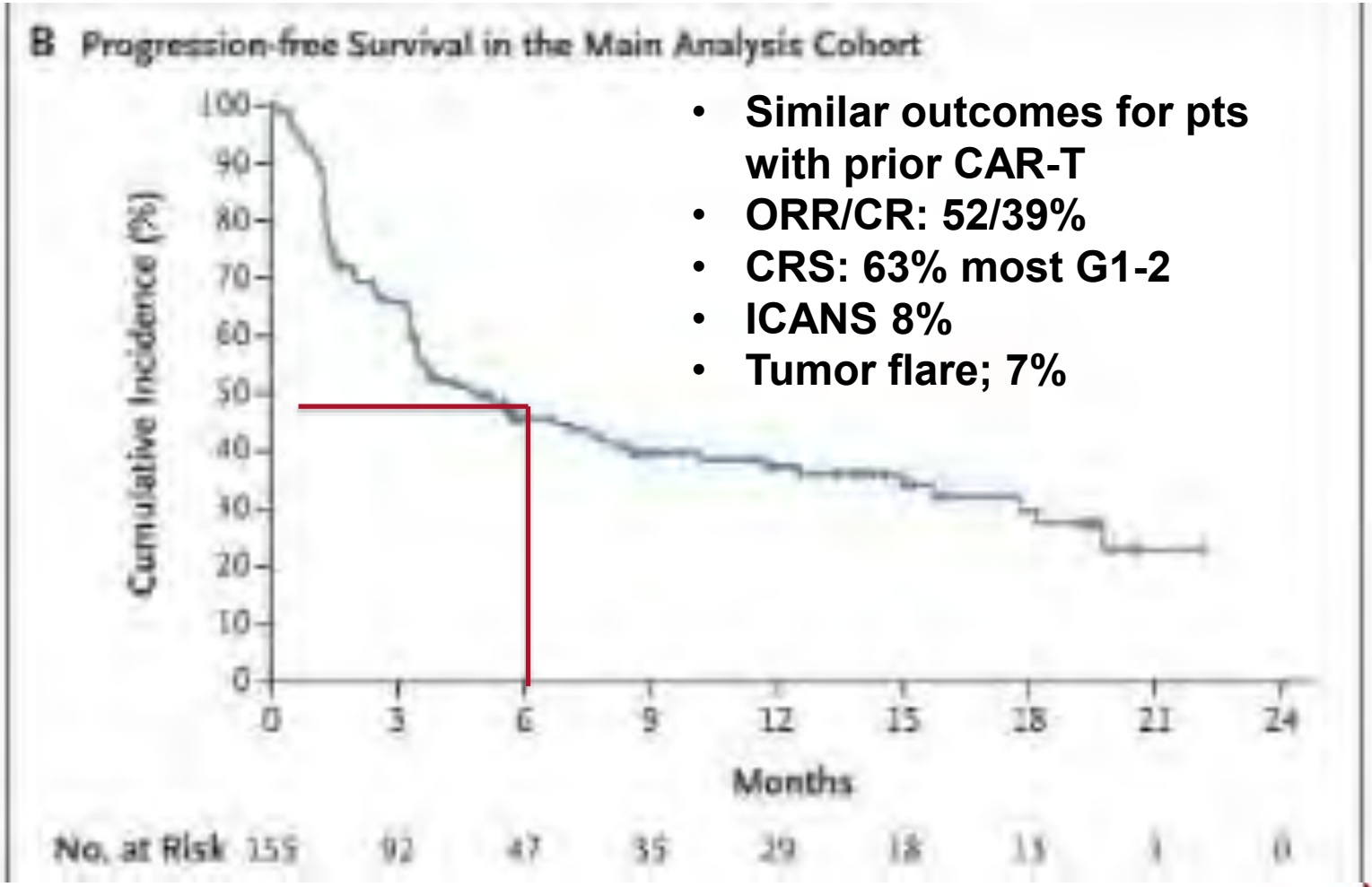
Glofitamab for DLBCL

- Step-up dosing
- Obinutuzumab pre-treatment x1
- Steroid pre-treatment gradually added
- 12 cycles q3w or ~9 months



Dickinson et al, *NEJM*, 2022

Glofitamab for DLBCL

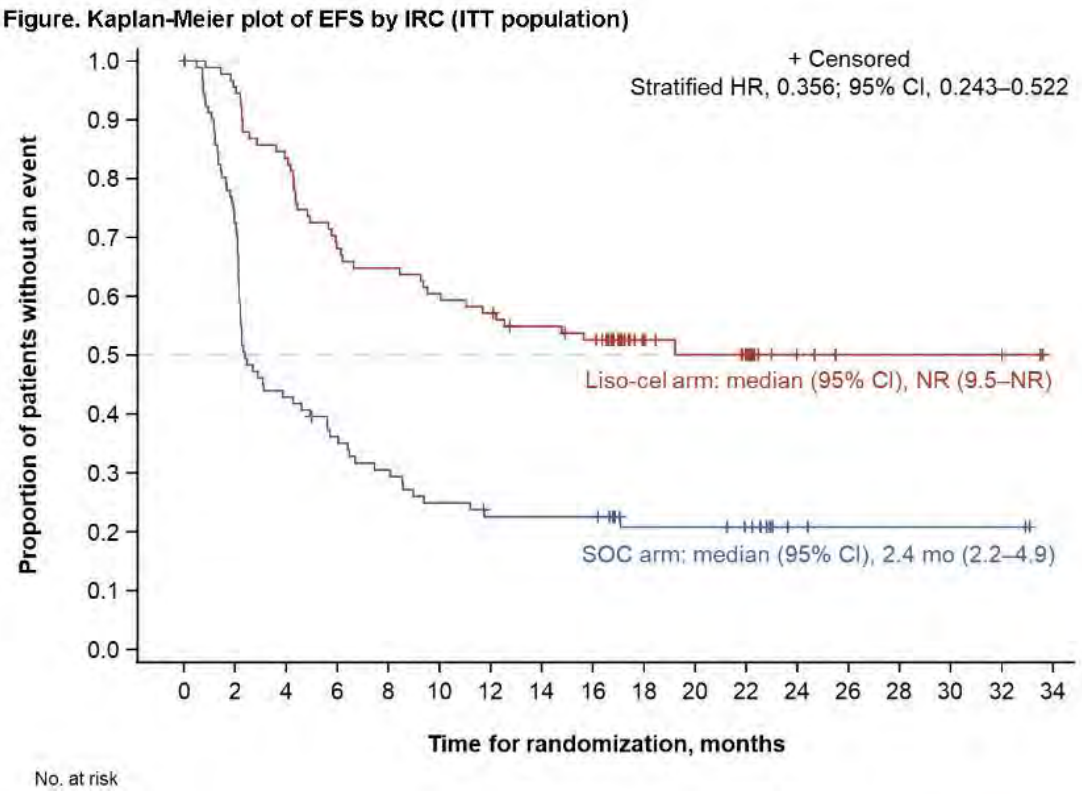


- **Similar outcomes for pts with prior CAR-T**
- **ORR/CR: 52/39%**
- **CRS: 63% most G1-2**
- **ICANS 8%**
- **Tumor flare; 7%**

Dickinson et al, *NEJM*, 2022

Liso-cel 2L Updated Analysis

- ORR 87%, CR 74%
- Duration of CR
  - 12mo – 73%
  - 18 mo- 65%

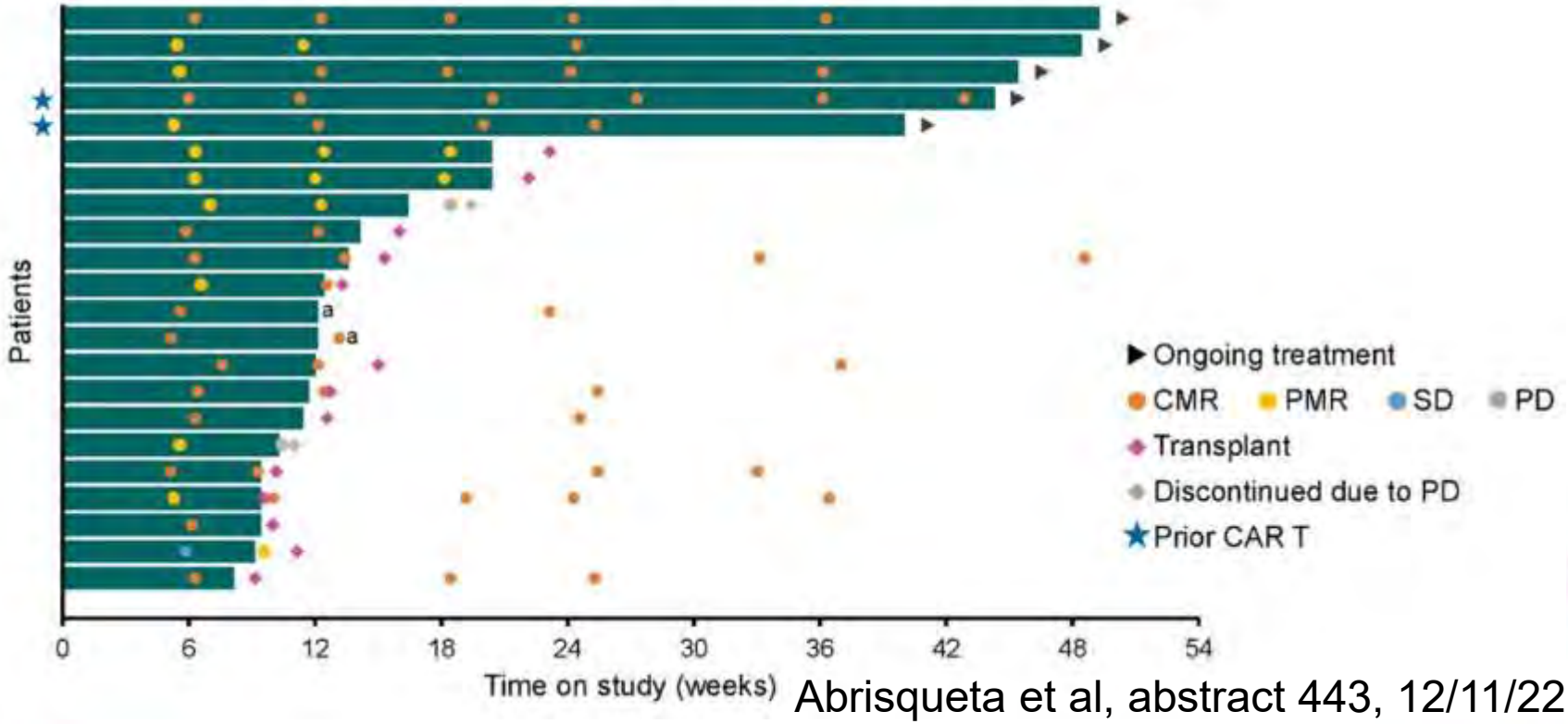


Abramson et al, abstract 655, 12/11/22

Epcoritamab + R-DHAX(C)

- Epco + R-DHAX for 3 cycles for transplant eligible patients
- N=29 Included prior CAR-T n=3
- Med f/u 9 months, ½ proceeded to ASCT and all remain in CR

Figure. Response profile with epcoritamab + R-DHAX/C in EPCORE NHL-2 arm 4.



Abrisqueta et al, abstract 443, 12/11/22

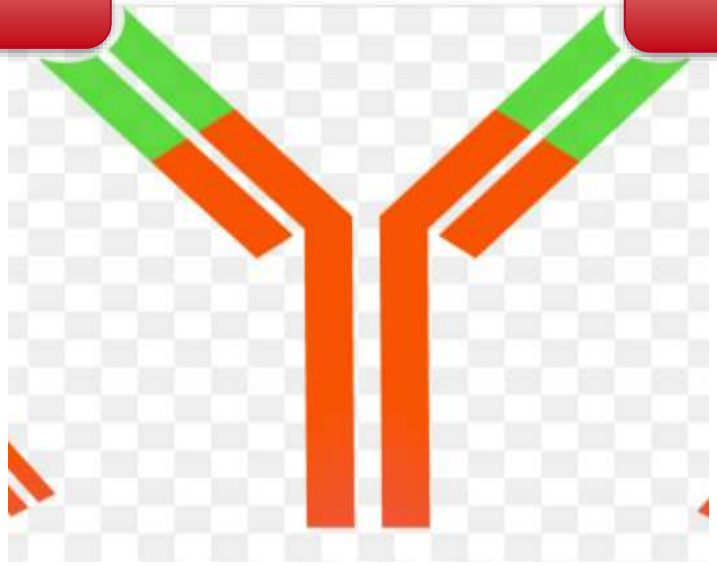
Bispecific? CAR-T?

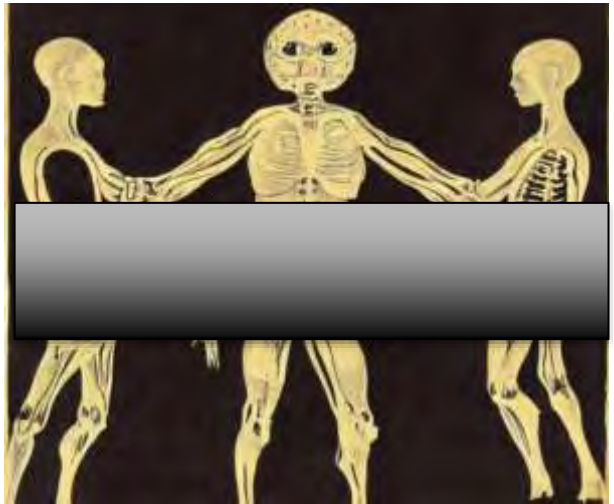
- Both!
- Sequencing is the next question
  - T-cell performance
  - Practical considerations
- More data for bi-specific post CAR
  - DESCAR-T cohort (Crochet et al Abstract #2026) suggest CAR-T efficacy post
- Up-front/bridging approaches rational
  - Improved disease control -> better CAR product?
  - CRS/ICANS mitigating?
- Communication and coordination will be key

Bi-specific Metaphor

Academic

Community





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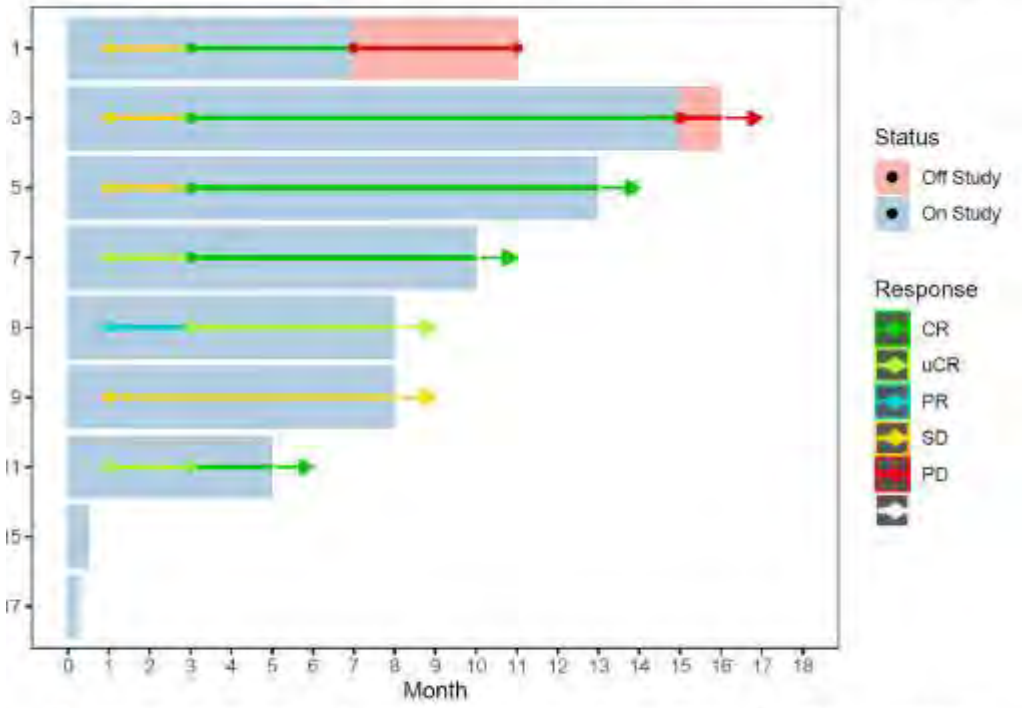
CAR-T CNS Lymphoma

- Proof of concept n=9
- CR 86%
- No increased signal for ICANS/CRS

Figure 1. Swimmer Plot of Response to Axi-cel Over Time

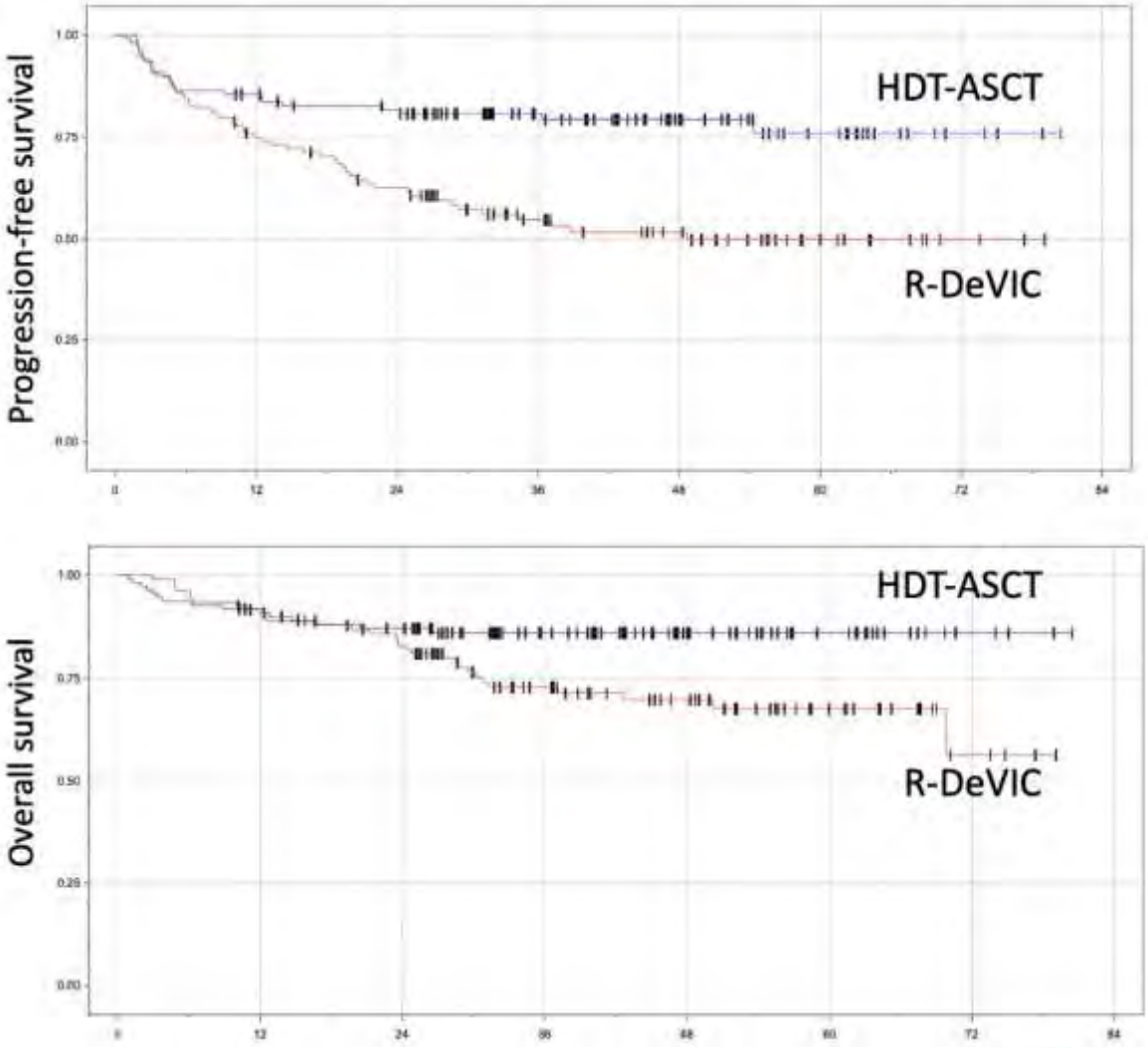


CR: complete response; uCR: unconfirmed complete response; PR: partial response; SD: stable disease (SD); PD: progressive disease

Jacobsen et al, abstract 440,12/11/22

Consolidation CNS Lymphoma

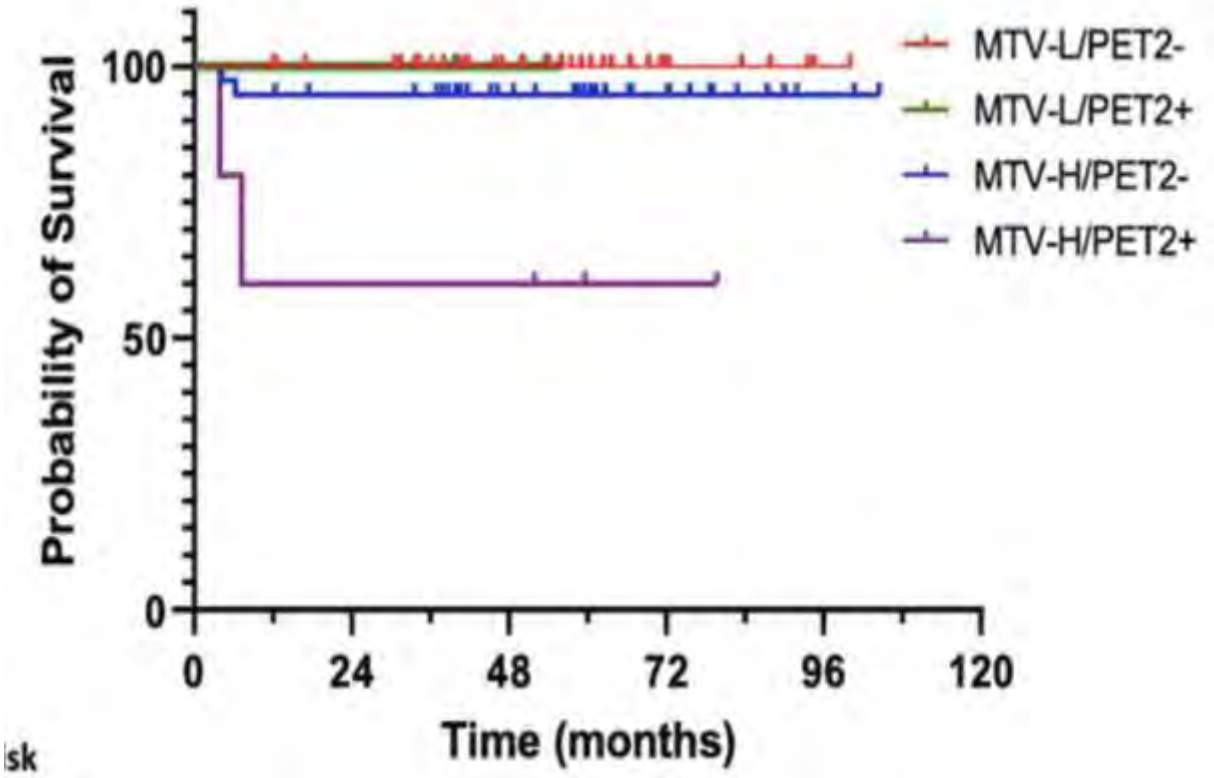
- Ph3 RCT
- MATRix induction
  - 25% did not proceed due to toxicity
  - 10% disease progression
- Response to MATRix
  - 69% ORR
  - 27% CR



Illerhaus et al, LBA-3, 12-13-2022

Hodgkin Lymphoma

- Early stage, bulky cHL
- 117 pts randomized to 4 arms:
  - All contained Bv-AVD x 4 cycles
  - 3 arms with XRT, 1 without



Stuver et al, abstract *Blood* (2022) 140 (Supplement 1): 1756–1758