Safety Modeling and Profiling, Immune-Related Adverse Events: Computational Science in Immuno-Oncology

Marcelo C Pasquini, MD, MS

Senior Scientific Director, CIBMTR

Professor of Medicine, Medical College of WI

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CELLULAR IMMUNOTHERAPY DATA RESOURCE

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The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the National Marrow Donor Program® (NMDP)/Be The Match® and the Medical College of Wisconsin (MCW).

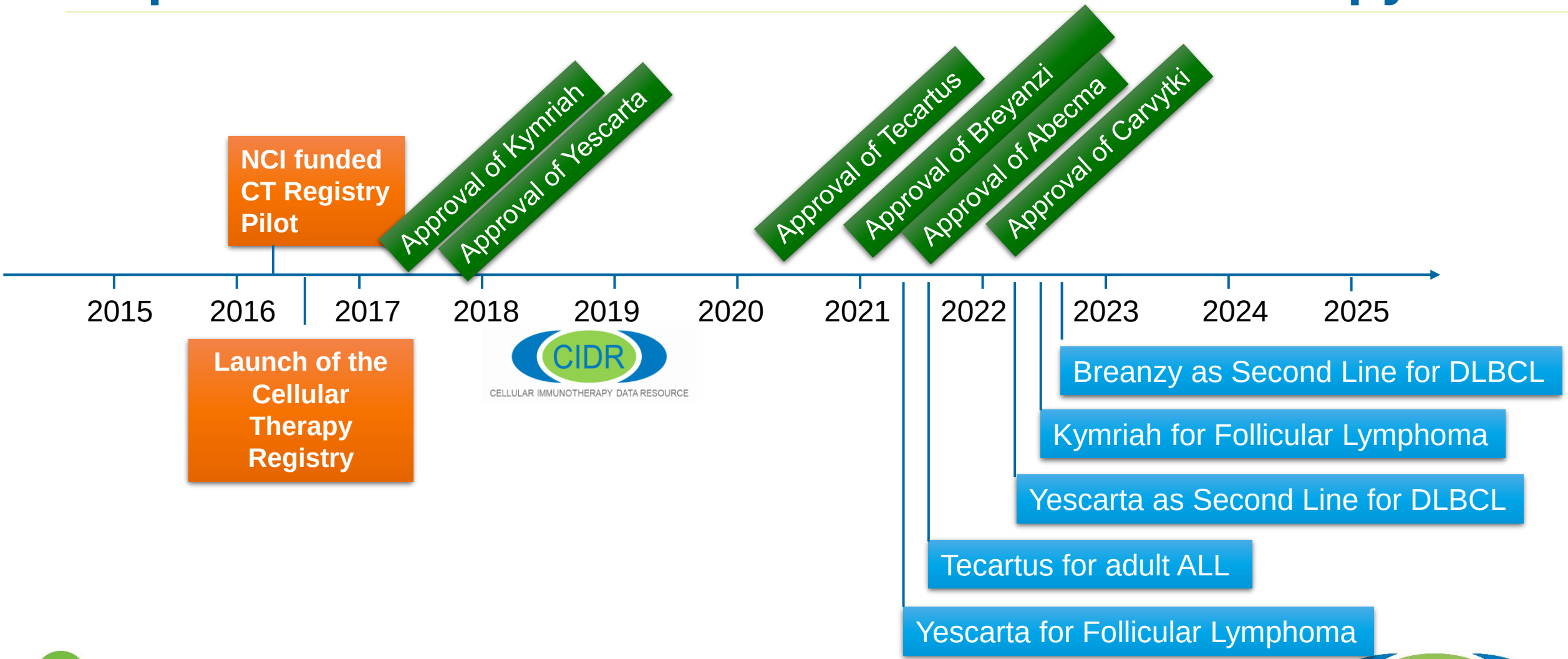
Disclosures

- Marcelo C Pasquini, MD, MS
- Research Support: BMS, Janssen, Kite Pharma, Novartis
- Honoraria: Kite/Gilead Brazil

Outline

- Development of the infrastructure to capture data on cellular immunotherapy and subsequent outcomes
- Numbers and trends of CAR T cells in the US
- Review of CAR T cell specific outcomes and analysis of these outcomes.

The Development of the Registry Parallel to the Expansion of the Field of Cellular Immunotherapy



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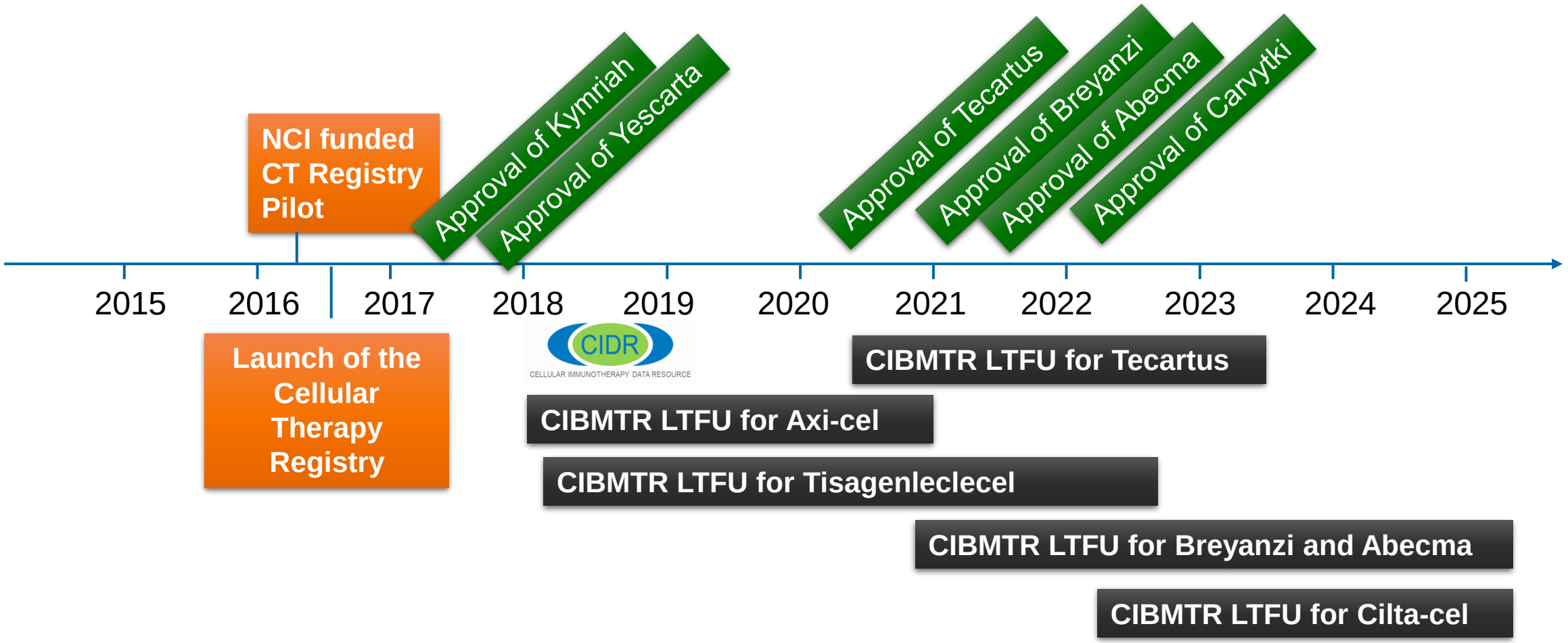
Timeline and Milestones of CT Registry



CAR T cell Post Approval Studies for LTFU

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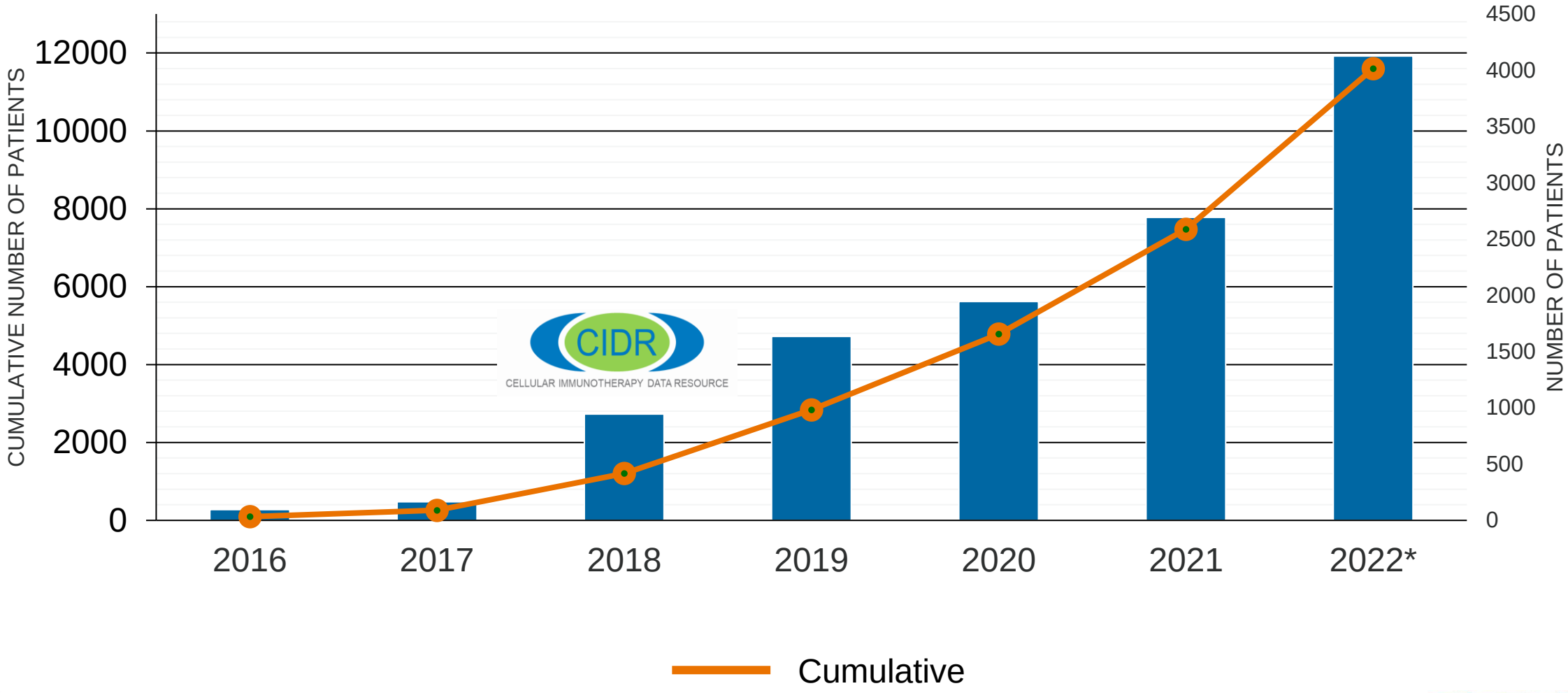
Project	Sponsor	Objective	Timeline/Duration
Yescarta LTFU (Axicabtagene ciloleucel)	**Kite**	Safety and efficacy outcomes (PASS) **N=1,800** (Current 1500 LBL, 300 FL) **Diseases: DLBCL (1500), FL (300)**	**07/2018** **3** years of accrual **15** years of follow up
Kymriah LTFU (Tisagenlecleucel)	**Novartis**	Safety and efficacy outcomes (PASS) **N=2,800** (*Current N=2500*) **Diseases: DLBCL (1500), ALL (1000), FL (300)**	**08/2018** **5** years of accrual **15** years of follow up
Breyanzi LTFU (Lisocabtagene maraleucel)	**BMS**	Safety and efficacy outcomes (PASS) **N=1,200** (Current N=660) **Disease: DLBCL (2nd line N=200)**	**02/2021** **5** years **15** years of follow up
Abecma LTFU (Idecabtagene vecleucel)	**BMS**	Safety and efficacy outcomes (PASS) **N=1,000** (Current N=1000) **Disease: Multiple Myeloma**	**03/2021** **3** years **15** years of follow up
Tecartus (Brexucatagene autoleucel)	**Kite**	Safety and efficacy outcomes (PASS) **N=1000** (Current, MCL N=500, ALL N=250) **Disease: Mantle Cell Lymphoma (500), ALL (500)**	**07/2020** **3** years **15** years of follow up
Carvytki Ciltacabtagene autoleucel	**Janssen /Legend**	Safety and efficacy outcomes (PASS) **N=1500** (Current N=500) **Disease: Multiple Myeloma**	**03/2022** **3** years **15** years of follow up

Number of CAR T cell infusions: 2016-2022 (11,603 patients and 12,098 infusions)



*Data Incomplete for 2022

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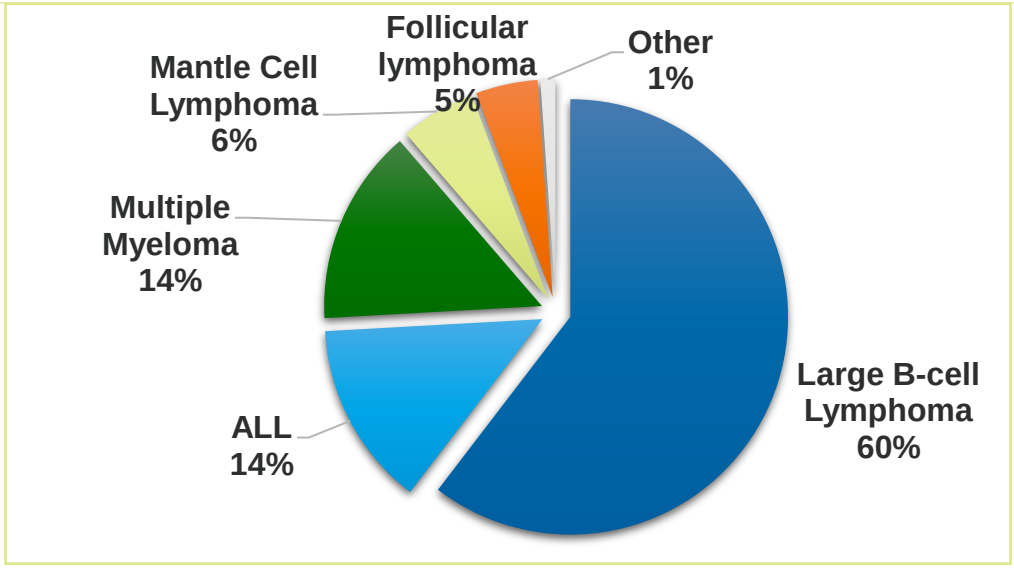
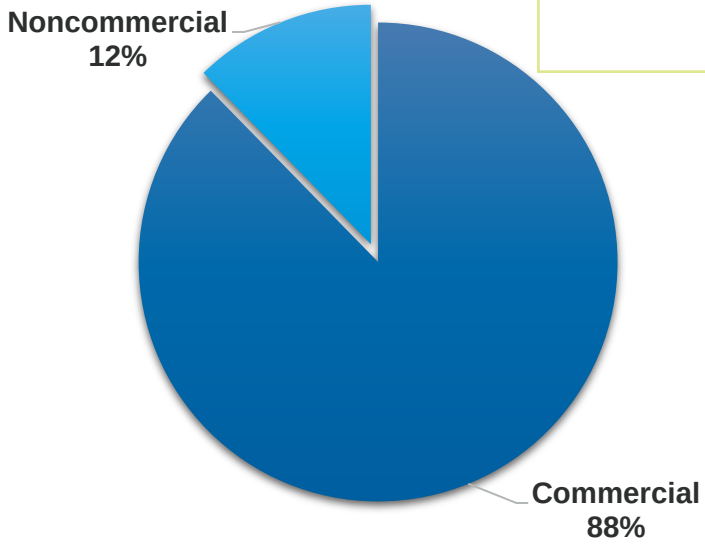
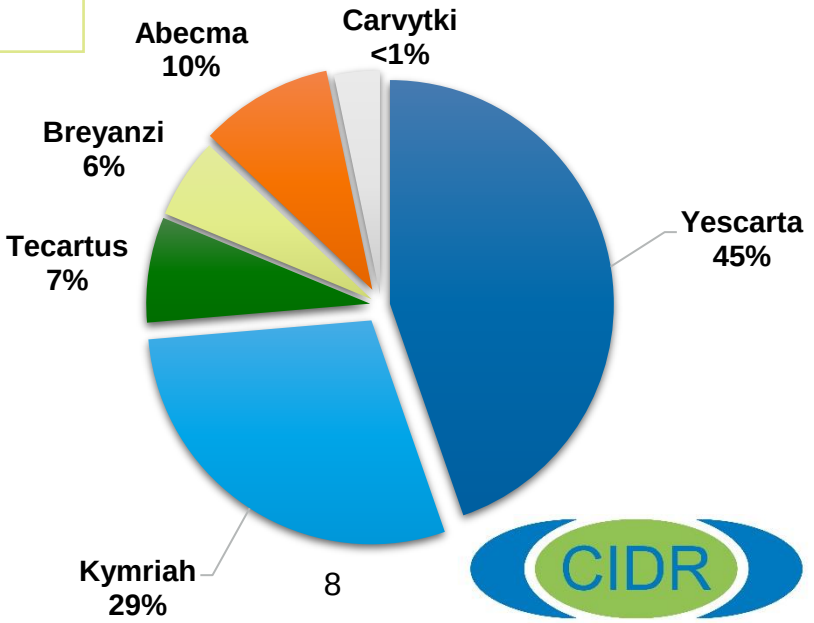
CAR T Cell Indications: 2016-2022 (N= 11,603)







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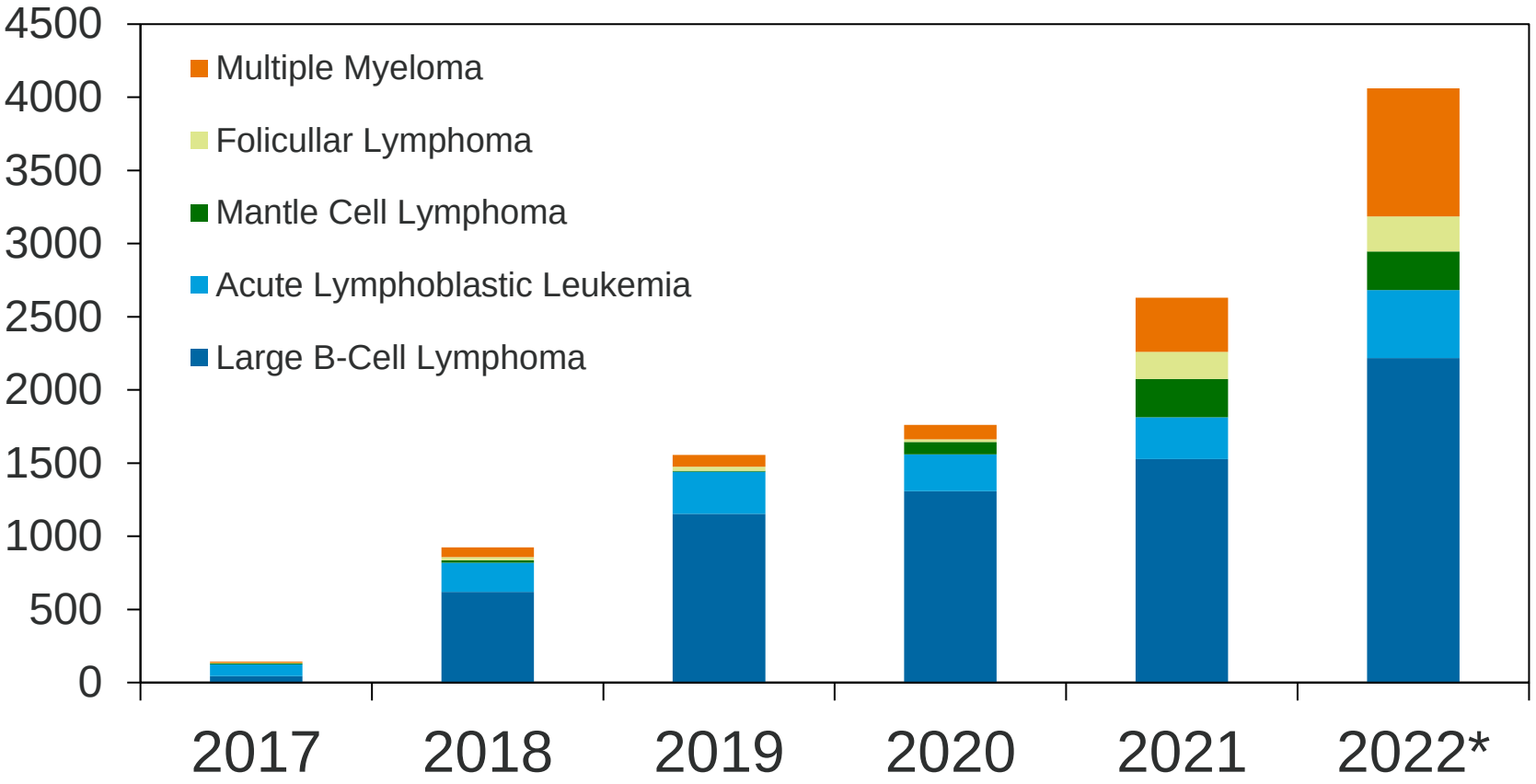
CAR T cell Indications Annually: 2017-2022



Use by indication (2022)

- Large B-cell lymphoma
  - ~2,200 patient/year
- ALL
  - ~ 460/year
- Multiple Myeloma
  - ~900/year
- Mantle Cell
  - ~260/year
- Follicular Lymphoma
  - ~240/year

*Data incomplete

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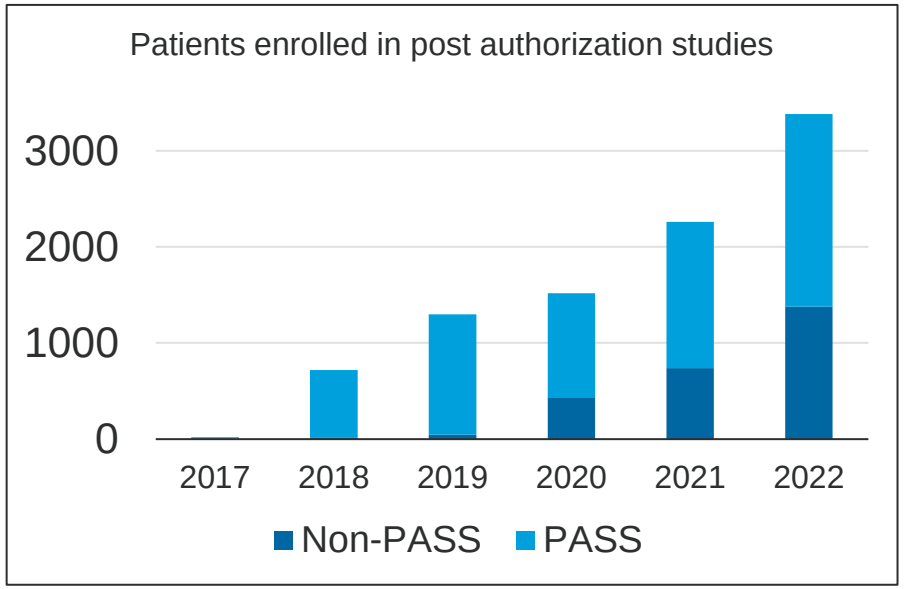
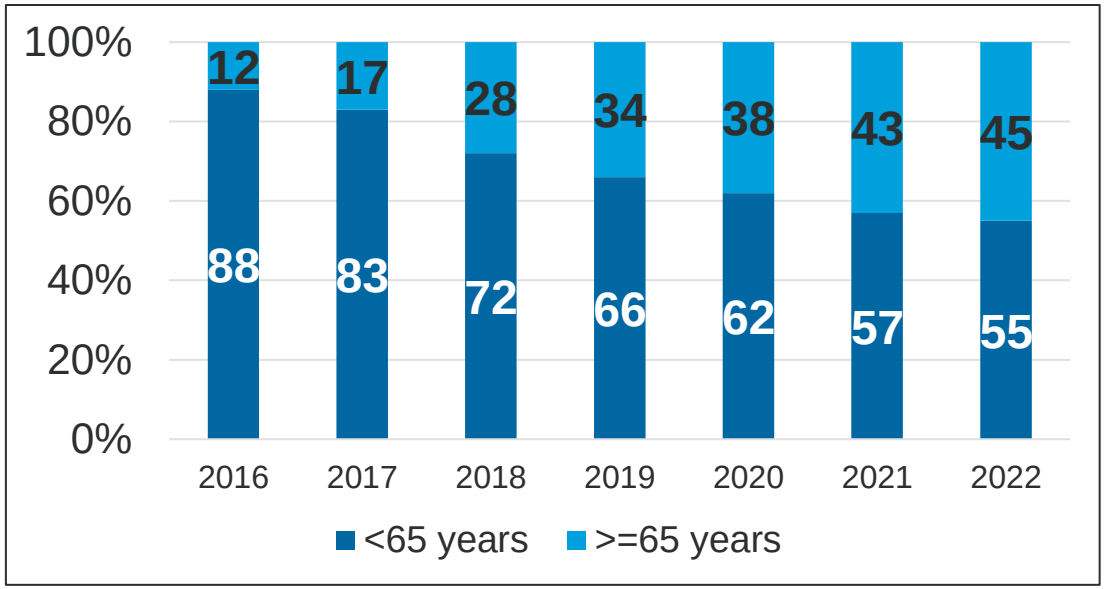
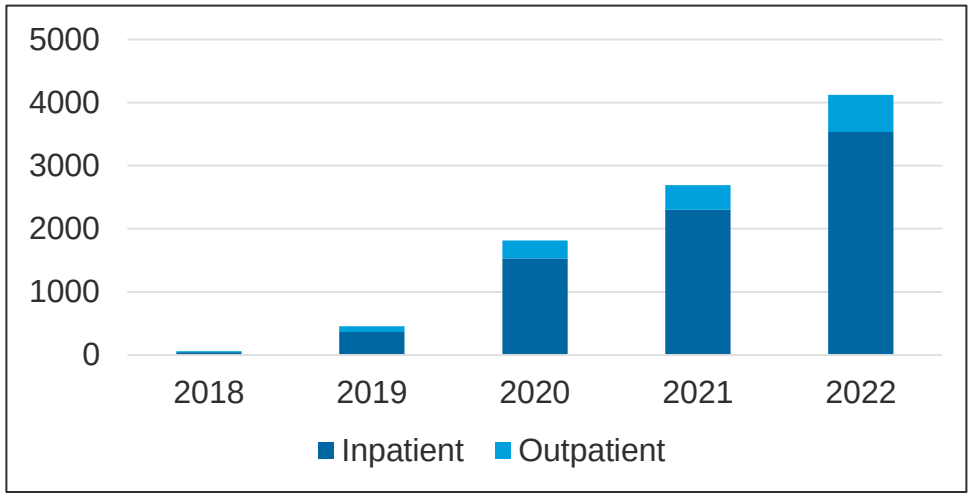
Pattern Changes over time







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CRS Toxicities by Organ System

Neurologic

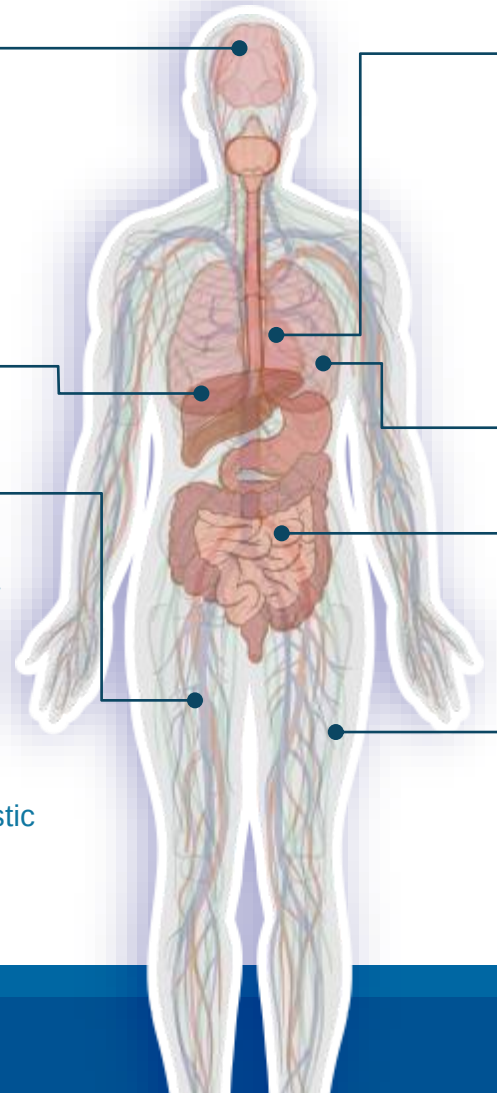
- Headaches
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial Nerve palsy
- Seizures

Hepatic

- Transaminitis
- Hyperbilirubinemia

Hematologic

- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile Neutropenia
- Lymphooenia
- B-Cell Aplasia
- Elevated D-Dimer
- Hypofibrinogenemia
- Dissembled Intravascular Coagulation
- Hemophagocytic Lymphohisticyclosis
- Prolonged Prothrombin time
- Prolonged Activated Partial Thromboplastic time



Cardiovascular

- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fracture
- Troponinemia
- QTprolongation

Pulmonary

- Tachypnea
- Hypoxia

Gastrointestinal

- Nausea
- Emesis
- Diarrhea

Musculoskeletal

- Myalgias
- Weakness
- Elevated creatine kinase

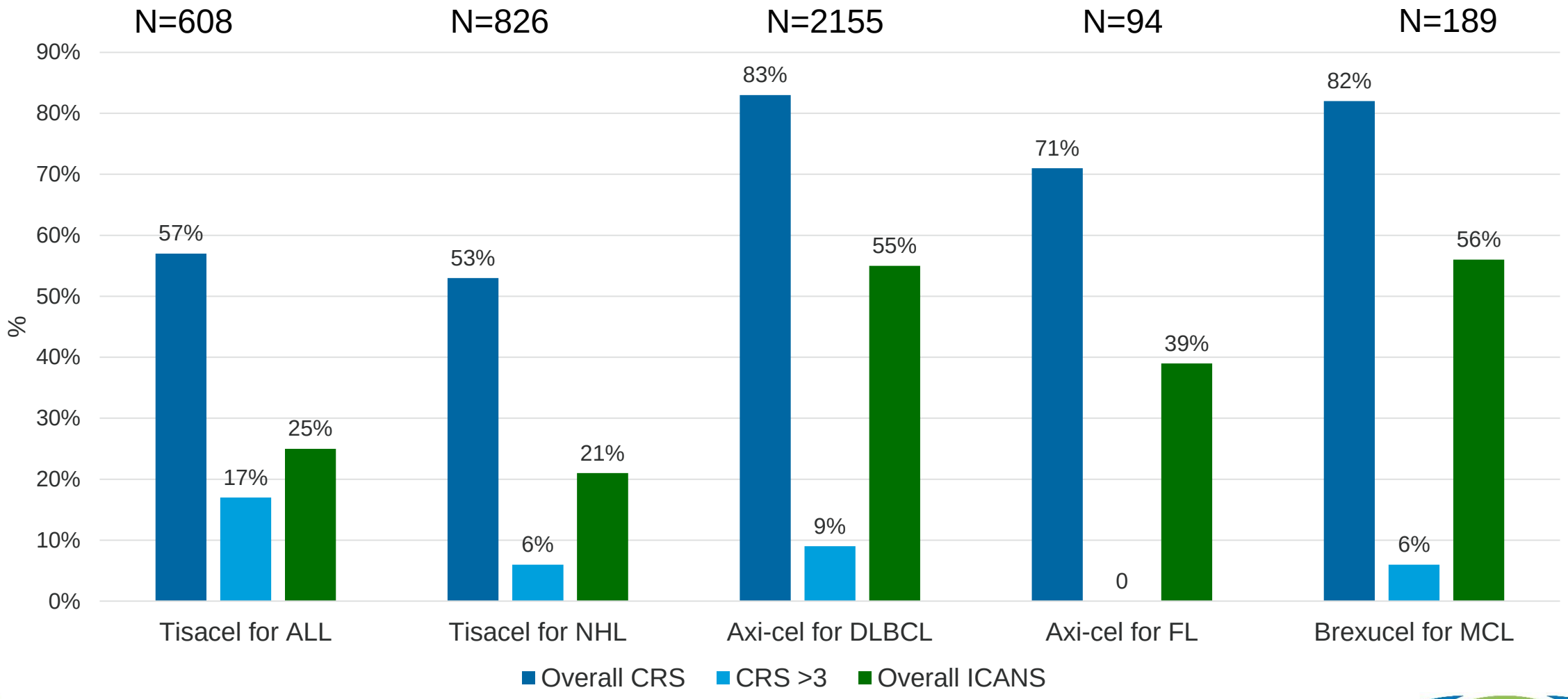
Constitutional

- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgais

Renal

- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

CRS and ICANS by Different Indications and Products (N=3872)



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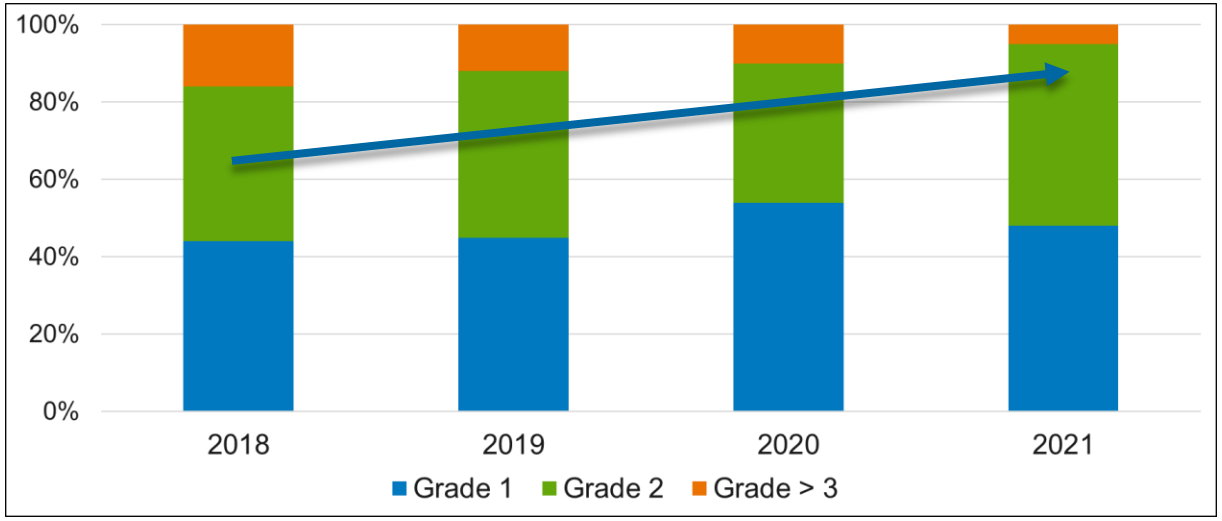
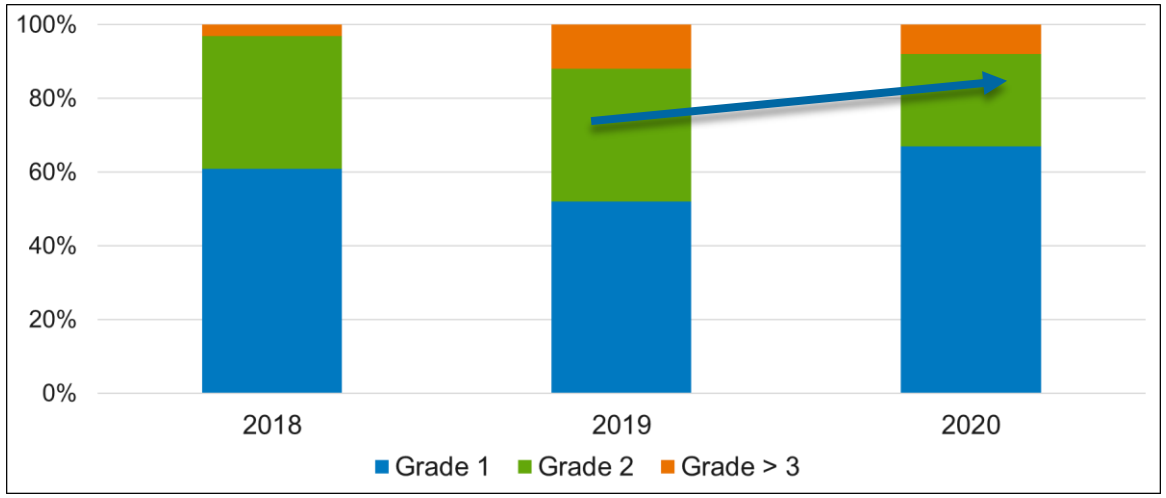
Patterns of care: CRS grade by year

Axicabtagene ciloleucel for DLBCL

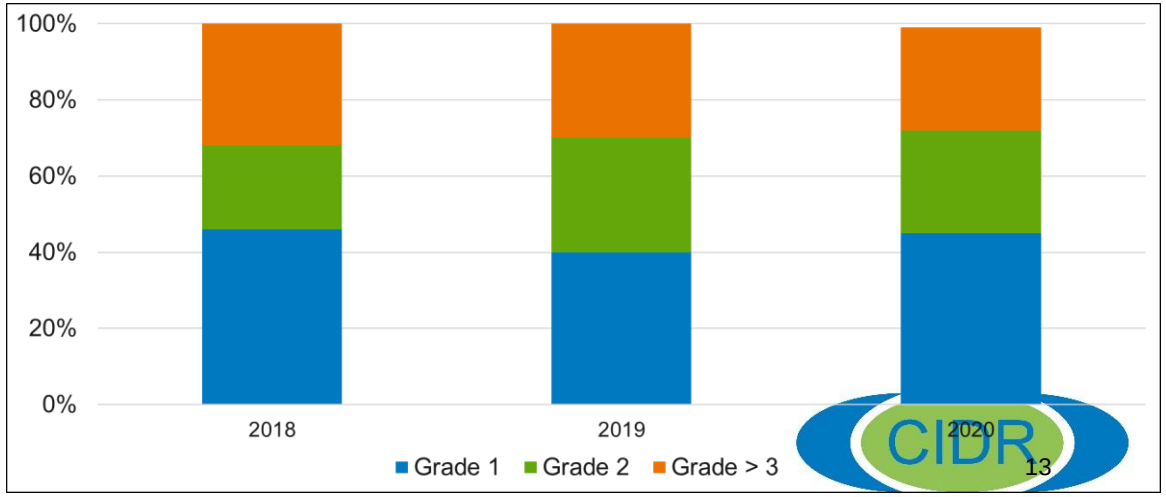


- Reduction in the proportion of patients with CRS Grade ≥3 with time among patients with lymphoma
- The same is not seen with ALL, however the median age of recipients of tisagenlecleucel increased from 12 to 17 years from 2018 to 2020

Tisagenlecleucel for DLBCL



Tisagenlecleucel for ALL



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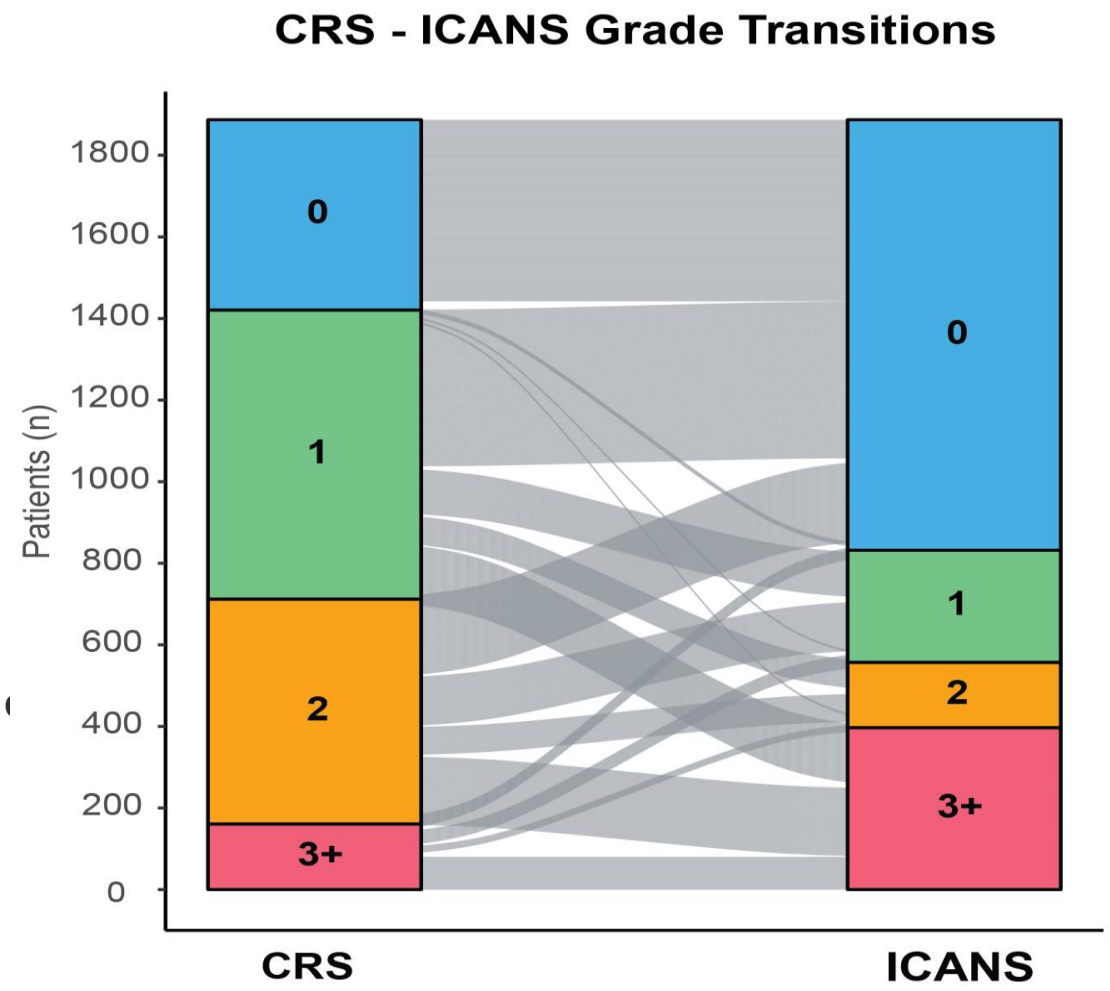
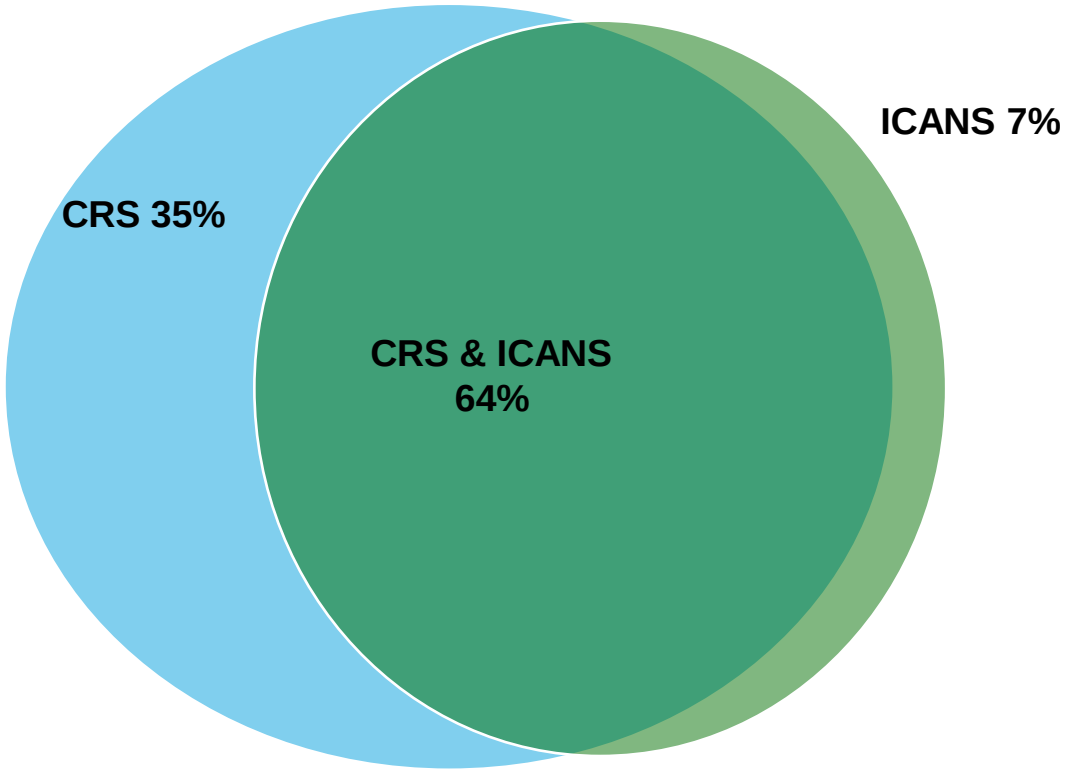
Neurologic Symptoms and Relationship between ICANS and CRS





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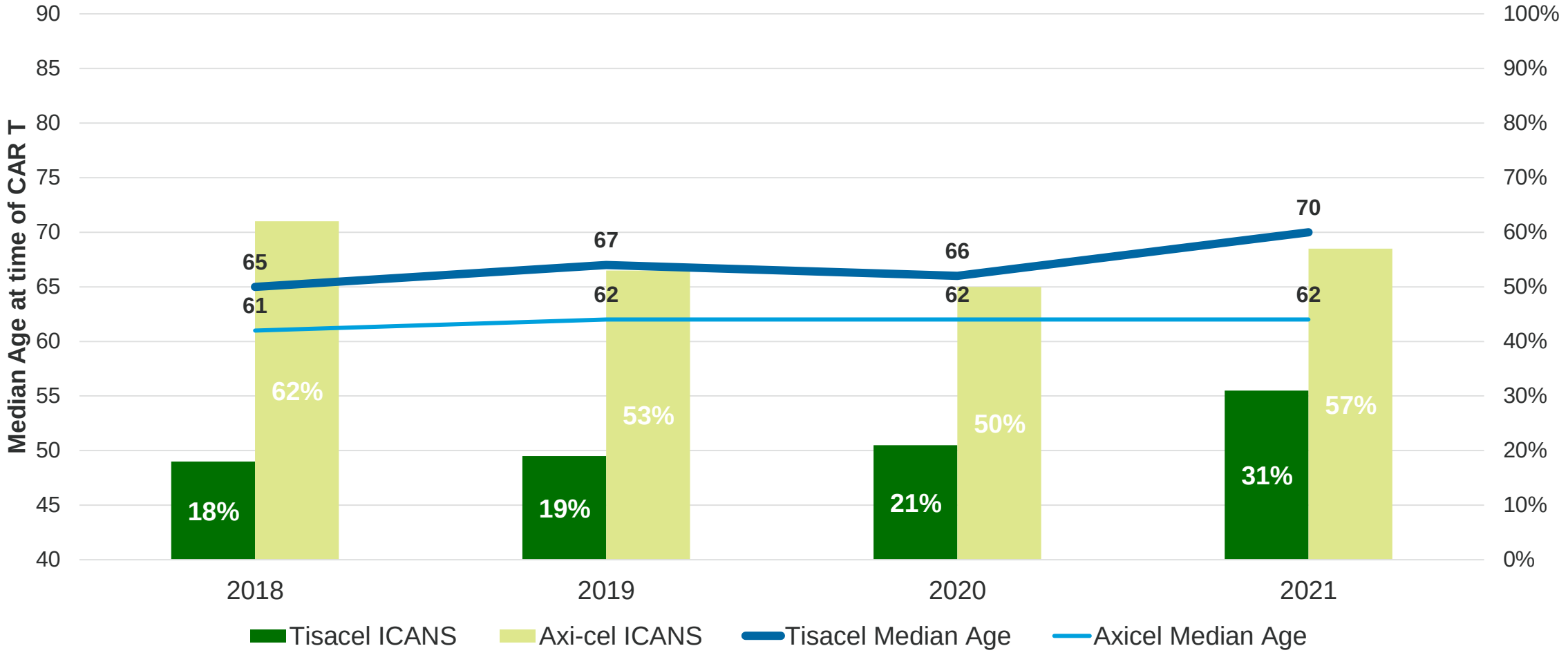
Patterns of care: median age and overall ICANS rates by year for Tisacel and Axi-cel for NHL



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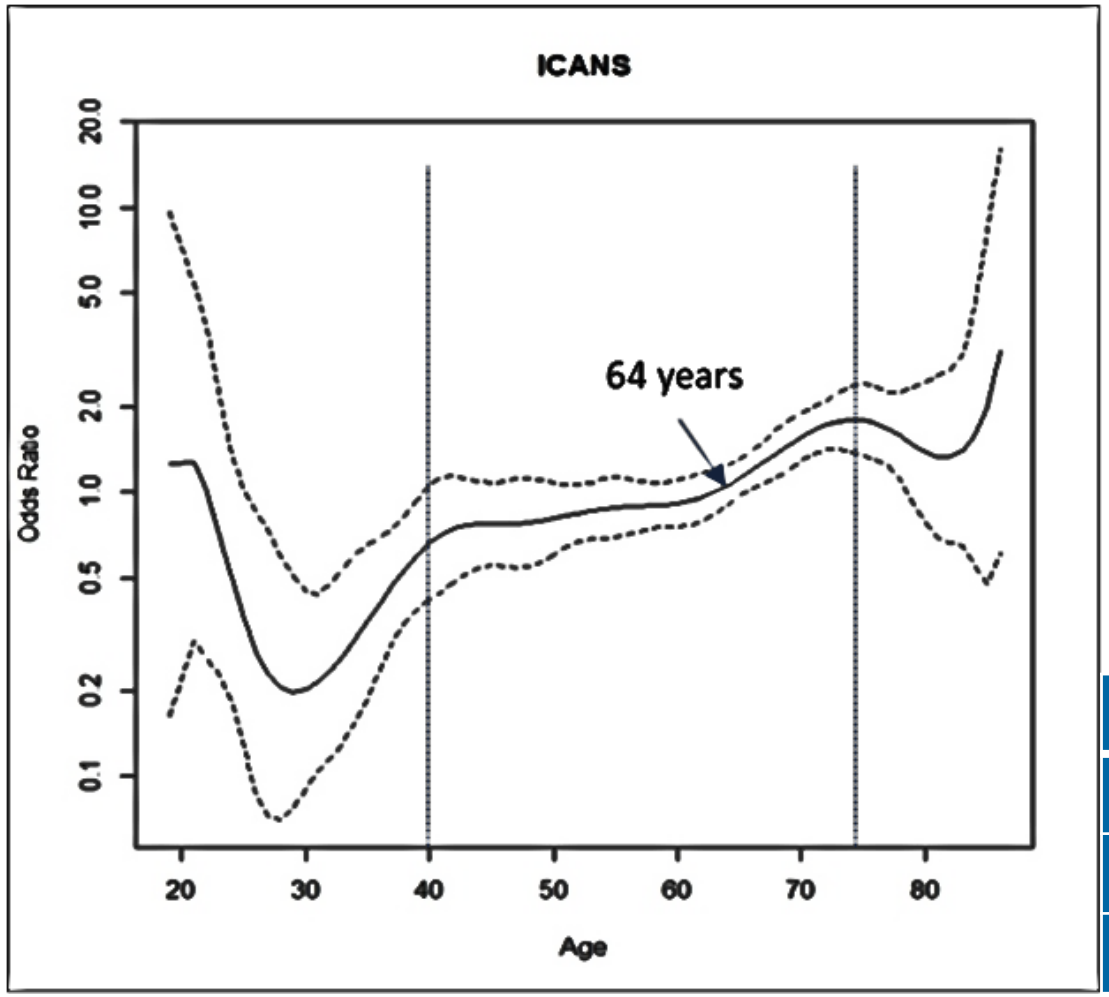
Impact of Age on Neurotoxicity: CAR T cell for lymphoma (DLBCL)



- Increase in age was associated with increase in the incidence of ICANS
- Age 64 years was the cut point associated with higher risk for ICANS

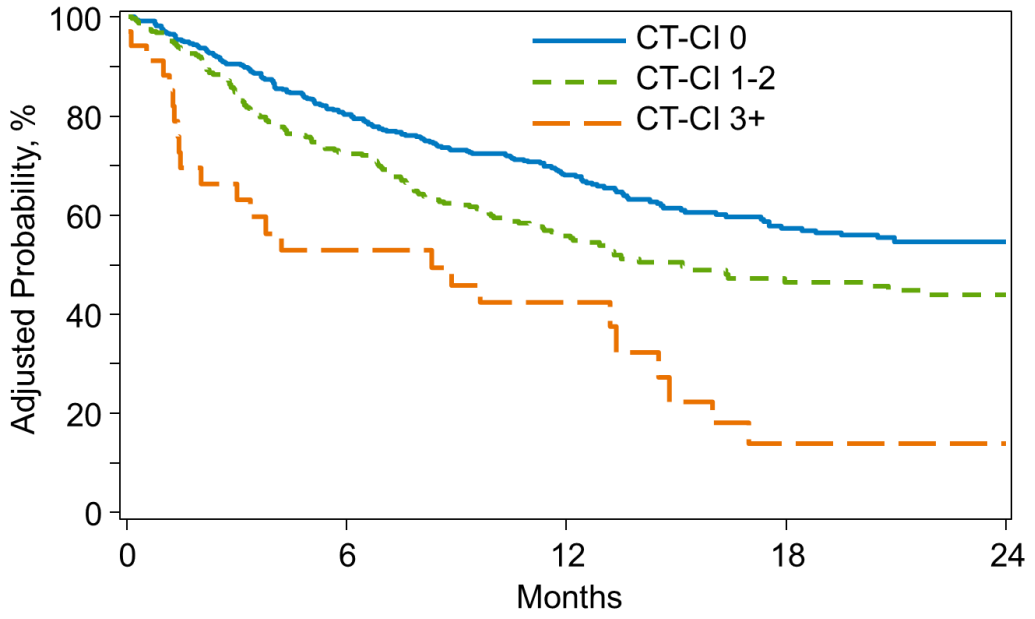
ICANS	N	OR	95% CI	p-value
Age group				
40 <=age <=64	944	1.0	-	<.0001
64 <age <=75	693	1.65	1.33-2.05	<.0001

Mirza AS et al, ASH 2022

Development of a comorbidity score for CAR T Cells prior to LBCL

Comorbidity	N=951	HR	Score
Arrhythmia, any history	62	0.990	
Cardiac, any history	111	0.969	
Cerebrovascular disease, any history	25	1.167	1
Diabetes requiring non-diet treatment, in the last 4 week	139	1.199	1
Heart valve disease	18	0.678	
Hepatic (mild), any history or at the time of infusion	80	1.480	1
Hepatic (moderate/severe), any history or at the time of infusion	19	3.839	3
Infection requiring antimicrobial treatment, continuation after day 0	32	1.945	2
Psychiatric disturbance requiring consult/treatment, in the last 4 weeks	169	0.867	
Pulmonary (moderate), at the time of infusion	141	1.027	
Pulmonary (severe), at the time of infusion	116	1.277	1
Renal (moderate/severe), at the time of infusion or prior renal transplant	18	1.273	1
Rheumatologic, any history	29	0.917	
Solid tumor (except non-melanoma skin cancer), any history	57	0.959	
BMI<20	70	1.387	1
BMI 30-35	149	0.874	
BMI >35	86	0.914	

Overall Survival by CT-CI (validation set)



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Greenbaum U et al, ASH 2022

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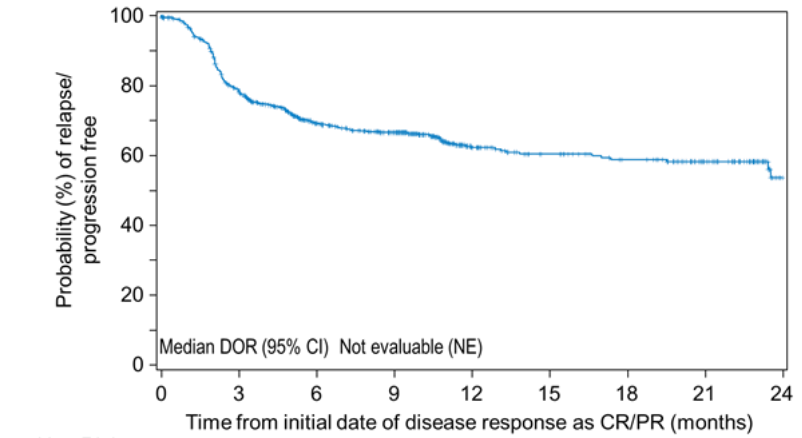
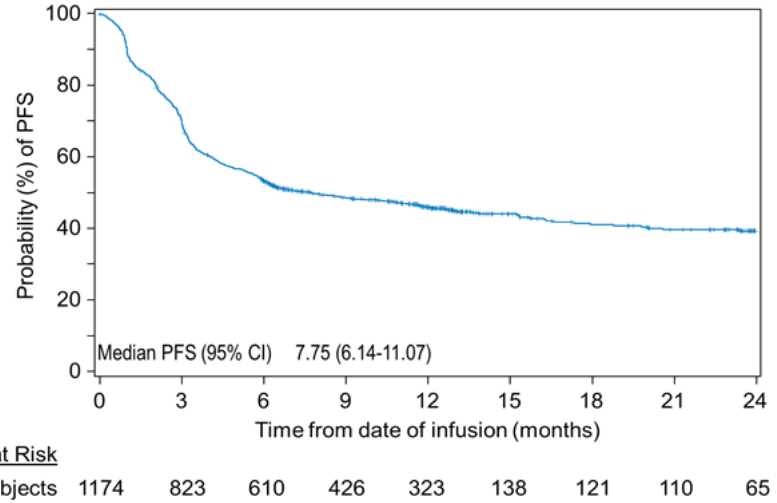
Comparable data between the CIBMTR and the pivotal trials: Axi-cel

Axi-cel PASS - CIBMTR



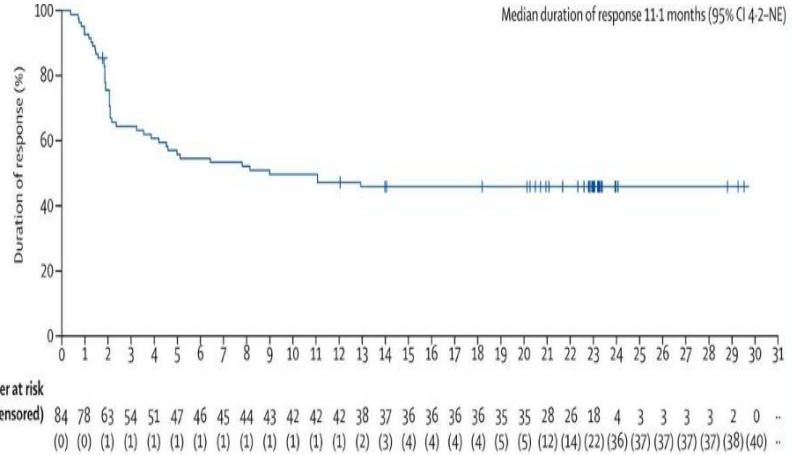
Patients who did not achieve CR/PR as best response during the follow-up period were excluded.

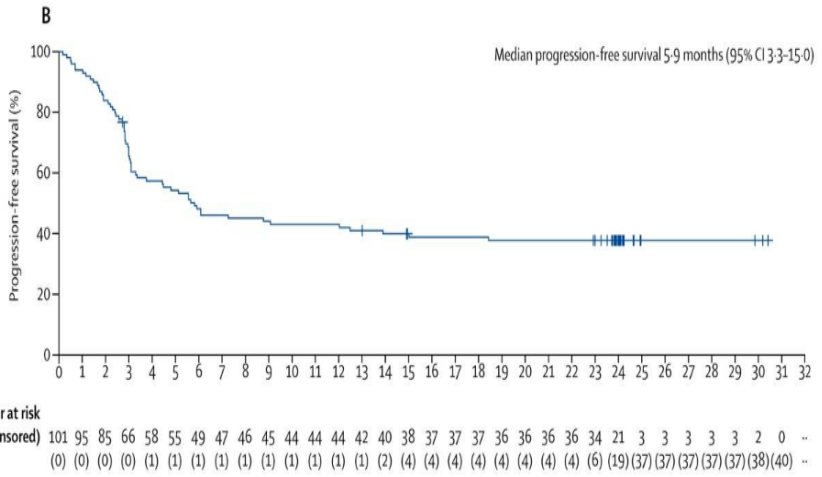


Duration of response

Progression-free Survival

Axi-Cel Zuma-1 LTFU





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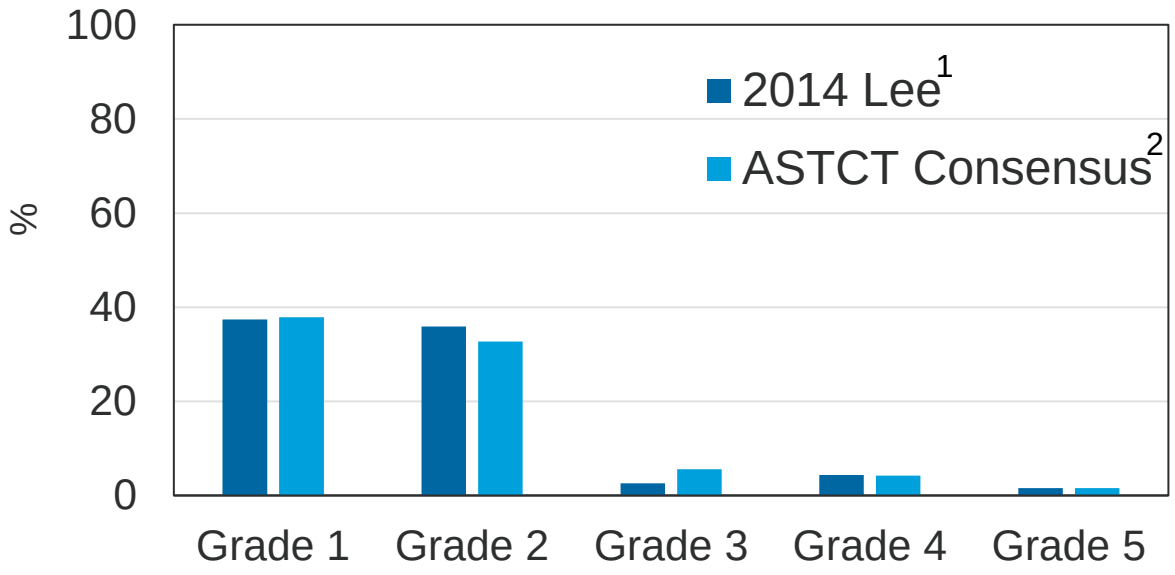
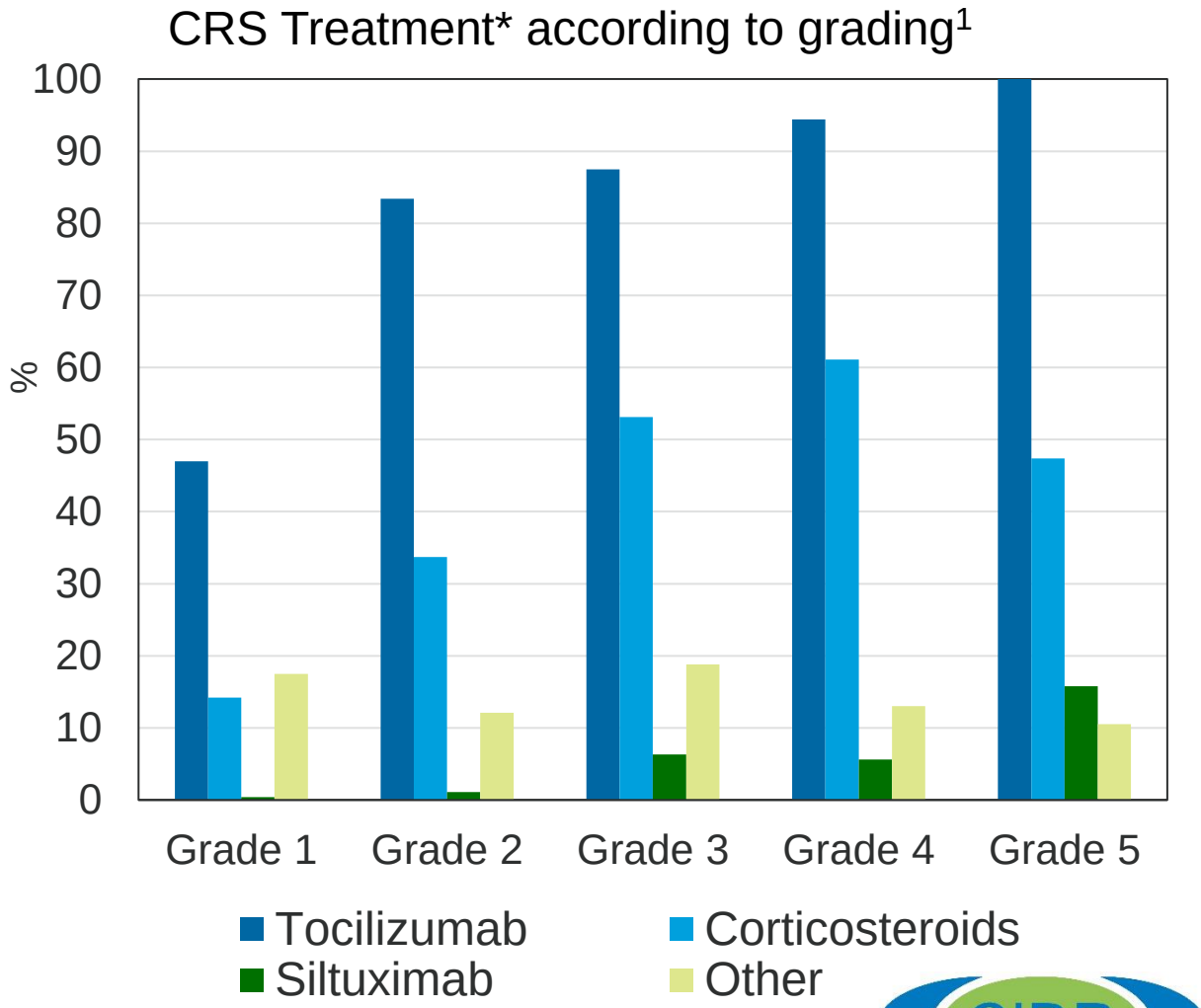
CRS Grading and Treatment Patterns after Axicabtagene Ciloleucel (N=1,223)

Characteristic	Total
Any CRS / Grade ≥3 [1]	82% / 9%
Time to CRS, median (range) in days	4 (1-28)
CRS resolved by day 14 post Axi-Cel	89%
Duration of CRS, median in days	7





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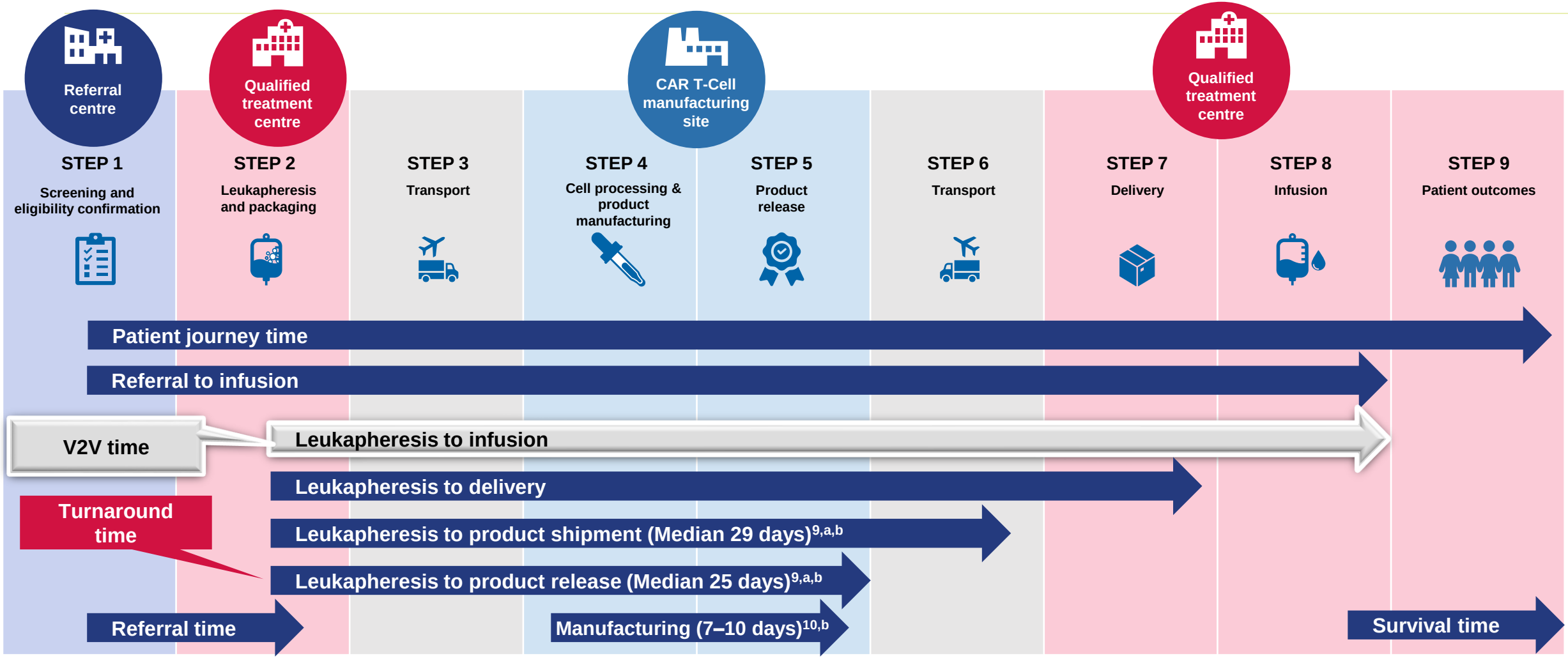
Patient journey and considerations for analyses of outcomes



[a] Values from initial European manufacturing experience which included 2 manufacturing sites (The Netherlands for processing and cryopreservation of PBMCs, transported to a US facility for CAR T-cell manufacturing, transported back to the Netherlands for quality release). [b] These timings are based on manufacturing of axicabtagene ciloleucel.
CAR, chimeric antigen receptor; V2V, vein-to-vein.

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Baseline Characteristics by Vein-to-Vein Time

	Vein-to-Vein Time		
	<28 Days n=697	≥28 to <40 Days n=533	≥40 Days n=153
Age ≥65 years at infusion, n (%)	239 (34)	217 (41)	65 (42)
Male sex, n (%)	455 (65)	348 (65)	91 (59)
Black or African American, n (%)	28 (4)	34 (6)	9 (6)
Hispanic or Latino, n (%)	76 (11)	56 (11)	18 (12)
High grade B-cell lymphoma, n (%)	115 (16)	96 (18)	20 (13)
Double/triple hit, n (%)[a]	106 (26)	87 (29)	18 (20)
ECOG PS ≥2 at infusion, n (%)	35 (5)	20 (4)	9 (6)
Chemoresistant prior to infusion, n (%)	469 (67)	355 (67)	101 (66)
No. of prior lines ≥3, n (%)[a,b]	485 (71)	361 (70)	118 (82)
Use of bridging therapy, n (%)[a]	132 (20)	109 (22)	65 (46)
Any comorbidities, n (%)[c,1]	479 (69)	382 (72)	125 (82)
Year of infusion: ≤2018, n (%)	210 (30)	155 (29)	30 (20)
Year of infusion: 2019, n (%)	324 (46)	252 (47)	69 (45)
Year of infusion: 2020, n (%)	163 (23)	126 (24)	54 (35)

- Vein-to-vein times were consistent regardless of disease histology, sex, race/ethnicity, ECOG PS at infusion, or chemosensitivity
- Patients with shorter vein-to-vein times appeared to be younger and less likely to have comorbidities
- Patients with vein-to-vein time ≥40 days were more heavily pretreated and more likely to receive bridging therapy

[a] Percentages were based on non-missing cases. [b] Not including prior transplant. [c] Defined based on the hematopoietic cell transplant-specific comorbidity index.

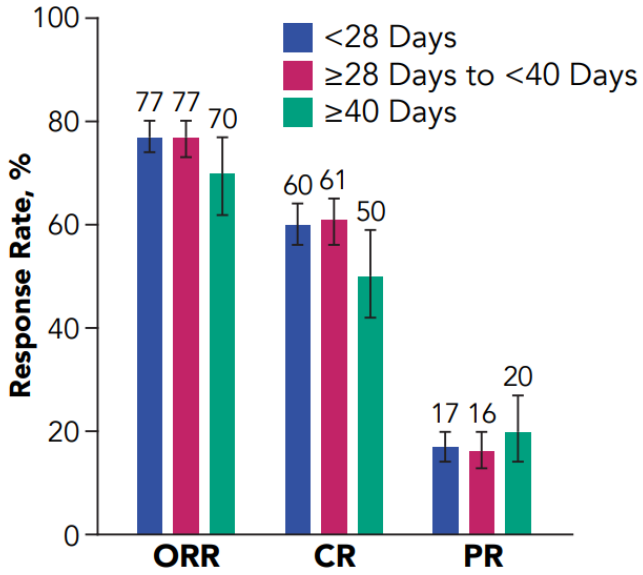
1. Sorror, ML, et al. *Blood*. 2005;106(8):2912-2919.

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

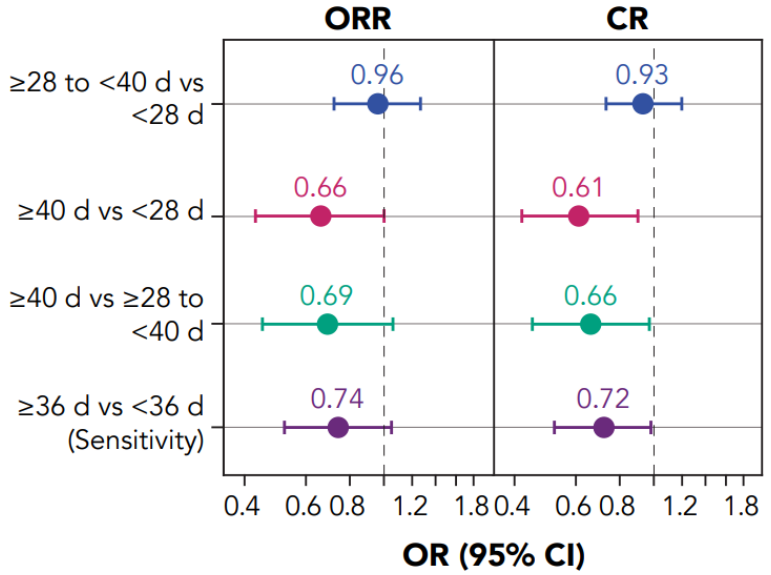
Locke F et al, ASH 2022

Axi-Cel Response Rate and Adjusted Odds Ratios of ORR and CR by Vein-to-Vein Time

Response Rate by Vein-to-Vein Time



Adjusted Odds Ratios for ORR and CR



- With a median follow-up of 24.2 months, CR rates were 60%, 61%, and 50% (ORR 77%, 77%, and 70%) for patients with vein-to-vein time <28 days, ≥28 to <40 days, and ≥40 days, respectively
- After other key prognostic factors were adjusted, patients with vein-to-vein time ≥40 days had a significantly lower CR rate compared with patients with shorter vein-to-vein time
  - ≥40 days versus <28 days: OR, 0.61 (95% CI, 0.42-0.90)
  - ≥40 days versus ≥28 to <40 days: OR, 0.66 (95% CI, 0.45-0.97)

Locke F et al, ASH 2022

Covariates for step-wise selection and multivariable adjustment: age, sex, race, ethnicity, ECOG performance status prior to infusion, comorbidities (pulmonary, cardiac/cerebrovascular/heart valve disease, hepatic, and renal), histologic transformation, disease characteristics at initial diagnosis (double/triple hit, disease stage, elevated LDH and >1 extranodal involvements), chemosensitivity prior to infusion, number of prior lines of therapy, prior HCT, year of infusion, time from initial diagnosis to infusion, and use of bridging therapy.
Axi-cel, axicabtagene ciloleucel; CR, complete response; d, day; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; LDH, lactate dehydrogenase; OR, odds ratio; ORR, objective response rate; PR, partial response.

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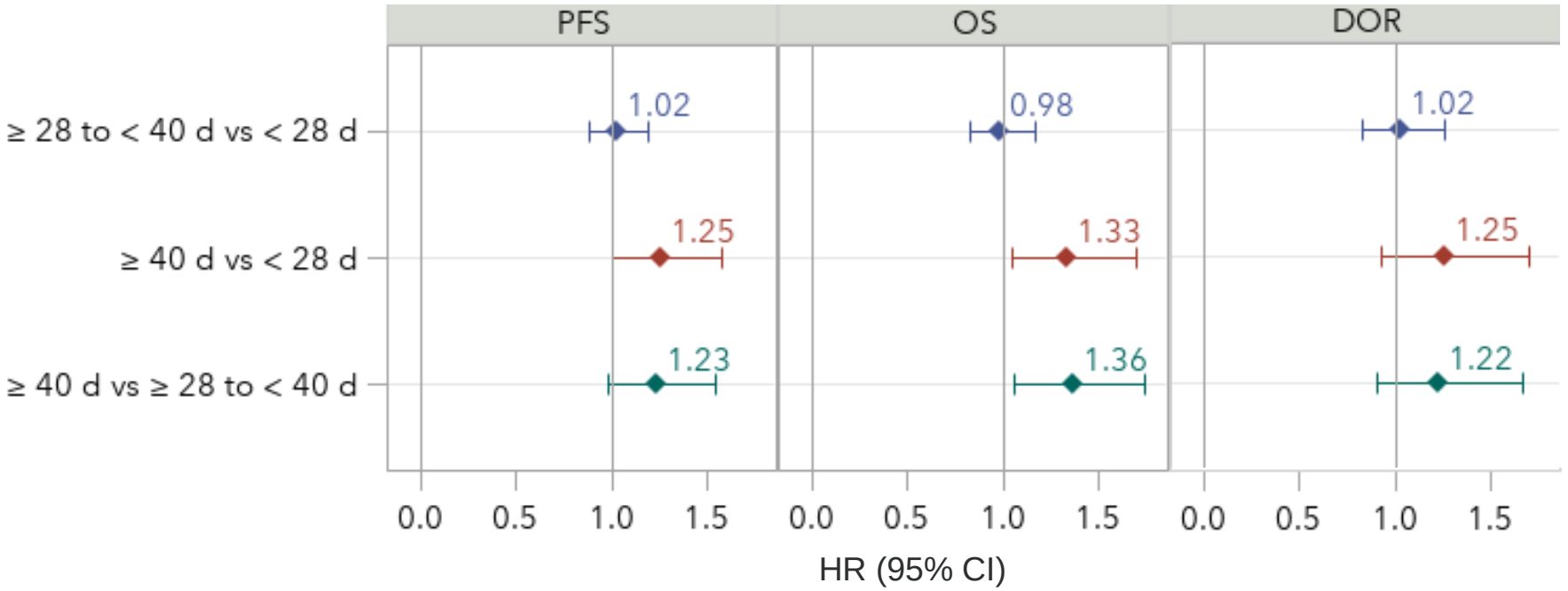
Axi-Cel for DLBCL Adjusted PFS, OS, and DOR by Vein-to-Vein Time



For PFS, subsequent cellular therapy and hematopoietic cell transplantation were censored. Covariates for step-wise selection and multivariable adjustment: age, sex, race, ethnicity, ECOG performance status prior to infusion, comorbidities (pulmonary, cardiac/cerebrovascular/heart valve disease, hepatic, and renal), histologic transformation, disease characteristics at initial diagnosis (double/triple hit, disease stage, elevated LDH and >1 extranodal involvements), chemosensitivity prior to infusion, number of prior lines of therapy, prior HCT, year of infusion, time from initial diagnosis to infusion, and use of bridging therapy.

Axi-cel, axicabtagene ciloleucel; d, day; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplantation; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

Determinants of Decreased CAR T-cell Efficacy in Large B-cell Lymphoma

PATIENT

- High tumor burden, high LDH
- High pretreatment inflammatory markers
- Need for bridging therapy

T-CELLS

- Decreased proportion of CCR7+ (early memory) T-cells in the CAR product
- Slower doubling time *in vitro* (more lines of treatment)
- Insufficient CAR T-cell peak to tumor burden ratio

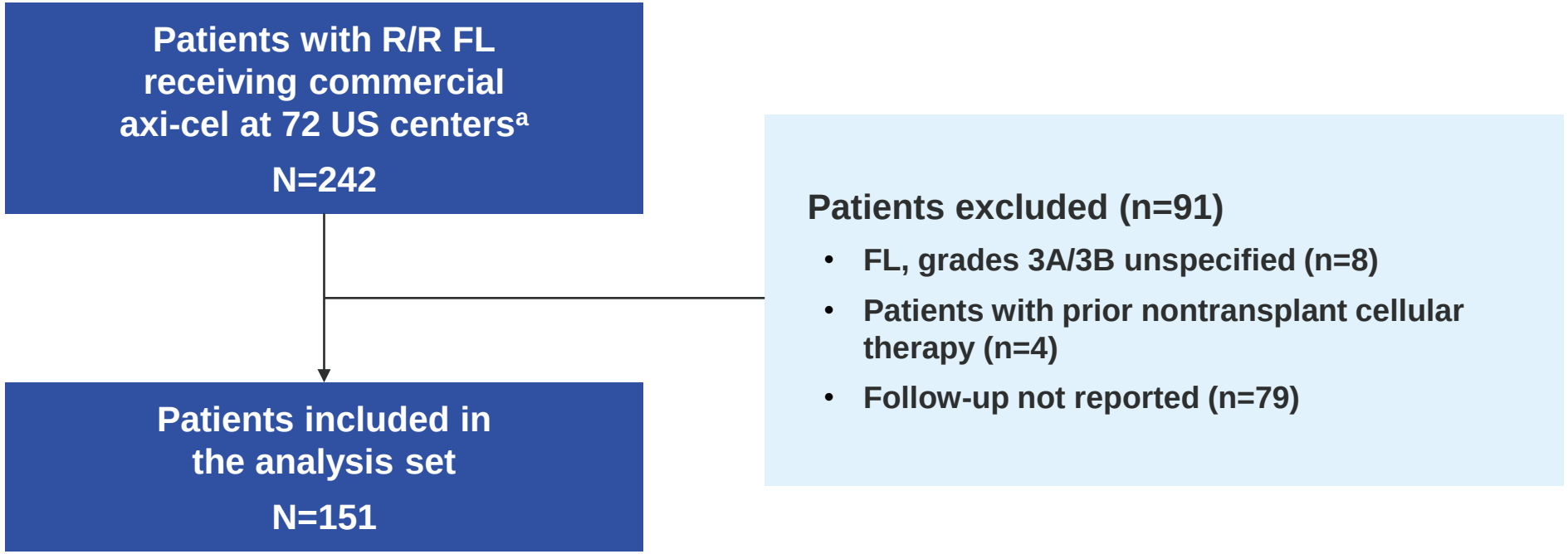
TUMOR

- Resistance mutations (ie CD58)
- High tumor MDSCs
- Low TILs

Courtesy of Dr. Jacobson

PRESENTED BY: Caron Jacobson, MD

Axi-cel for Follicular Lymphoma: Analysis Population



- Data cutoff date: September 23, 2022
- Median follow-up: 6.2 months (95% CI, 6.0-6.3)
- Median time from leukapheresis to infusion was 28 days (IQR, 26-33)

[a] Identified from the CIBMTR registry.

Axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; FL, follicular lymphoma; IQR, interquartile range; R/R, relapsed/refractory; US, United States.

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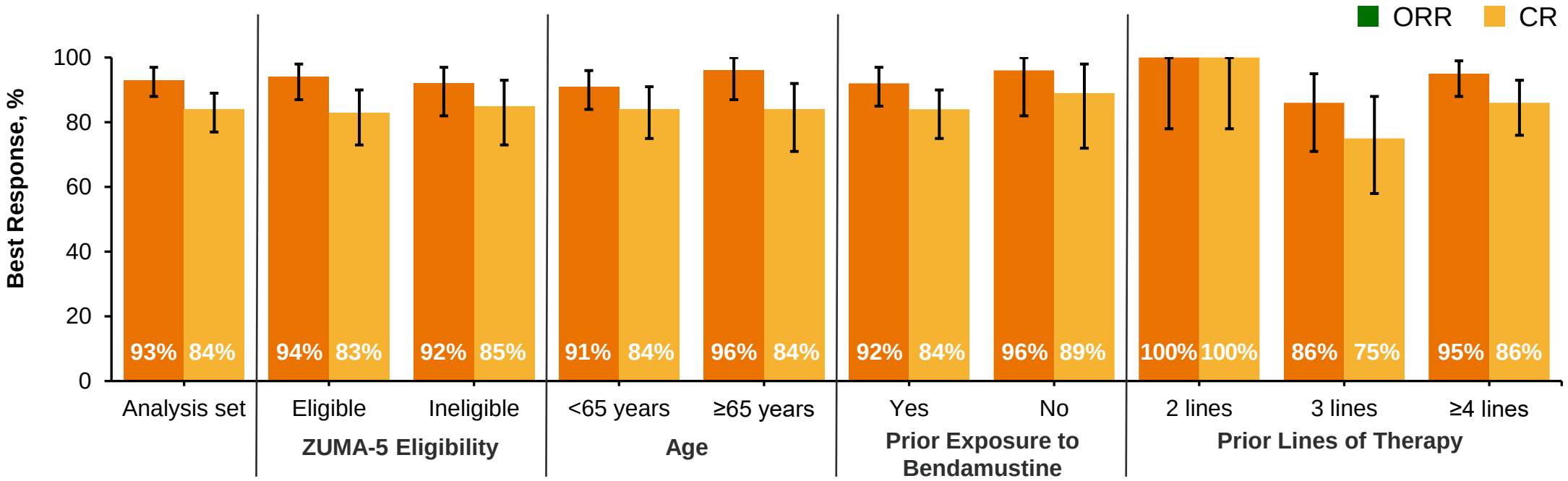
Axi-cel for Follcular Lymphoma: Baseline Characteristics for Analysis Set, by ZUMA-5 Eligibility, and by Age

Key Variable of Interest	Enrolled Patients in Analysis Set N=151	ZUMA-5 Eligibility[a]		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Median age (IQR), years	61 (55-68)	60 (54-68)	62 (55-69)	57 (51-61)*	70 (68-74)*
Male sex, n (%)	94 (62)	50 (56)*	44 (72)*	66 (69)*	28 (50)*
White race, n (%)	132 (87)	80 (89)	52 (85)	82 (86)	50 (89)
Hispanic ethnicity, n (%)	12 (8)	8 (9)	4 (7)	8 (9)	4 (7)
ECOG PS 0-1 at infusion,[b] n (%)	143 (98)	87 (100)	56 (95)	88 (97)	55 (100)
Clinically significant comorbidities,[c] n (%)	113 (75)	56 (62)*	57 (93)*	69 (73)	44 (79)
Disease stage at diagnosis[d]: III-IV, n (%)	79 (76)	46 (78)	33 (73)	57 (78)	22 (71)
Median no. of lines of prior therapies (IQR)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
Prior bendamustine,[e] n (%)	107 (79)	62 (78)	45 (80)	69 (79)	38 (79)
Prior ASCT, n (%)	20 (13)	12 (13)	8 (13)	16 (17)	4 (7)
Elevated LDH prior to infusion,[f,g] n (%)	26 (28)	15 (26)	11 (32)	15 (26)	11 (32)
Chemoresistant prior to infusion,[h] n (%)	101 (80)	61 (82)	40 (77)	65 (78)	36 (84)
Median time from last line of therapy to infusion (IQR), months	7.1 (3.0-19.3)	7.9 (3.1-20.0)	5.8 (3.0-18.8)	5.6 (2.7-11.1)*	13.7 (4.6-25.7)*
Bridging therapy[i]: any type / systemic / radiation, n (%)	12 (9) / 10 (8) / 2 (2)	6 (8) / 5 (6) / 1 (1)	6 (11) / 5 (9) / 1 (2)	7 (8) / 7 (8) / 0	5 (10) / 3 (6) / 2 (4)
Outpatient,[j] n (%)	22 (15)	16 (18)	6 (10)	13 (14)	9 (16)

- Of 151 patients enrolled in the analysis set, 61 (40%) would have been considered ineligible for ZUMA-5
  - Reasons for ineligibility included comorbidities (70%), history of prior malignancy (18%), platelet count <75,000/μL (15%), pleura extranodal involvement (15%), cerebrovascular disease (11%), and ECOG PS ≥2 (5%)

[a] Reasons for ZUMA-5 ineligibility are not mutually exclusive. [b] The remaining 2% pertain to patients with an ECOG PS >1 or missing information.
[c] Comorbidities were defined per the HCT-CI and included a body mass index <20.5 (Sorror ML, et al. *Blood.* 2005;106:2912-2919). [d] Forty-seven patients did not report disease stage at initial diagnosis. [e] Sixteen patients did not report prior bendamustine exposure. [f] Elevated LDH is defined as above the upper limit of normal. [g] Fifty-nine patients did not report LDH prior to infusion. [h] Chemoresistance is defined as patients who had SD or PD prior to infusion. Twenty-five patients did not report chemoresistant status prior to infusion. [i] Nineteen patients did not report the presence or absence of bridging therapy.
[j] Planned number of outpatients.
*P<0.05 per Fisher's exact test.
ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT-CI, hematopoietic cell transplantation-specified comorbidity index; IQR, interquartile range; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease.

Follicular Lymphoma: Overall Response in Analysis Set, by ZUMA-5 Eligibility, Age, Prior Bendamustine Exposure, and Prior Lines of Therapy



No. of patients	138	124	83	73	55	51	85	78	53	46	96	87	27	25	15	15	31	27	75	68
N	148	148	88	88	60	60	93	93	55	55	104	104	28	28	15	15	36	36	79	79

- Among 148 patients evaluable for response, for whom the median follow-up was 6.2 months, **138 patients (93%; 95% CI, 88-97) had an overall response, with 124 patients (84%; 95% CI, 77-89) achieving a CR**
- Overall response was comparable regardless of ZUMA-5 eligibility, age, prior exposure to bendamustine, and prior lines of therapy

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Error bars denote 95% CIs.
CR, complete response; ORR, overall response rate.

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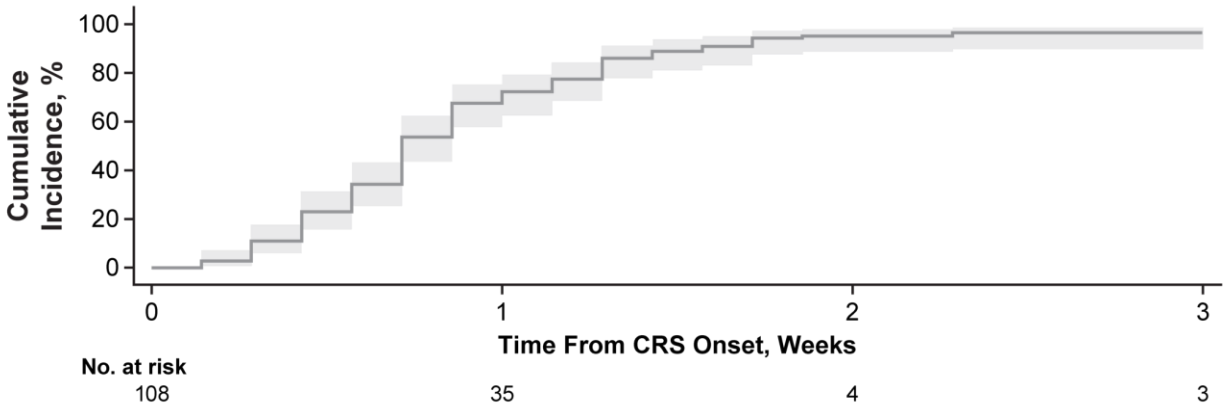
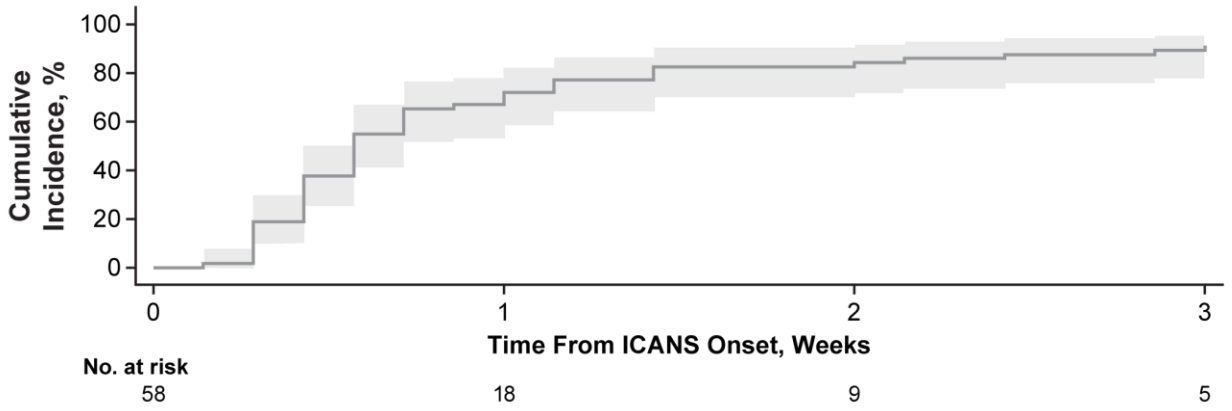
Axi-cel for Follicular Lymphoma: Cumulative Incidence Rate of Any-Grade CRS Resolution and Any-Grade ICANS Resolution in the Analysis Set

Cumulative Incidence of Any-Grade CRS[a] Resolution



Cumulative Incidence of Any-Grade ICANS[b] Resolution



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[a] Among patients experiencing CRS onset within 30 days post-infusion. The date of CRS resolution was not reported for 1 patient.
[b] Among patients experiencing ICANS onset within 100 days post-infusion.
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

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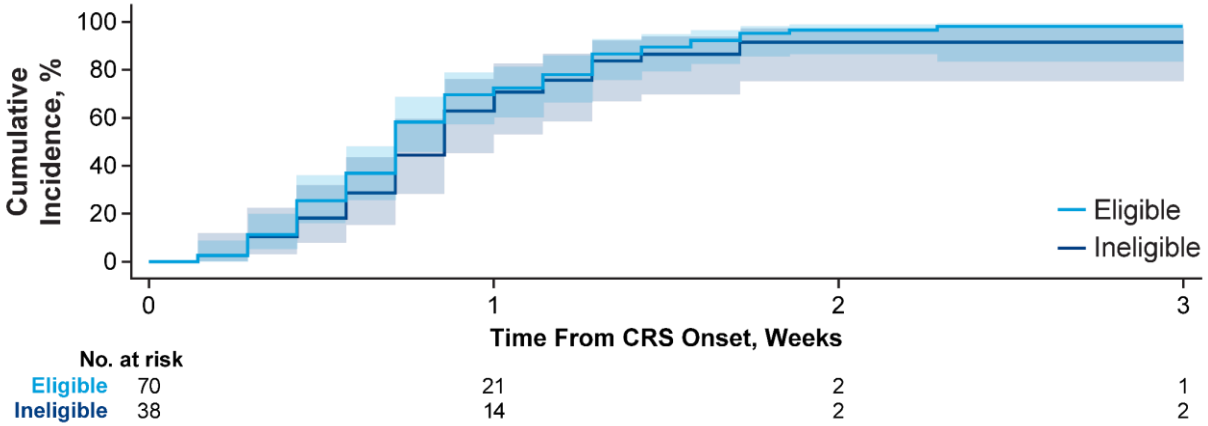
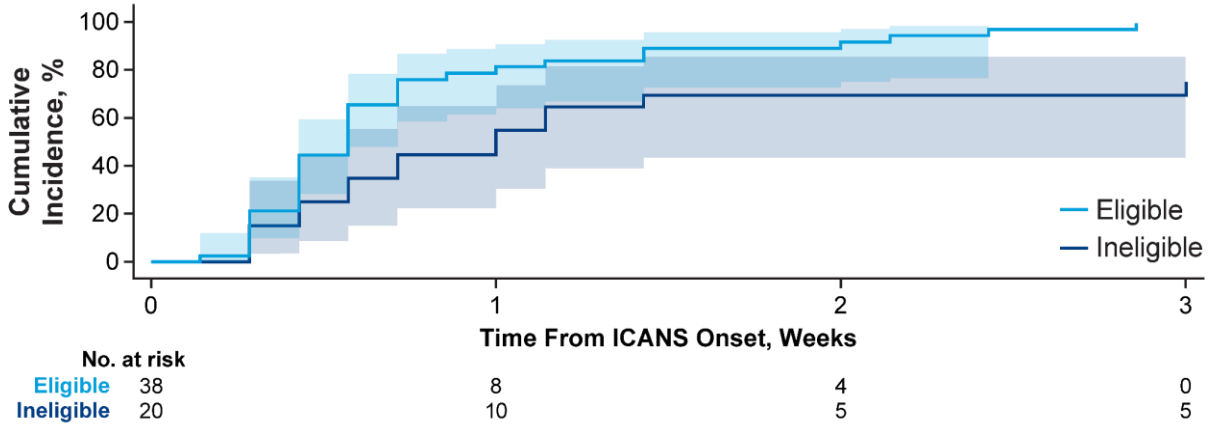
Axi-cel for Follicular Lymphoma: Cumulative Incidence Rate of Any-Grade CRS Resolution and Any-Grade ICANS Resolution by ZUMA-5 Eligibility and Age

Cumulative Incidence of Any-Grade CRS[a] Resolution by ZUMA-5 Eligibility



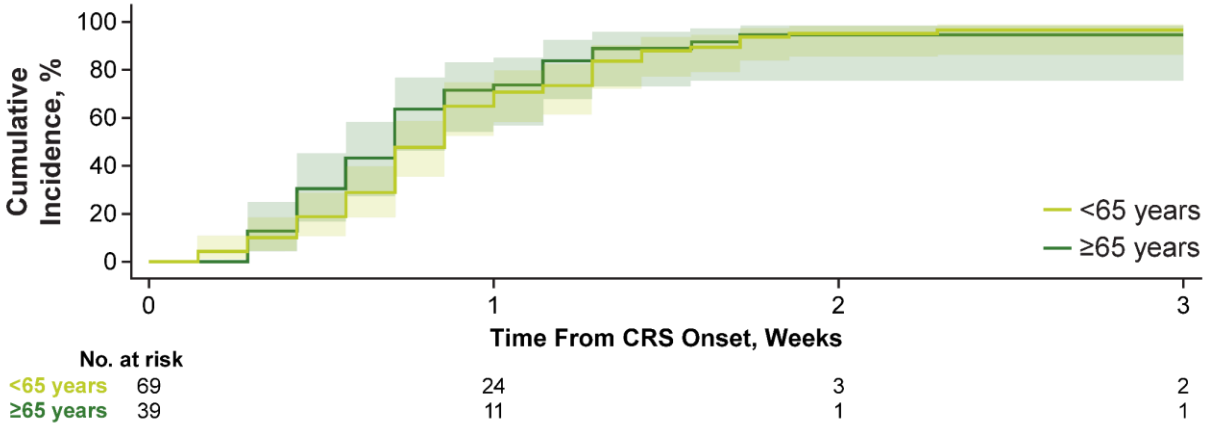
No. at risk				
Eligible	70	21	2	1
Ineligible	38	14	2	2

Cumulative Incidence of Any-Grade ICANS[b] Resolution by ZUMA-5 Eligibility



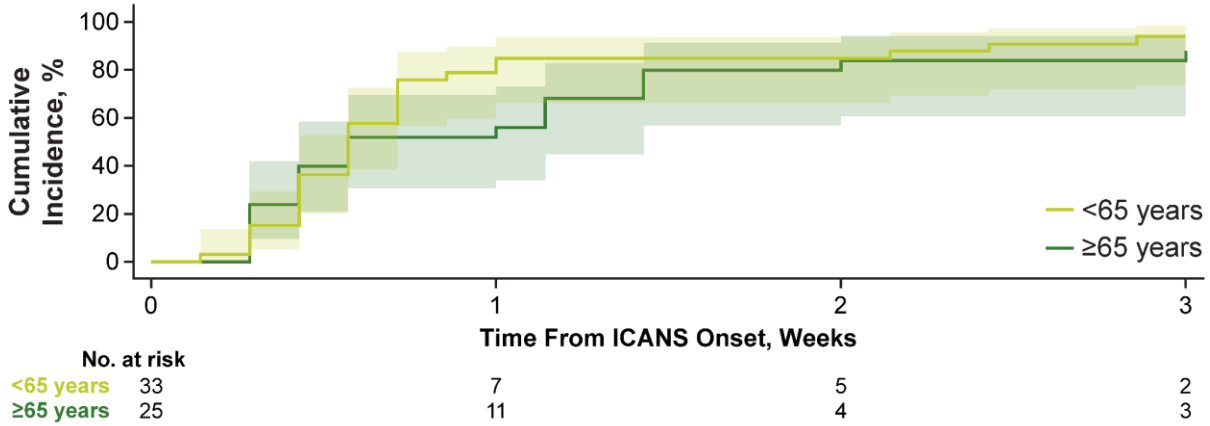
No. at risk				
Eligible	38	8	4	0
Ineligible	20	10	5	5

Cumulative Incidence of Any-Grade CRS[a] Resolution by Age



No. at risk				
<65 years	69	24	3	2
≥65 years	39	11	1	1

Cumulative Incidence of Any-Grade ICANS[b] Resolution by Age



No. at risk				
<65 years	33	7	5	2
≥65 years	25	11	4	3

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[a] Among patients experiencing CRS onset within 30 days post-infusion. The date of CRS resolution was not reported for 1 patient.
[b] Among patients experiencing ICANS onset within 100 days post-infusion.
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

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Brexucabtagene Autoleucel for Mantle Cell Lymphoma: Study Design and Analysis Population

- **Prospective** noninterventional cohort study of FDA-approved brexu-cel using patient data from the CIBMTR registry

Analysis Population:
Patients with r/r MCL treated with brexu-cel in the US from July 2020–December 2022[a]

500 registrants in CIBMTR database from **84 centers**

Patients excluded due to:
- prior history of non-transplant cellular therapy (n=7)
- effectiveness and/or safety follow-up data not due or not reported (n=64)[b]
- missing data (n=49)[c]

380 patients included in the analysis[d]

- Data cutoff date: February 7, 2023
- Median follow-up: 12.0 months (range, 0.0–25.3)[e]

Effectiveness Endpoints

- ORR, CR, and PR rates
- DOR
- PFS
- OS
- Relapse/PD

Key Safety Endpoints

- CRS
- ICANS
- Prolonged thrombocytopenia
- Prolonged neutropenia
- NRM

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[a]This was a PASS study; all patient enrollment and follow-up was prospective. [b]Only patients with 100-day follow-up were included. [c]Patients were excluded due to incomplete baseline data (n=32), missing data on prior treatment (n=7), missing data required to derive HCT-CI (n=3), or missing data on vein-to-vein time (n=7). [d]Patients included in the analysis are from 73 centers in the US. [e]One patient died of cardiac failure on the day of infusion.
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NRM, non-relapse mortality.

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Brexu-cel for MCL: Baseline Patient Characteristics

‡

Characteristics[a]	BTKi		Bendamustine		ASCT		Prior Therapies		Overall N=380
	Exposed n=329	Naive n=51	Prior n=211	No prior n=169	Prior n=114	No prior n=266	1–2 Lines n=87	≥3 Lines n=293	
Median age (range), years	66.9 (34.1–84.9)	65.5 (44.2–83.7)	**69.2 (44.2–84.9)**	**64.3 (34.1–83.7)**	**65.4 (34.1–82.3)**	**67.7 (34.3–84.9)**	66.9 (34.3–83.0)	66.5 (34.1–84.9)	66.8 (34.1–84.9)
ECOG PS ≥2, n (%) [b,c]	20 (7)	1 (2)	12 (6)	9 (6)	7 (6)	14 (6)	1 (1)	20 (7)	21 (6)
Ki-67 proliferation index ≥50%, n (%)[c,d]	**88 (47)**	**9 (28)**	**44 (37)**	**53 (52)**	23 (37)	74 (47)	27 (47)	70 (43)	97 (44)
TP53/17p deletion, n (%)[c,d]	32 (19)	8 (25)	16 (16)	24 (25)	6 (12)	34 (23)	13 (30)	27 (18)	40 (20)
Extranodal CNS involvement, n (%)[b,c]	17 (6)	0	11 (6)	6 (4)	7 (7)	10 (4)	1 (1)	16 (6)	17 (5)
Median no. of prior lines of therapy before leukapheresis (min–max)	**4 (1–12)**	**2 (1–7)**	**4 (1–12)**	**3 (1–10)**	**4 (1–12)**	**3 (1–11)**	**2 (1–2)**	**4 (3–12)**	4 (1–12)
Bridging therapy (any type), n (%)[c]	**159 (50)**	**11 (23)**	99 (48)	71 (44)	52 (47)	118 (46)	**29 (35)**	**141 (50)**	170 (46)

- Older patients were more likely to have had prior bendamustine and less likely to have received prior ASCT
- BTKi-naive patients tended to receive brexu-cel in earlier lines and were less likely to receive bridging therapy

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[a]In the overall population, 76% of patients were male, 30% were chemo-sensitive prior to infusion, 76% had clinically significant comorbidities, 8% were planned outpatient infusions, and median time from leukapheresis to infusion was 28 days; these baseline characteristics were consistent across all subgroups. [b]Prior to infusion. [c]Percentages are based on the number of patients with available data. [d]At diagnosis.
Values in bold text denote statistically significant difference within a subgroup.

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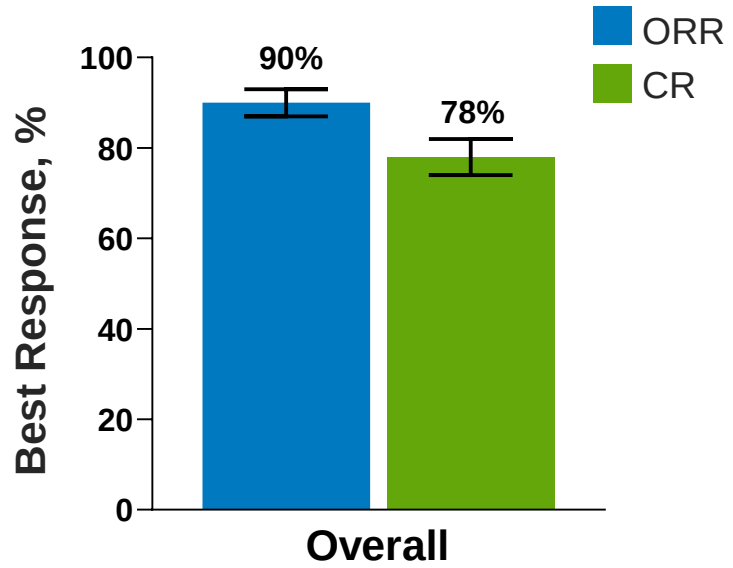
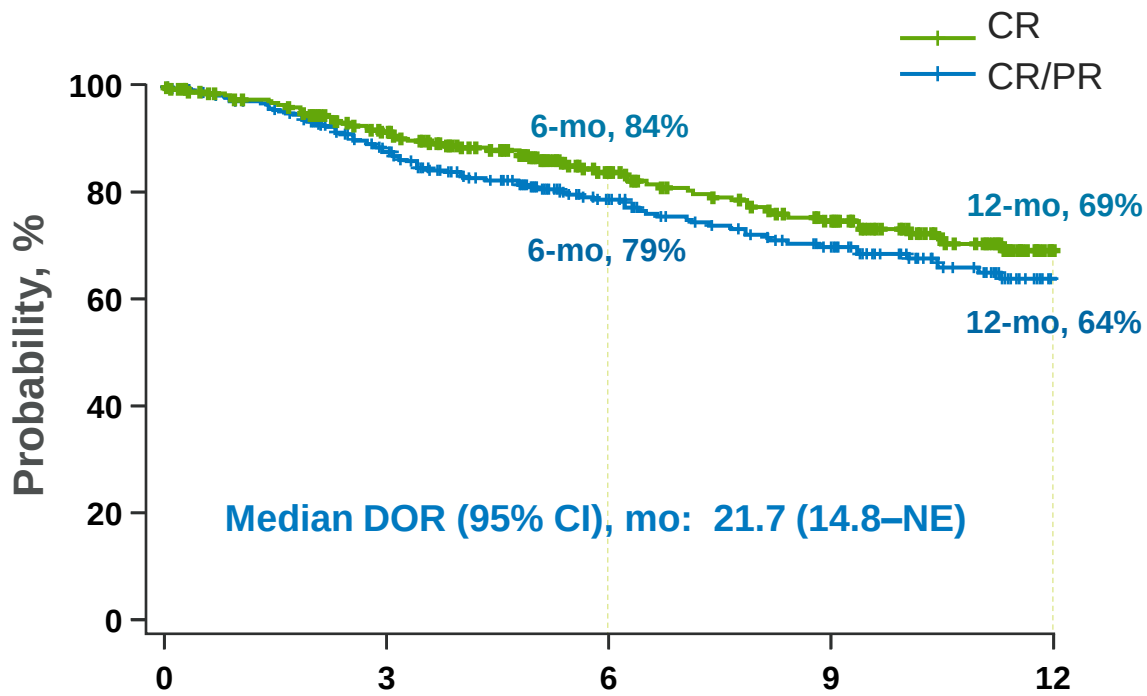
Brexu-cel for MCL: ORR, CR Rate, and DOR Overall Population

ORR and CR Rate



- ORR and CR rates were similar to those seen in ZUMA-2[1] (91% and 68%, respectively)
- ORR/CR rates for subgroups:
  - BTKi naive (92%/83%) vs exposed (90%/78%)
  - Prior bendamustine (89%/76%) vs no prior (92%/81%)
  - Prior ASCT (91%/82%) vs no prior (90%/77%)
  - 1–2 prior lines (94%/88%) vs ≥3 (89%/76%)

Kaplan–Meier Estimates for DOR



No. at risk					
CR[a,b]	285	223	150	113	24
CR/PR[b,c]	324	242	156	117	25

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[a]Among patients who achieved CR as a best response. [b]Subsequent cellular therapy and HCT without previously documented relapse or disease progression were censored; median follow-up was 12 months (range, 0.0–25.3). [c]Among patients who achieved CR/PR as a best response. NE, not estimable.

1. Wang M, et al. *J Clin Oncol*. 2023;41(3):555–567.

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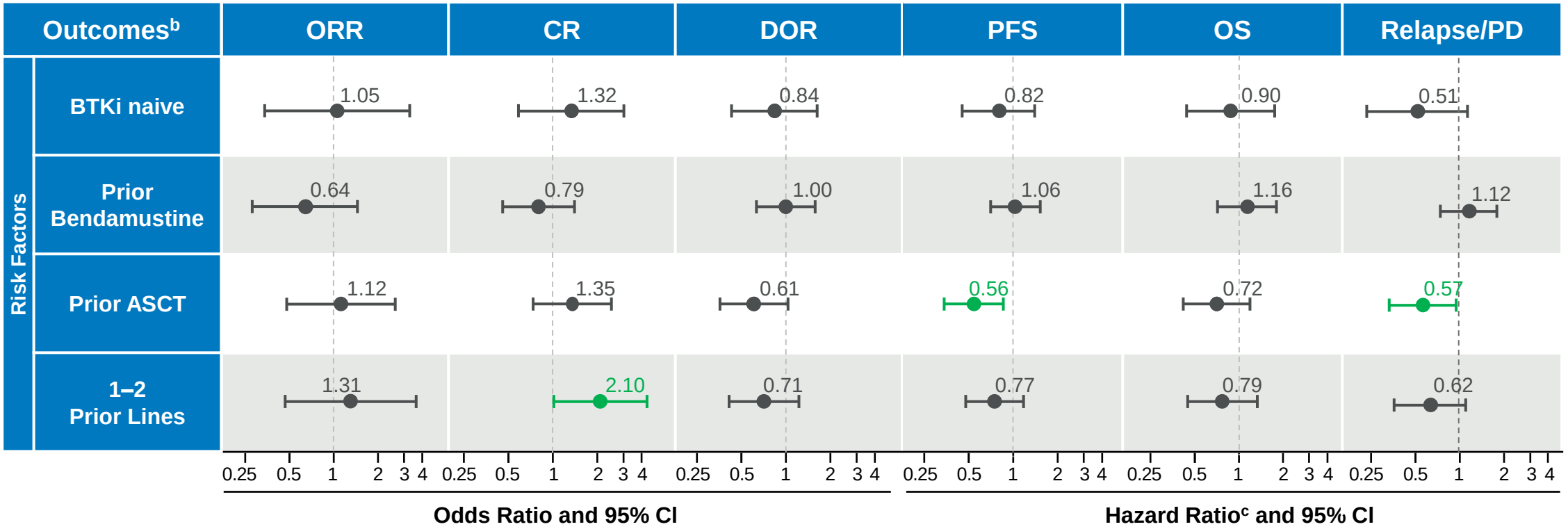
Effectiveness Outcomes With Multivariate Adjustment

Adjusted ORR, CR, DOR, PFS, OS, and Relapse/PD[a]



- CR rate was higher in patients with 1–2 prior lines of therapy (OR 2.10; 95% CI, 1.01–4.34) compared with those who had ≥3 prior lines
- PFS (HR 0.56; 95% CI, 0.35–0.88) and relapse/PD (HR 0.57; 95% CI, 0.34–0.96) were improved in patients with prior ASCT versus those without prior ASCT

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[a]Age and sex were adjusted for in all models. Other covariates were subject to a step-wise selection process that included ECOG PS, elevated LDH, >1 extranodal involvement site, and chemosensitivity prior to infusion; Ki-67 proliferation index and TP53/17p deletion at diagnosis; and race/ethnicity, HCT-CI, year of infusion, time from leukapheresis to infusion, and use of bridging therapy. [b]Variables with multivariate $P<0.05$ are highlighted in either green (favorable) or red (unfavorable). [c]Cause-specific hazard ratio.

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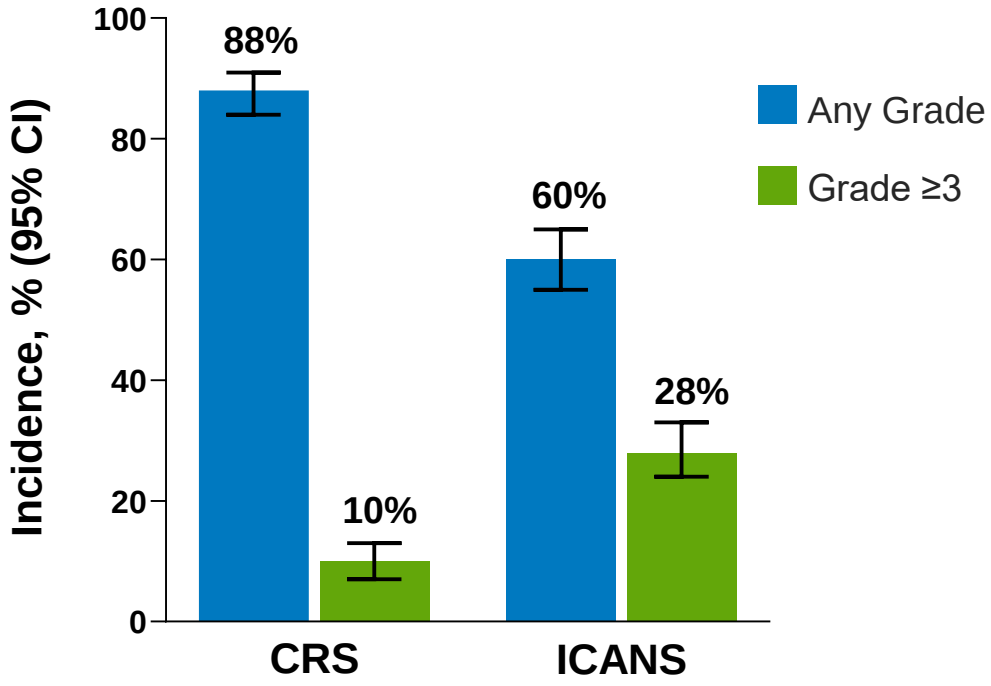
Brexu-cel for MCL: CRS and ICANS - Overall Population

‡

CRS and ICANS[a]



CRS and/or ICANS Onset, Resolution, and Treatment

CRS (Any grade)	n=335
Median time to onset (range), days	5 (1–46)
Median time from onset to resolution (range), days	6 (1–176)
ICANS (Any grade)	**n=228**
Median time to onset (range), days	7 (1–31)
Median time from onset to resolution (range), days	8 (1–98)
Treatment for CRS and/or ICANS, n (%)[b]	
Tocilizumab	290 (76)
Corticosteroids	233 (61)

- CRS and ICANS resolved by Week 3 from onset in 95% (95% CI, 92–97) and 78% (95% CI, 72–83) of patients, respectively
- Rates of CRS and ICANS were similar to those from ZUMA-2[1]
  - ZUMA-2: CRS 91% (any grade), 15% (Grade ≥3); NEs 63% (any grade), 31% (Grade ≥3)[c]

[a]ASTCT consensus. [b]Among all patients (n=380). [c]CRS grade based on Lee 2014 criteria; NE grade based on CTCAE, version 4.03.
NE, neurologic event.

1. Wang M, et al. *N Engl J Med*. 2020;382(14):1331–1342.

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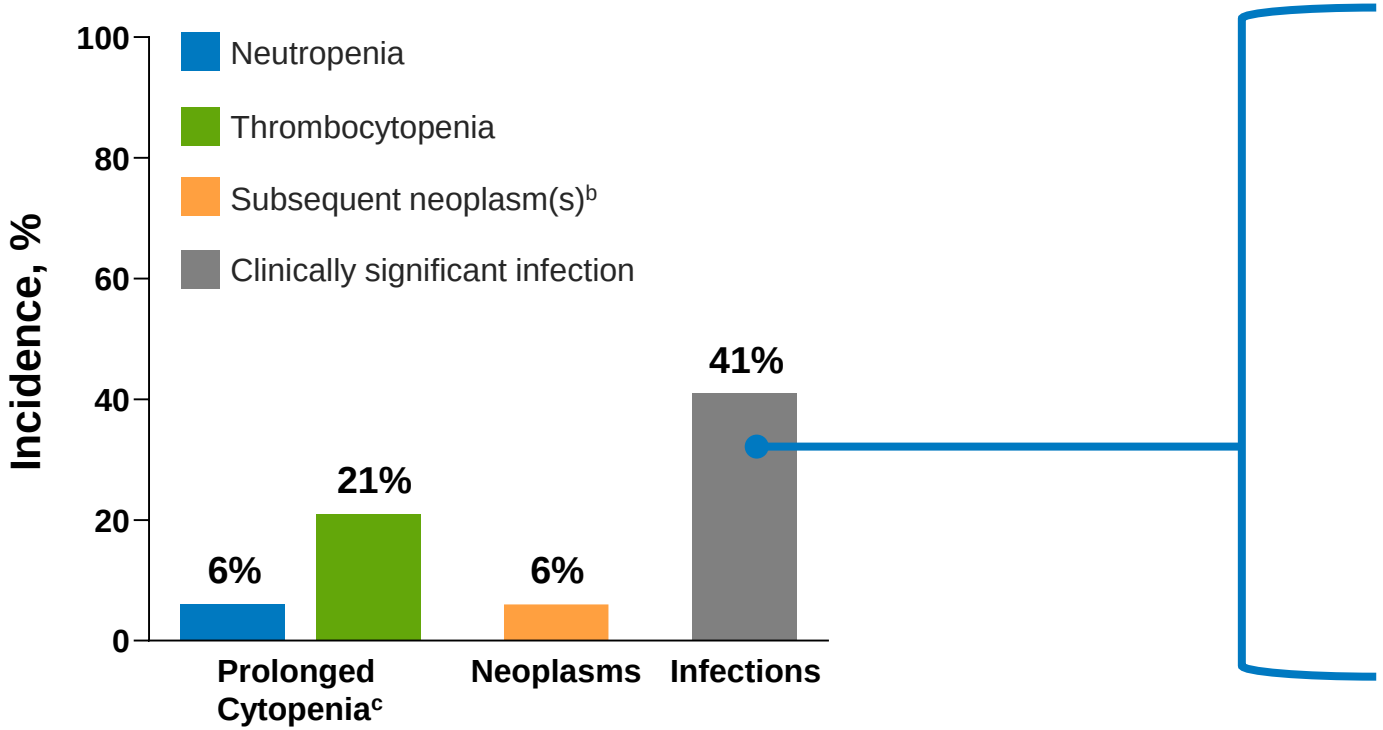
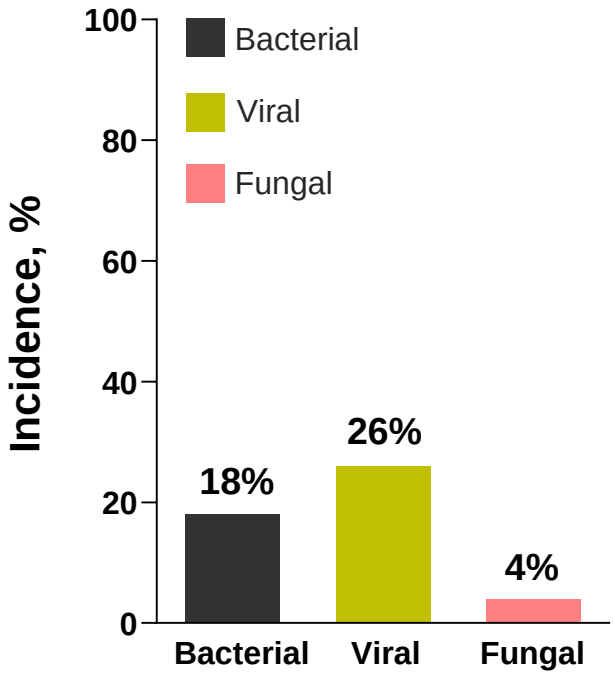
Brexu-cel for MCL: Other Safety Outcomes — Overall Population

Prolonged Cytopenia, Neoplasms, and Infections



Types of Infections[a]



- Prolonged neutropenia and thrombocytopenia occurred in 6% and 21% of patients, respectively
- The most common clinically significant infections were bacterial (18%) and viral (26%)

[a]Types of infections were not mutually exclusive; percentages are based on the overall analysis population (n=380). [b]Defined as the diagnosis of a new or secondary malignancy that is not a recurrence, progression, or transformation of the primary disease after initial brexu-cel infusion. [c]Prolonged neutropenia (failure to recover absolute neutrophil count ≥0.5 × 10^9/L and/or sustain 3 lab values) or thrombocytopenia (failure to recover platelet count ≥20 × 10^9/L) among patients who survived 30 days after infusion.

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Brexu-cel for MCL: NRM — Overall Population

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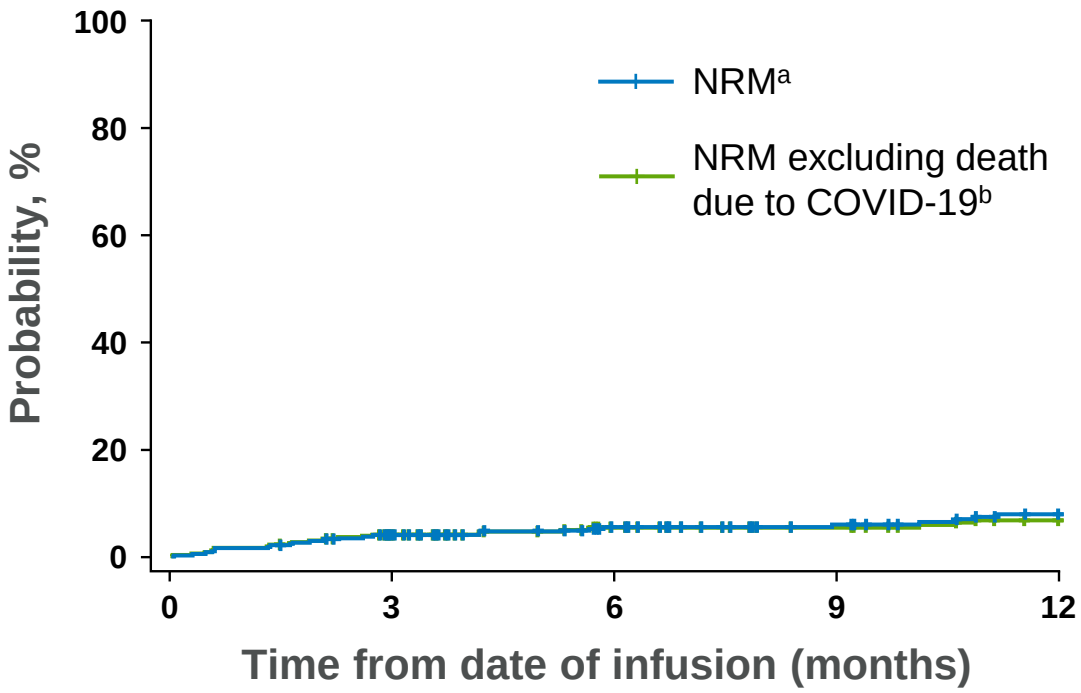
Cumulative Incidence Function for NRM



Primary Causes of Death[c]

Deaths, n (%)	All Patients n=89
Primary disease	53 (60)
Malignancy	3 (3)
CRS	2 (2)
Neurotoxicity/ICANS	5 (6)
Chronic GVHD	1 (1)
Infection	11 (12)
Organ failure[d]	5 (6)
Hemorrhage	2 (2)
Other	6 (7)
Not reported	1 (1)

- NRM at Day 100 and Year 1 were 4% and 8% (7% excluding COVID-19–related deaths), respectively; mainly due to infections

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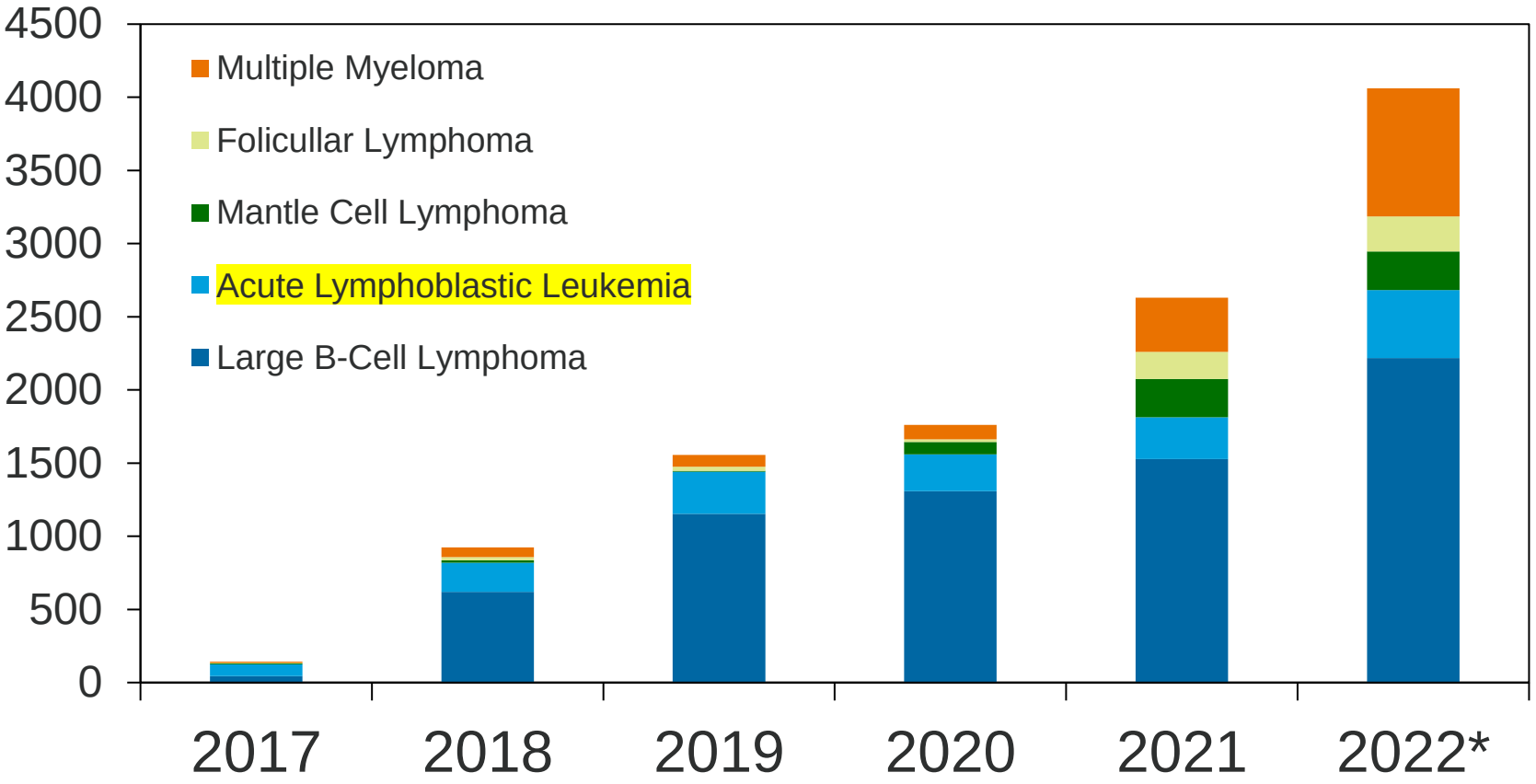
[a]Subsequent cellular therapy and HCT without previously documented relapse or PD were censored. [b]Subsequent cellular therapy and HCT were censored. [c]Among patients who died during follow-up. [d]Not due to GVHD. NRM, non-relapse mortality.

CAR T cell Indications Annually: 2017-2022



Use by indication (2022)

- Large B-cell lymphoma
  - ~2,200 patient/year
- ALL
  - ~ 460/year
- Multiple Myeloma
  - ~900/year
- Mantle Cell
  - ~260/year
- Follicular Lymphoma
  - ~240/year

*Data incomplete

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Comparable data between the CIBMTR and the pivotal trials: Tisa-cel

B

Endpoint	CIBMTR (N=249), % (95% CI)	ELIANA (N=79), % (95 % CI)
BOR of CR	85.5% (80.6, 89.7)	82.3% (72.1,90.0)
MRD negative	99.1% (115/116) (95.3, 100)	100.0% (64/64) (94.4, 100)
DOR		
At 6 mo	78.1% (70.5, 84.0)	80.8% (68.0, 88.9)
At 12 mo	60.9% (49.4, 70.5)	67.4% (53.2, 78.1)
EFS		
At 6 mo	68.6% (62.0, 74.4)	71.7% (59.8, 80.6)
At 12 mo	52.4% (43.4, 60.7)	57.2% (44.5, 68.0)
OS		
At 6 mo	88.5% (83.6, 92.0)	88.6% (79.3, 93.9)
At 12 mo	77.2% (69.8, 83.1)	77.1% (66.1, 84.9)

D

Endpoint	CIBMTR (N=152), % (95% CI)	JULIET (N=115), % (95% CI)
ORR (CR+PR)	61.8% (53.6,69.6)	52.2% (42.7, 61.6)
BOR of CR	39.5% (31.6, 47.7)	38.3% (29.4, 47.8)
DOR		
At 6 mo	55.3% (42.2, 66.6)	66.6% (52.8, 77.3)
At 12 mo	48.4%* (33.9, 61.5)	62.7% (48.7, 73.9)
PFS		
At 6 mo	38.7% (30.5, 46.9)	39.0% (29.7, 48.2)
At 12 mo	26.4%* (17.2, 36.6)	34.7% (25.7, 43.9)
OS		
At 6 mo	70.7% (62.2, 77.6)	61.2% (51.6, 69.5)
At 12 mo	56.3% (44.2, 66.8)	48.2% (38.6, 57.1)

*Indicates less than 10 patients at risk at this time point

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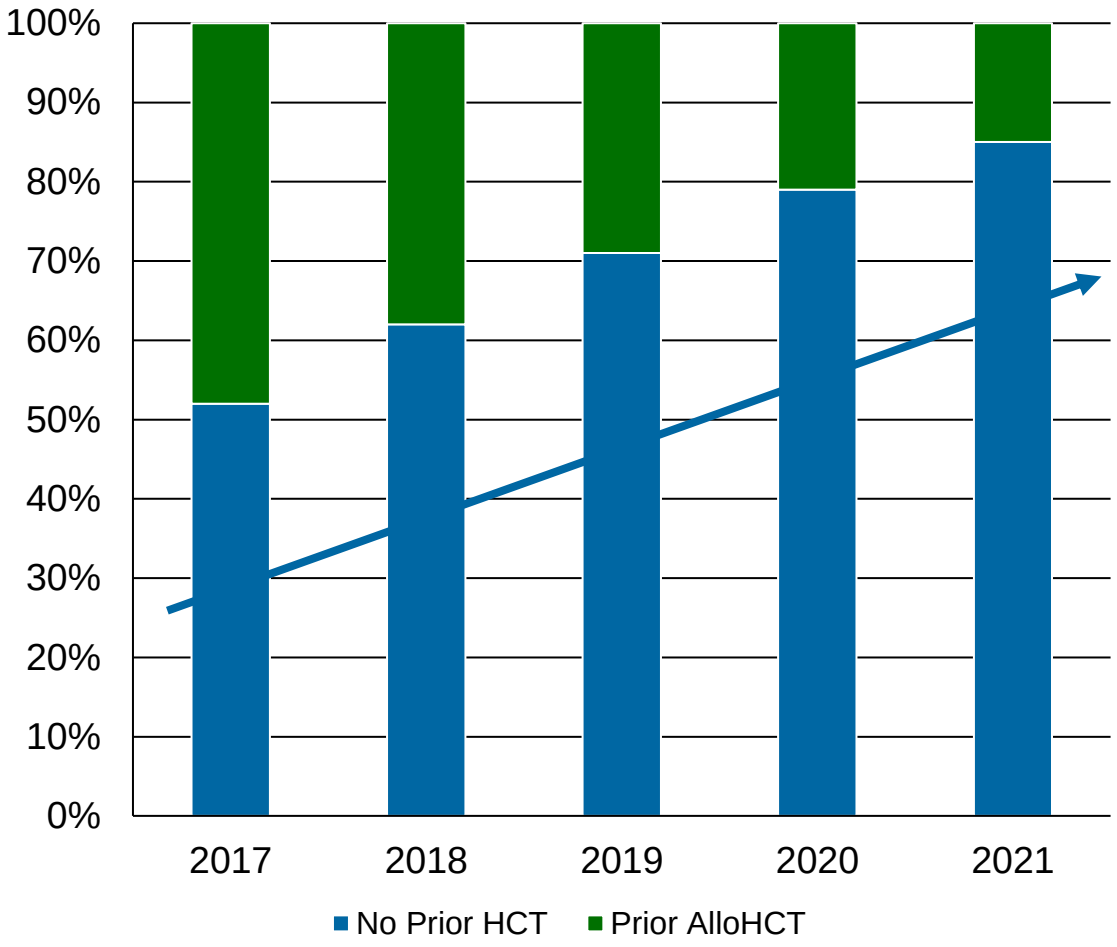
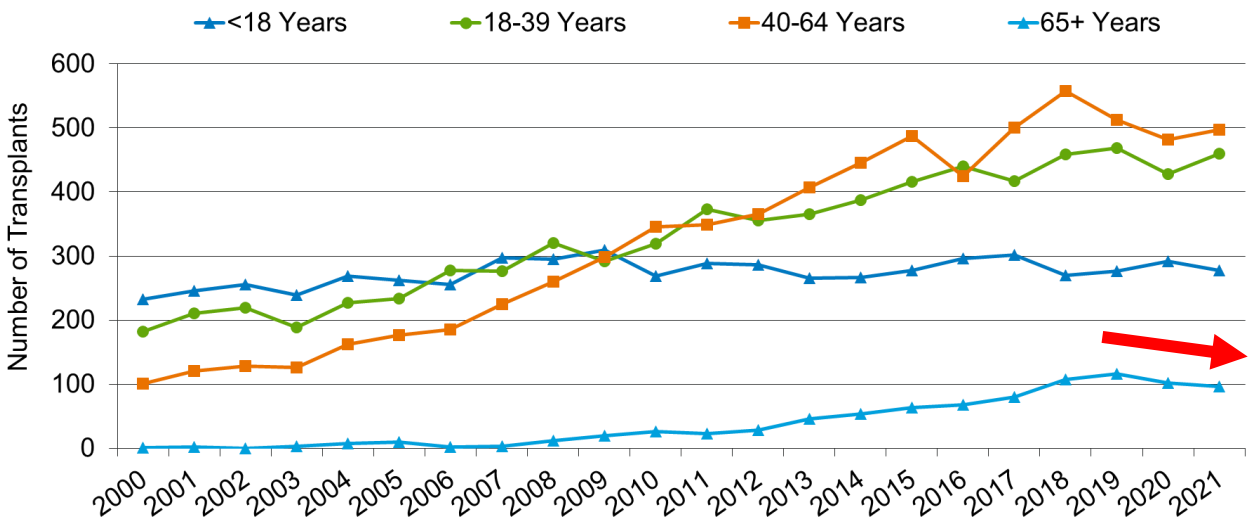
Pasquini MC et al, Blood Advances 2020

CIDR CELLULAR IMMUNOTHERAPY DATA RESOURCE

Rapidly evolving practices: most CAR T cell recipients with ALL have no prior transplant



Number of Allogeneic HCTs for Acute Lymphoblastic Leukemia (ALL) by Recipient Age in the US



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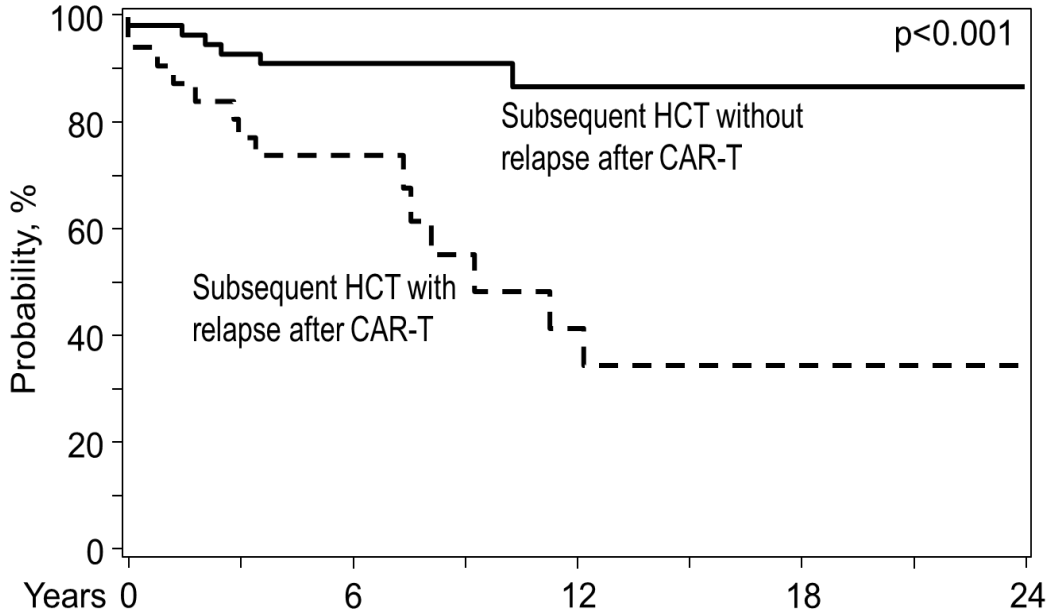
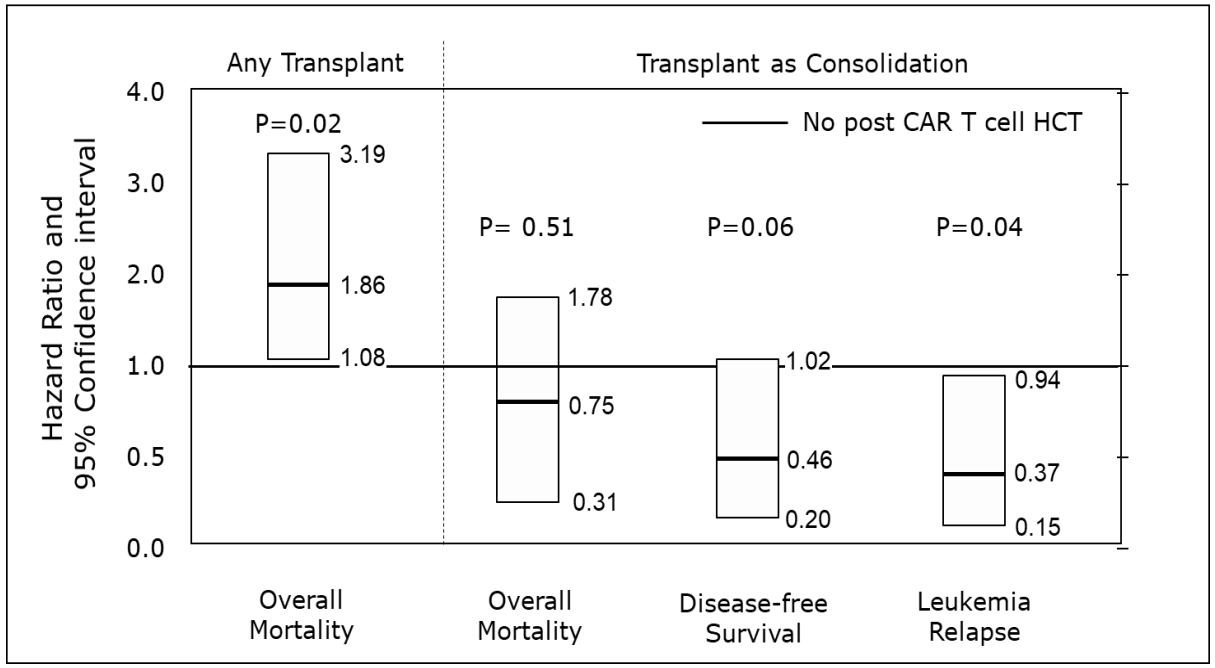
AlloHCT post CAR T Cell for ALL: Outcomes Depend on Failure post CAR T cell



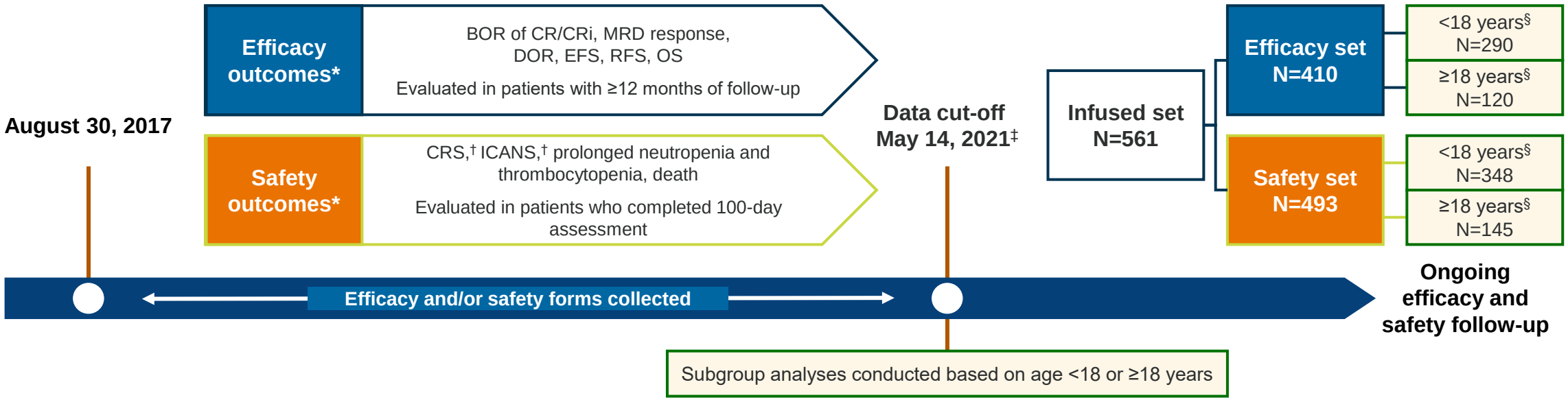
# at Risk					
Subsequent HCT without relapse after CAR-T	59	40	15	8	2
Subsequent HCT with relapse after CAR-T	28	15	6	3	1



Park J et al, ASH 2021

Tisagenlecleucel in the real-world setting: Study design

- Non-interventional prospective study using data from the CIBMTR cellular therapy registry
- Patients treated in the USA and Canada
- Descriptive comparisons of CIBMTR data with ELIANA and between the <18 and ≥18 years age groups



*Center-reported; †ASTCT grading criteria; ‡Patients who died or discontinued prior to data cut-off were also included; §At time of infusion
ASTCT, American Society of Transplant and Cellular Therapy; BOR, best overall response; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CRS, cytokine release syndrome; DOR, duration of response; EFS, event-free survival; ICANS, immune effector cell-associated neurotoxicity syndrome; MRD, minimal residual disease; OS, overall survival; RFS, relapse-free survival

Tisagenlecleucel in the real-world setting: Baseline characteristics

In general, patient characteristics were similar between patients aged <18 and ≥18 years

Baseline characteristics (all infused patients)	All patients (N=561)	<18 years (N=389)	≥18 years (N=172)
Median age at infusion, years (range)	13.80 (0.40–25.90)	10.40 (0.40–17.90)	21.95 (18.00–25.90)
Age <3 years, n (%)	40 (7.1)	40 (10.3)	NA
Male sex, n (%)	334 (59.5)	228 (58.6)	106 (61.6)
Down syndrome, n (%)	30 (5.3)	27 (6.9)	3 (1.7)
Cytogenetics, n (%)			
Abnormal 11q23/MLL rearrangement	82 (14.6)	63 (16.2)	19 (11.0)
Ph+ ALL prior to infusion	34 (6.1)	18 (4.6)	16 (9.3)
Karnofsky/Lansky score <80, n (%)	77 (13.7)	50 (12.9)	27 (15.7)
Median prior lines of therapy, n	3	3	4
Prior treatment, n (%)			
Allogeneic HCT	144 (25.7)	98 (25.2)	46 (26.7)
CAR-T cell therapy	11 (2.0)	7 (1.8)	4 (2.3)
Blinatumomab/inotuzumab	98 (17.5)/51 (9.1)	55 (14.1)/23 (5.9)	43 (25.0)/28 (16.3)

- The median time from receipt of leukapheresis product at the manufacturing site to shipment was 26 days (N=522; IQR: 25–32)
- Patients received a median CAR-positive T-cell dose of 1.9 x 10^6 cells/kg (N=534; range: 0.1–5.3)

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; HCT, hematopoietic cell transplant; IQR, interquartile range; MLL, mixed-lineage leukemia; NA, not applicable; Ph+, Philadelphia chromosome-positive

Oral presentation at the 2021 ASH Annual Meeting & Exposition, held December 11–14, 2021

Tisagenlecleucel in the real-world setting: Baseline characteristics

Patients aged ≥18 years appeared to have greater disease burden at baseline than those aged <18 years

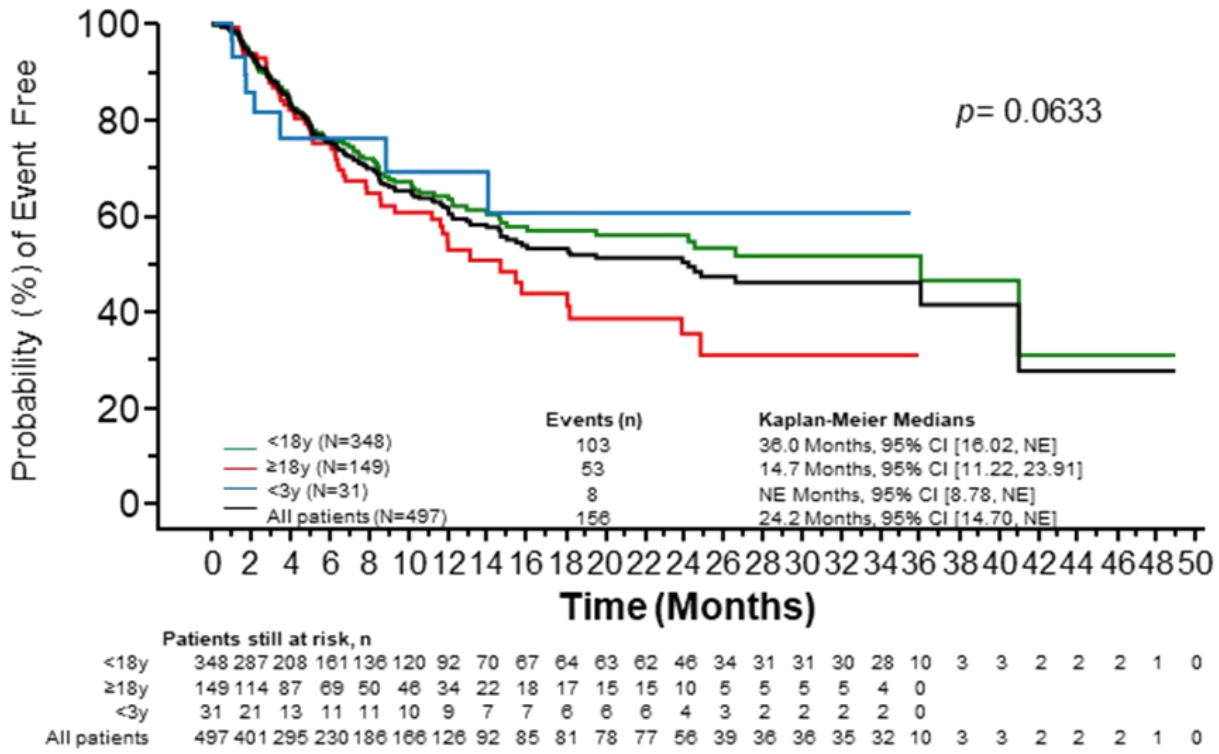
Baseline characteristics (all infused patients)	All patients (N=561)	<18 years (N=389)	≥18 years (N=172)
Most recent disease status prior to infusion, n (%)*			
Primary refractory	75 (13.4)	53 (13.6)	22 (12.8)
First relapse	153 (27.3)	103 (26.5)	50 (29.1)
Second relapse	89 (15.9)	58 (14.9)	31 (18.0)
≥Third relapse	50 (8.9)	28 (7.2)	22 (12.8)
Morphologic CR	193 (34.4)	146 (37.5)	47 (27.3)
MRD negative	102 (18.2)	75 (19.3)	27 (15.7)
MRD positive	84 (15.0)	67 (17.2)	17 (9.9)
Bone marrow blast percentage prior to infusion, n (%)			
0%	131 (23.4)	93 (23.9)	38 (22.1)
>0 to <5%	117 (20.9)	86 (22.1)	31 (18.0)
≥5%	176 (31.4)	119 (30.6)	57 (33.1)
≥50%	82 (14.6)	49 (12.6)	33 (19.2)
Extramedullary disease prior to infusion, n (%)			
No	410 (73.1)	295 (75.8)	115 (66.9)
Yes	89 (15.9)	51 (13.1)	38 (22.1)
Isolated CNS disease	56 (10.0)	33 (8.5)	23 (13.4)

*Disease status prior to infusion was not reported for one patient in the <18 years age group
CNS, central nervous system; CR, complete remission; MRD, minimal residual disease

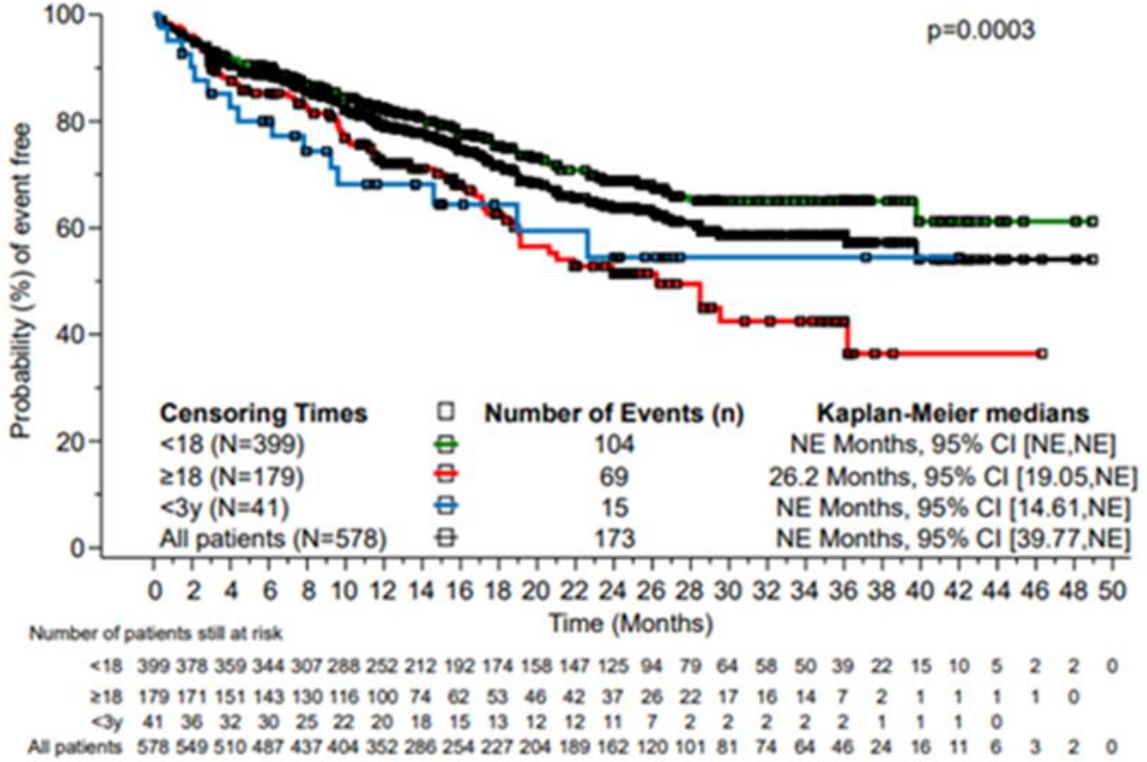
Oral presentation at the 2021 ASH Annual Meeting & Exposition, held December 11–14, 2021

Updated Relapse-free and Overall Survival of recipients of Tisagenlecleucel for ALL: by age

A



B



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References

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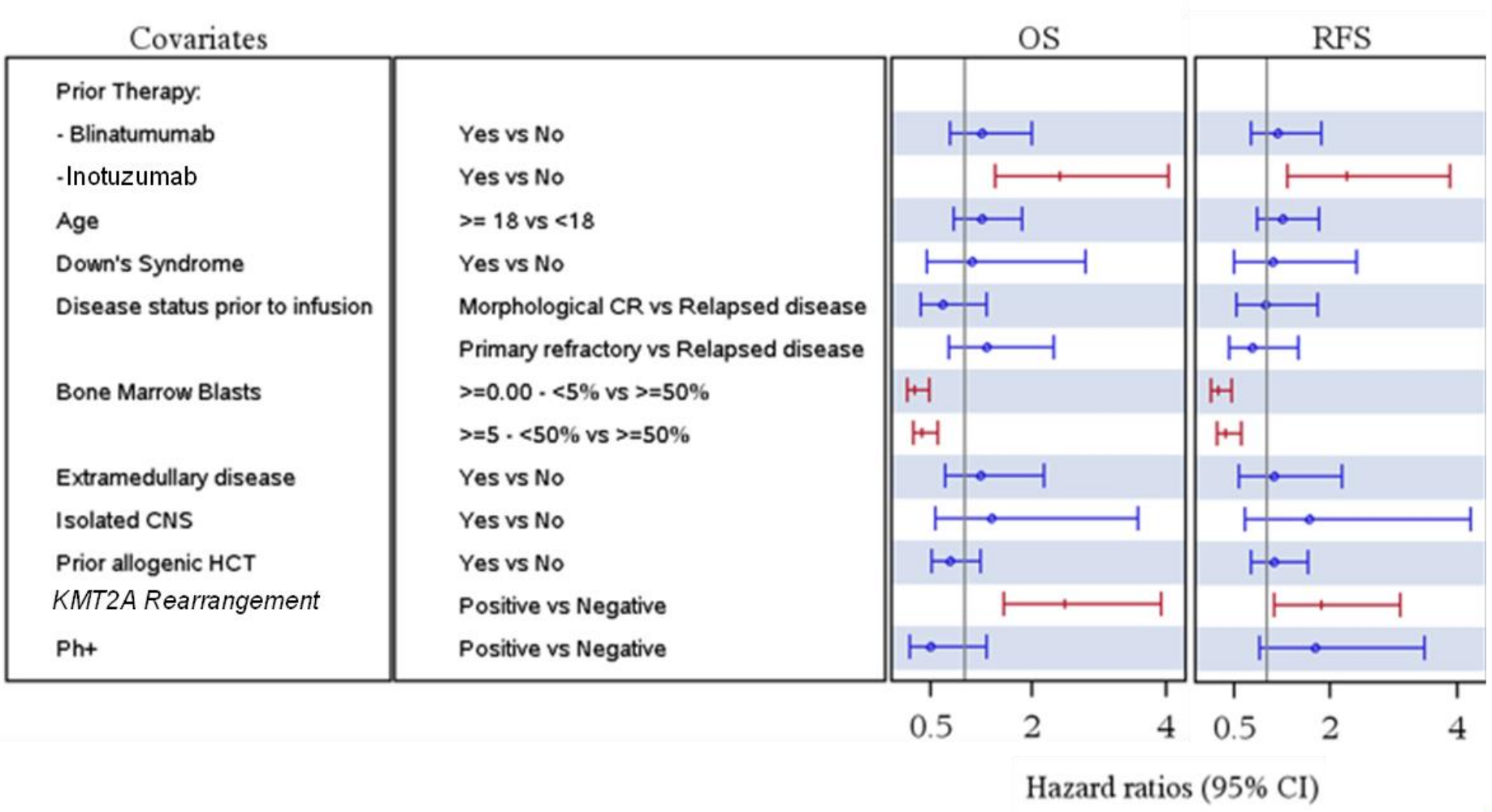
Updated Relapse-free and Overall Survival of recipients of Tisagenlecleucel for ALL: Multivariate analysis



Conclusions

- Rapid expansion of CAR T cell in the real world setting in the US with new indications and approval in earlier lines
- Outcomes in the real world setting appear comparable to ones described in the pivotal trials. Even expanding to patients who were ineligible to trials.
- CAR T Cell toxicities do impact patient care and need attention, even with improvement with earlier treatment.

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