iNHL and HD Review

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22nd Annual Hematology and Breast Cancer Review

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Discussion:

- –CAR-T cells for iNHL
- –Bispecific antibodies
- –Salvage regimens for R/R cHD

Disclosures: None

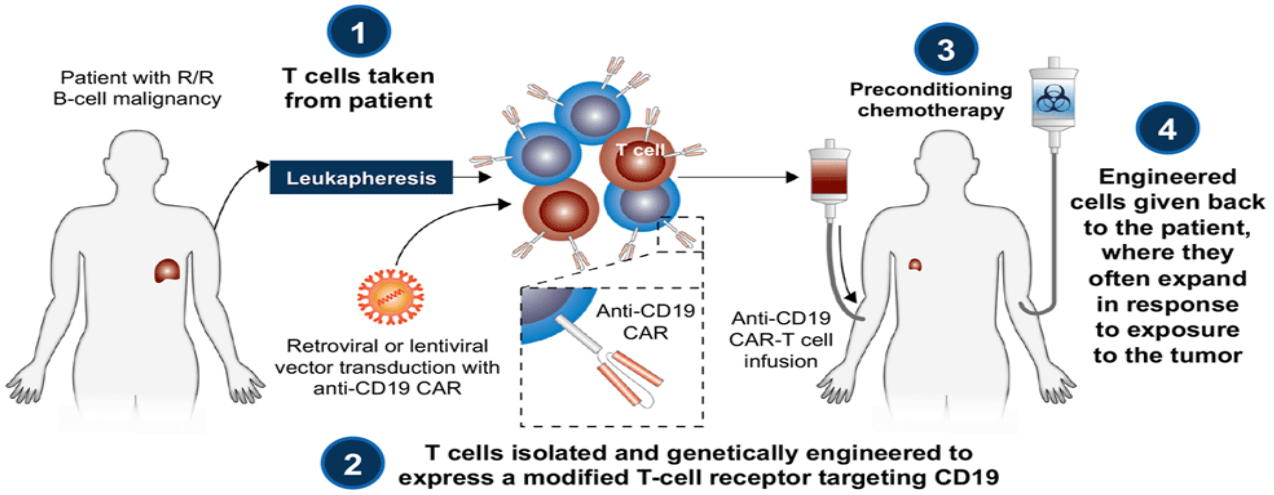
93 Long-Term Follow-up Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma

- ***Sattva S. Neelapu, MD***[1], *Julio C. Chavez, MD*[2], *Alison R. Sehgal, MD*[3], *Narendranath Epperla, MD, MS*[4], *Matthew L. Ulrickson, MD*[5], *Emmanuel Bachy, MD, PhD*[6*], *Pashna N. Munshi, MD*[7], *Carla Casulo, MD*[8], *David G. Maloney, MD, PhD*[9], *Sven de Vos*[10], *Ran Reshef, MD, MSc*[11], *Lori A. Leslie, MD*[12*], *Olalekan O. Oluwole, MBBS, MPH*[13], *Ibrahim Yakoub-Agha*[14], *Rashmi Khanal, MD*[15*], *Joseph D. Rosenblatt, MD*[16], *Marika Sherman, MSHS*[17*], *Jinghui Dong, PhD*[17*], *Alessandro Giovanetti, BSc*[17*], *Yin Yang, MS, MD*[17*], *Christine Lui, MS*[17*], *Zahid Bashir, MBBS, MS*[17*], *A Scott Jung, MD*[17*] *and Caron Jacobson, MD*[18]

93 Long-Term Follow-up Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in R/R Indolent NHL

- Axicabtagene Ciloleucel (Axi-Cel)
  - Autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy
  - FDA approved for treatment of R/R large B cell lymphoma
    - After ≥ 2 lines of systemic therapy
    - Recently approved for 2nd line treatment

Overview of CAR-T Cell Therapy[1,2]



1. https://labiotech.eu/immuno-oncology-history-car-t-nyt/. 2. Levine BL. *Cancer Gene Ther.* 2015;22:79-84.

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93 Long-Term Follow-up ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) for R/R iNHL

- Study design
  - Phase 2
  - Multicenter, single arm
    - 15 US site
    - 2 French site
- Key eligibility
  - R/R iNHL (gr 1-3a or MZL)
  - ≥ 2 prior lines of therapy
    - Including and anti-CD20 combined with an alkylating agent
- Bridging therapy allowed
- Conditioning regimen
  - Fludarabine 30 mg/m2 IV d -5, -4, -3
  - Cyclophosphamide 500 mg/m2 IV day -5, -4, -3
- Tx: Axi-cel 2 x 10^6 CAR+ cells/kg

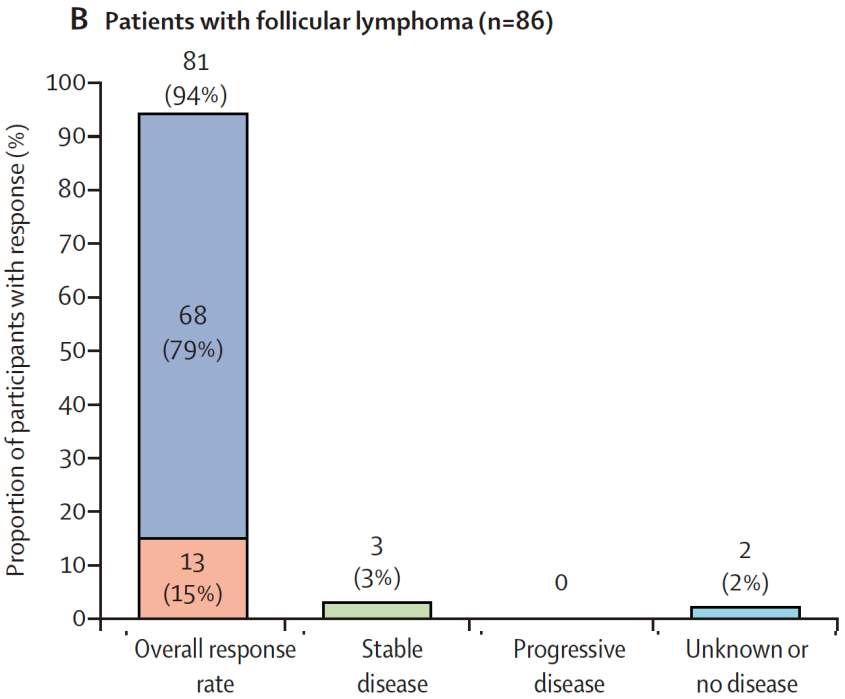
93 Long-Term Follow-up ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) for R/R iNHL

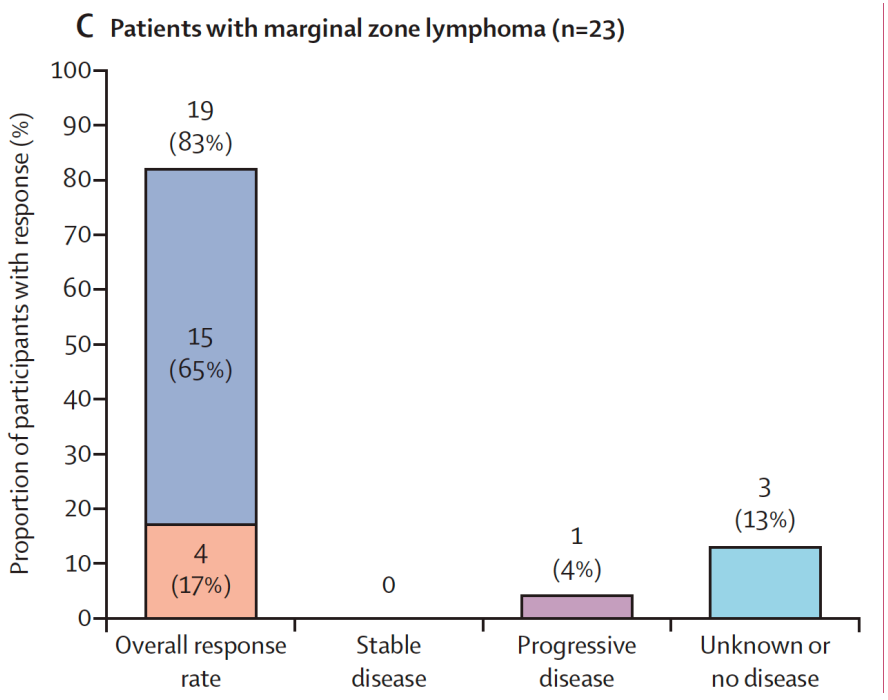
- Primary endpoint: ORR
- Secondary endpoints
  - CR rate
  - DOR, PFS, OS
  - AE's
  - CAR-T cell and cytokine levels
- Enrollment
  - Enrolled between 6/20/2017 and 7/6/2020
  - 181 patients screened
  - 153 patient enrolled
    - 127 (83%) follicular
    - 25 (16%) with MZL
- Axi-Cel production
  - Product made for all patients
  - Median time from leukapheresis to axicabtagene ciloleucel delivery: 17 days

93 Long-Term Follow-up ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) for R/R iNHL

Previous Tx	FL (n=124)	MZL (n=24)	All pts
Median	3 (2-4)	3 (2-5)	3 (2-4)
≥ 3 prior Tx	78 (63%)	16 (67%)	94 (64%)
PI3K	34 (27%)	9 (38%)	43 (29%)
Autologous SCT	30 (24%)	3 (13%)	43 (29%)
Lenalidomide	38 (31%)	8 (33%)	46 (31%)
Relapsed or refractory subgroups			
To last previous Tx	84 (68%)	18 (75%)	102 (69%)
POD24 from initial Tx	68 (55%)	12 (57%)	81 (55%)

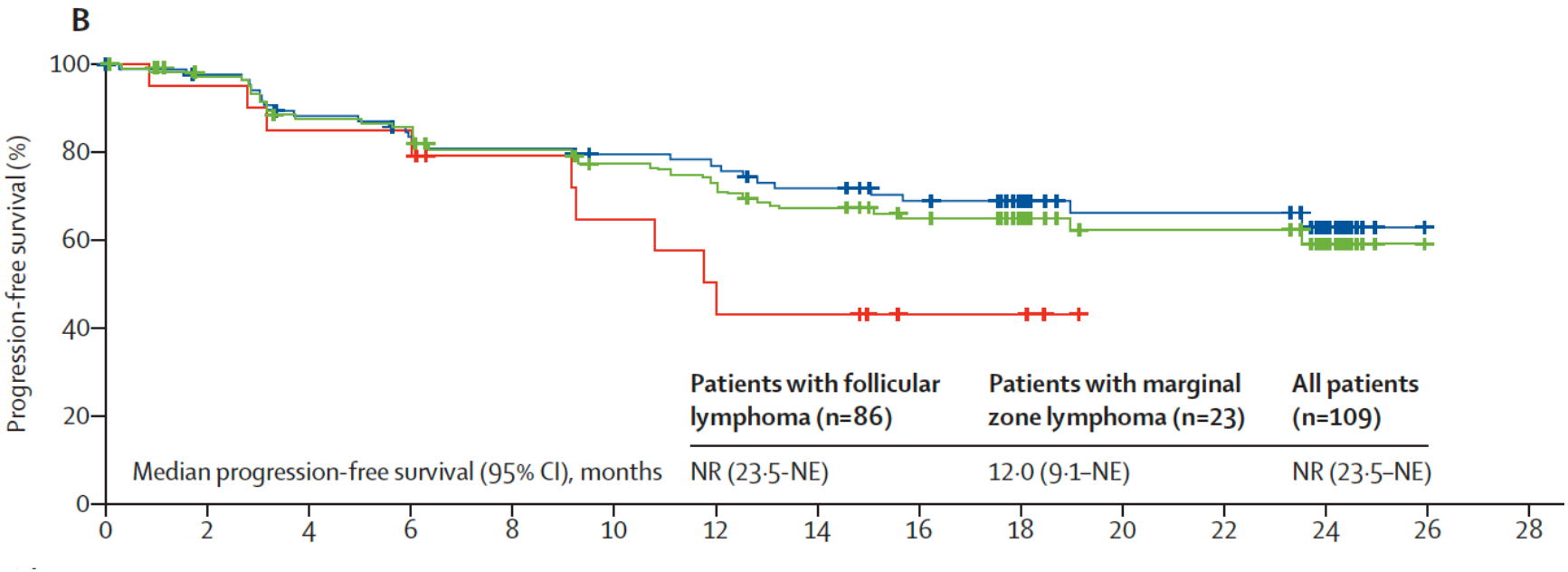
93 Long-Term Follow-up ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) for R/R iNHL





93 Long-Term Follow-up ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) for R/R iNHL

Progression free survival



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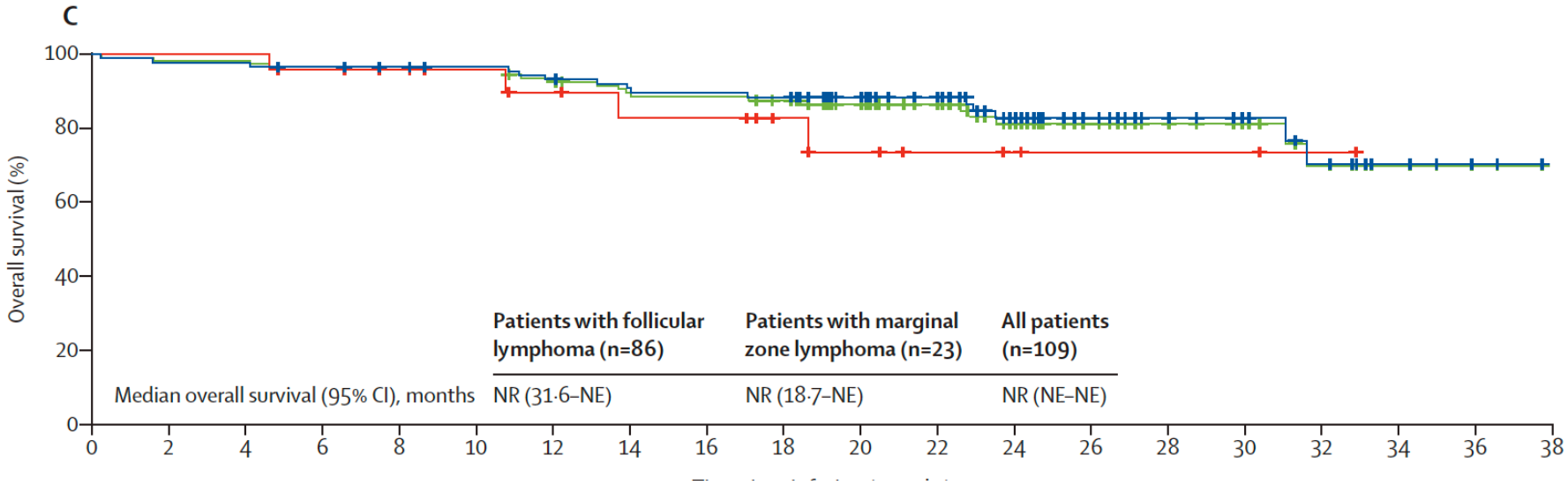
Overall Survival



	Patients with follicular lymphoma (n=86)	Patients with marginal zone lymphoma (n=23)	All patients (n=109)
Median overall survival (95% CI), months	NR (31·6–NE)	NR (18·7–NE)	NR (NE–NE)

93 Long-Term Follow-up ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) for R/R iNHL – Safety

Parameter	Grade 1-2	Grade ≥3
CRS	75%	7%
Neurologic	40%	19%
Pyrexia	77%	7%
Hypotension	46%	4%
Neutropenia	3%	33%
Anemia	14%	25%

–Tocilizumab given in 50% of the patients; corticosteroids in 18%, vasopressors 5%
–Median time to neurologic event: 7 days
–Median duration of neurologic events: 14 days
–Cytopenia gr ≥3 present ≥ 30 days: 34%

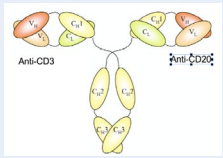
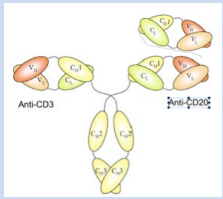
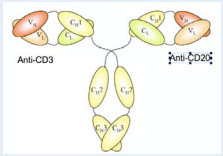
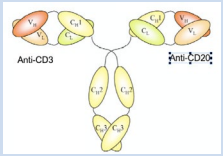
93 Long-Term Follow-up ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) for R/R iNHL – Safety

- Axicabtagen ciloeucel
  - Approved for R/R follicular lymphoma following ≥2 lines of systemic therapy
  - Approved 5/2021
- Results published
  - Axocabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single arm, multicentre, phase 2 trial
  - Caron A Jacobson et al
  - Lancet Oncol 2022; 23:91-103
  - https://doi.org/10.1016/ S1470-2045(21)00591-X

Other CAR-T studies with iNLH

- MB-106
  - Abs 3872. Author: Shadman, M et al
  - CD20 CAR-T with both 4-1bb and CD28 costimulatory domains
  - Phase I/II
  - R/R Follicular Lymphoma: ORR 92% (11/12), CR 75% (9/12) PR 17% (2/12)
  - CSR gr ≥3: 0
- Relmacabtagene autoleucel
  - Conducted in China (approved in China for R/R DLBCL)
  - CD19 CAR-T
  - Phase II
  - R/R FL: ORR 100% (19/19), CR 63% (12/19)

Bispecific Antibodies in Clinical Development

Bispecific Ab	Targets	Design	Structure
Blinatumomab	CD19 x CD3		–2 murine scFV joined together –Monovalent CD19 and CD3 binding
Mosunetuzumab	CD20 x CD3		–Monovalent CD20 and CD3 binding –Modified Fc that will not bind to FcγR or complement
Glofitamab	CD20 x CD3		–Bivalent CD20 binding with monovalent CD3 binding. –Modified Fc that will not bind to FcγR or complement
Epcoritamab	CD20 x CD3		–Monovalent CD20 and CD3 –Modified Fc to minimize Fc dependent effector functions
Odronextamab	CD20 x CD3		–Fully human Mab –Monovalent CD20 and CD3 –Modified Fc

Bispecific Antibodies

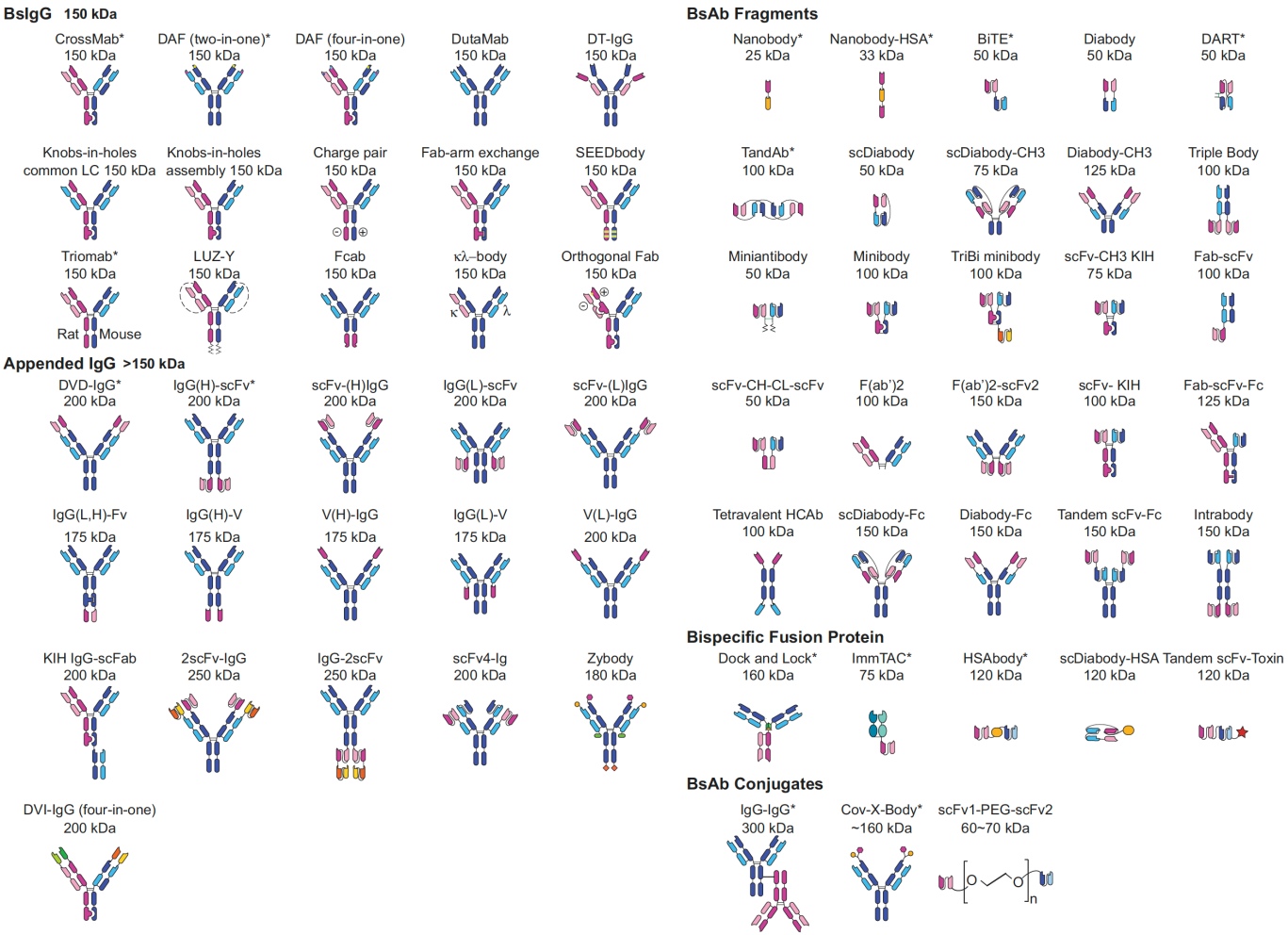


Fig. 1. Alternative formats for bispecific antibodies and other bispecific immunotherapeutics subdivided into five major classes: BsIgG, appended IgG, BsAb fragments, bispecific fusion proteins and BsAb conjugates. Heavy chains are shown in dark blue, dark pink and dark green and corresponding light chains are in lighter shades of the same colors. Connecting peptide linkers are shown by thin black lines and engineered disulfide bonds by thin green lines. Approximate molecular weights are shown assuming ~12.5 kDa per immunoglobulin domain. BsAb formats that have advanced into clinical testing are highlighted (*). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

127 Mosunetuzumab Monotherapy Is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) Who Have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study

- ***L. Elizabeth Budde***[1], *Laurie H. Sehn, MD*[2], *Matthew Matasar, MD*[3], *Stephen J. Schuster, MD*[4], *Sarit Assouline, MD*[5], *Pratyush Giri*[6*], *John Kuruvilla*[7], *Miguel Canales, MD*[8], *Sascha Dietrich*[9], *Keith Fay*[10*], *Matthew Ku*[11], *Loretta Nastoupil, MD*[12], *Michael C. Wei*[13*], *Shen Yin*[13], *Michelle Y. Doral*[13*], *Chi-Chung Li*[13*], *Huang Huang*[14*], *Raluca Negricea*[15*], *Elicia Penuel*[13*], *Carol O'Hear*[13*]*and Nancy L. Bartlett, MD*

127 Mosunetuzumab for Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

- Single arm pivotal expansion cohort
  - FL (gr 1-3a)
  - ECOG PS≤1
  - R/R ≥ 2 prior lines of therapy including an anti-CD20 and an alkylator
- Treated with a cycle 1 step-up dosing with cycle every 21 days (no mandatory hospitalization)
  - C1D1: 1 mg
  - C1D8: 2 mg
  - C1D15: 60 mg
  - C2D1: 60 mg
  - C3D1 and subsequent cycles: 30 mg
- Treat until
  - Stop after cycle 8 if in CR
  - If in PR or SD, continue for total of 17 cycles
  - Stop for PD or unacceptable toxicity
- Primary endpoint: Response rate (by PET)

127 Mosunetuzumab for Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

- Patient characteristics
  - 90 patient
  - Median age: 60 yr (range 29-90)
  - Stage II/IV: 76%
  - FLIPI 3-5: 44%
  - Prior treatments
    - Anthracyclines: 82%
    - ASCT: 21.1%
    - PI3K inhibitors: 18.9%
    - IMiDs (14.4%)
    - BTK inhibitors (6.7%)
    - CAR-T: 3.3%
  - Median number prior therapies: 3 (range 2-10)
  - Refractory to last therapy: 68.9%

127 Mosunetuzumab for Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

- Results
  - Median time on study: 18.3 months
  - Response rate
    - CR 60% (54/90 pt)
    - PR 20% (20/90 pt)
  - Median time to first response: 1.4 months
  - Median time to CR: 3.0 months
  - Median duration of response: 22.8 months
    - DOR for CR not reached
  - EFS
    - 12 month: 62%
    - 18 month: 57%

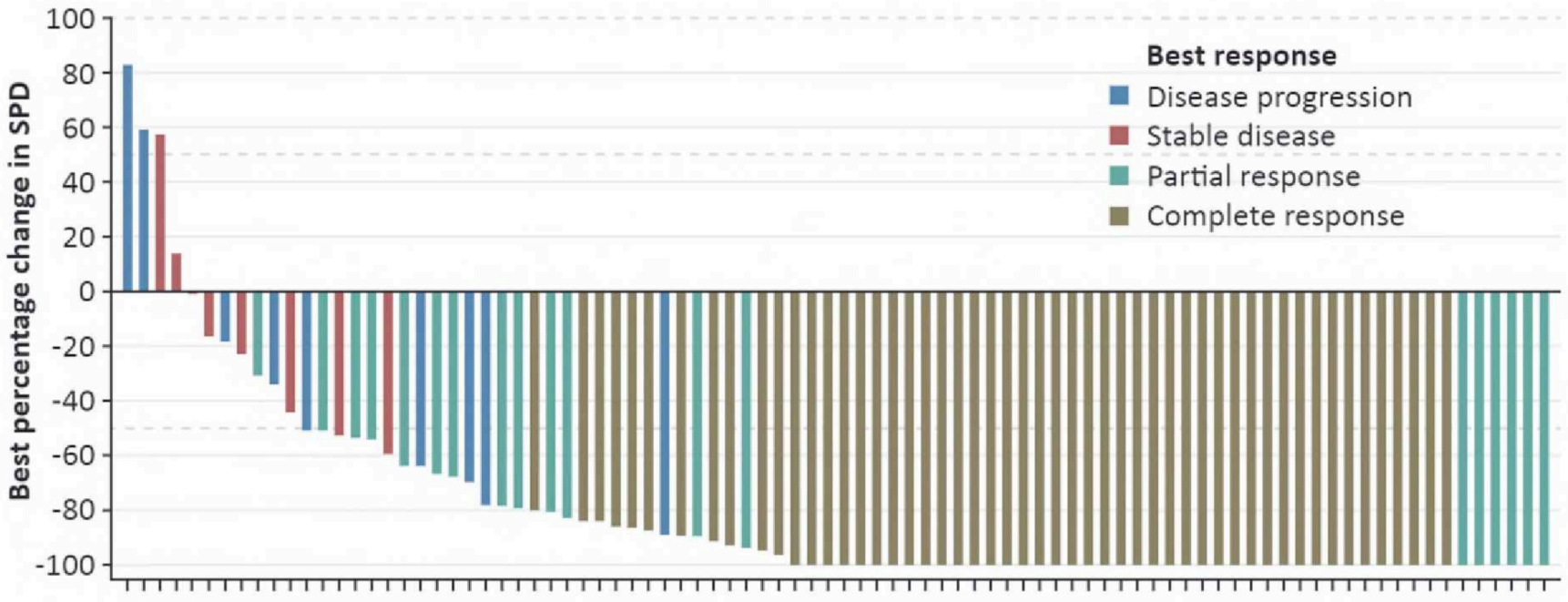
127 Mosunetuzumab for Relapsed/Refractory (R/R) Follicular Lymphoma (FL) – Pre-specified subgroups

Population	ORR, % (95% CI)	CR rage, % (95% CI)
All 3L+ R/R FL pts, n=90	70 (69-87)	58 (47-68)
Pts with POD24, n=47	83 (69-92)	55 (40-70)
Pts with 2 prior lines of Tx, n=34	85 (69-95)	68 (49-83)
Pts with ≥3 prior lines of Tx, n=56	75 (62-86)	52 (38-65)
Pts with disease refractory to any prior anti-CD20 Ab and alkylator, n=48	69 (54-81)	48 (33-63)
Pts with disease refractory to their last prior therapy, n=62	76 (63-86)	48 (35-61)

3L+ R/R FL: pts with relapsed/refractory follicular lymphoma who have received ≥2 prior lines of therapy. Ab: antibody. CI: confidence interval, CR: complete response. ORR: objective response rate. POD24: progression of disease within 24 months from the start of initial therapy

127 Mosunetuzumab for Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

Figure. Waterfall plot of best percentage change in SPD as assessed by PET/CT and independent review facility in all 3L+ R/R FL pts



127 Mosunetuzumab for Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

- Adverse events
  - Cytokine release syndrome (CRS): 44%
    - Predominantly gr 1 (25.6%) and gr 2 (16.7%)
    - Mostly confined to cycle 1
    - Resolved in all patients (median duration 3 days)
      - 7 pt received tocilizumab
      - 10 pt received corticosteroids
  - ICANS: 4.4%
    - Grade 3: 0%
  - Fatigue: 36.7%
  - Headaches: 31/1%
  - Neutropenia and fevers: 28.9% each
  - Hypophosphatemia: 22.2%
  - Pruritis: 21.1%

127 Mosunetuzumab for Relapsed/Refractory (R/R) Follicular Lymphoma (FL)

- Conclusions
  - Treatment with mosunetuzumab (Mosen) resulted in a CR rate of 60% and an ORR of 80% by IRF in patient with R/R FL after prior exposure to ≥ lines of therapy
    - Met its primary phase II endpoint
    - Historical control CR rate of 14%
  - A fixed-duration treatment approach demonstrated deep and durable responses in high-risk patient subgroups, including those with double-refractory FL and those who experienced PD within 2 yr of initial therapy
  - Safety profile manageable
    - CRS mostly low grade and mostly occurred in cycle 1
  - Mosunetuzumab is a promising outpatient therapy for patients with R/R FL
- Has FDA breakthrough therapy designation
  - Expected to file with the FDA by end of the year.

Other Mosunetuzumab abstracts

- Mosunetuzumab given subcutaneously (Abs #3573)
  - Authors: Bartlett et al
  - Mosunetuzumab given subcutaneously with cycle 1 step-up dosing.
  - Multiple NHL subtypes, N=74
  - CRS, all grades: 24.3%
    - Gr 1:17.6%: Gr 2: 6.8% Gr ≥3: 0%
  - No noted loss of efficacy
- Mosunetuzumab & polatuzumab vedotin (Abs #533)
  - Authors: Buddle LE et al
  - Phase II expansion, R/R aggressive NLH
  - ORR: 65.9% (27/41), CR: 48.8% (20/41)
  - Post CAR-T ORR: 64.7% (11/17), CR 47.1% (8/17)
- Mosunetuzumab & lenalidomide (Abs #129)
  - Authors: Morschhauser et al
  - Phase 1b R/R FL
  - ORR: 92% (12/13), CR 77% (11/13)
  - CRS Gr 1: 26% (7/27), Gr 2: 4% (1/27) Gr 3: 0%

Other bispecific antibody abstracts

- Glofitamab (CD20-bivalent x CD3 monovalent) (Abs #128)
  - Authors: Morschheauser F et al
  - Monotherapy or with obinutuzumab in R/R FL
    - Monotherapy ORR: 81% (43/53), CR 70% (37/52)
    - Combination ORR: 100% (19/19), CR 73.7% (14/19)
- Glofitamab & polatuzumab vedotin (Abs #525)
  - Phase Ib/II, R/R NHL
    - Obinutuzumab 1000 mg given day -7 to decrease CRS
  - ORR 73% (24/33) and CR of 51.5% (17/33)
- IGM-2323 (IgM bispecific CD20 x CD3) (Abs #132)
  - Authors: Buddle LE et al
  - Dose escalation, R/R NHL
  - ORR 35% (8/23), CR 13% (3/23)

878 Novel Salvage Regimens Lead to Better Response and Survival in Relapsed Refractory Classic Hodgkin Lymphoma after Autologous Stem Cell Transplant

- ***Sanjal H Desai, MBBS***[1], *Michael A Spinner, MD*[2], *Kevin A. David, MD* [3], *Veronika Bachanova, MD, PhD*[4], *Gaurav Goyal, MD*[5], *Jacques Azzi, MD*[6*], *Kathleen Dorritie, MD*[7], *Vaishalee P. Kenkre, MD*[8], *Cheryl Chang, BA*[9*], *Sally Arai, MD, MS*[10], *Brendon Fusco, MD*[11*], *Nuttavut Sumransub, MD*[12], *Haris Hactic, MD*[13*], *Uroosa Ibrahim, MD, MBBS*[14*], *Elyse Harris, MD*[8*], *Matthew J. Maurer, MS, DMSc*[15*], *KC Rappazzo, MD*[16*], *Victor M. Orellana-Noia, MD*[17], *Catherine S. Diefenbach, MD*[18], *Saba Raya, MD*[19*], *Grzegorz S. Nowakowski, MD*[20], *Ranjana Advani, MD*[21] *and Ivana N. Micallef, MD*[1]

878 Brentuximab & Nivolumab Salvage Regimen for Relapsed/Refractory Classic Hodgkin Lymphoma

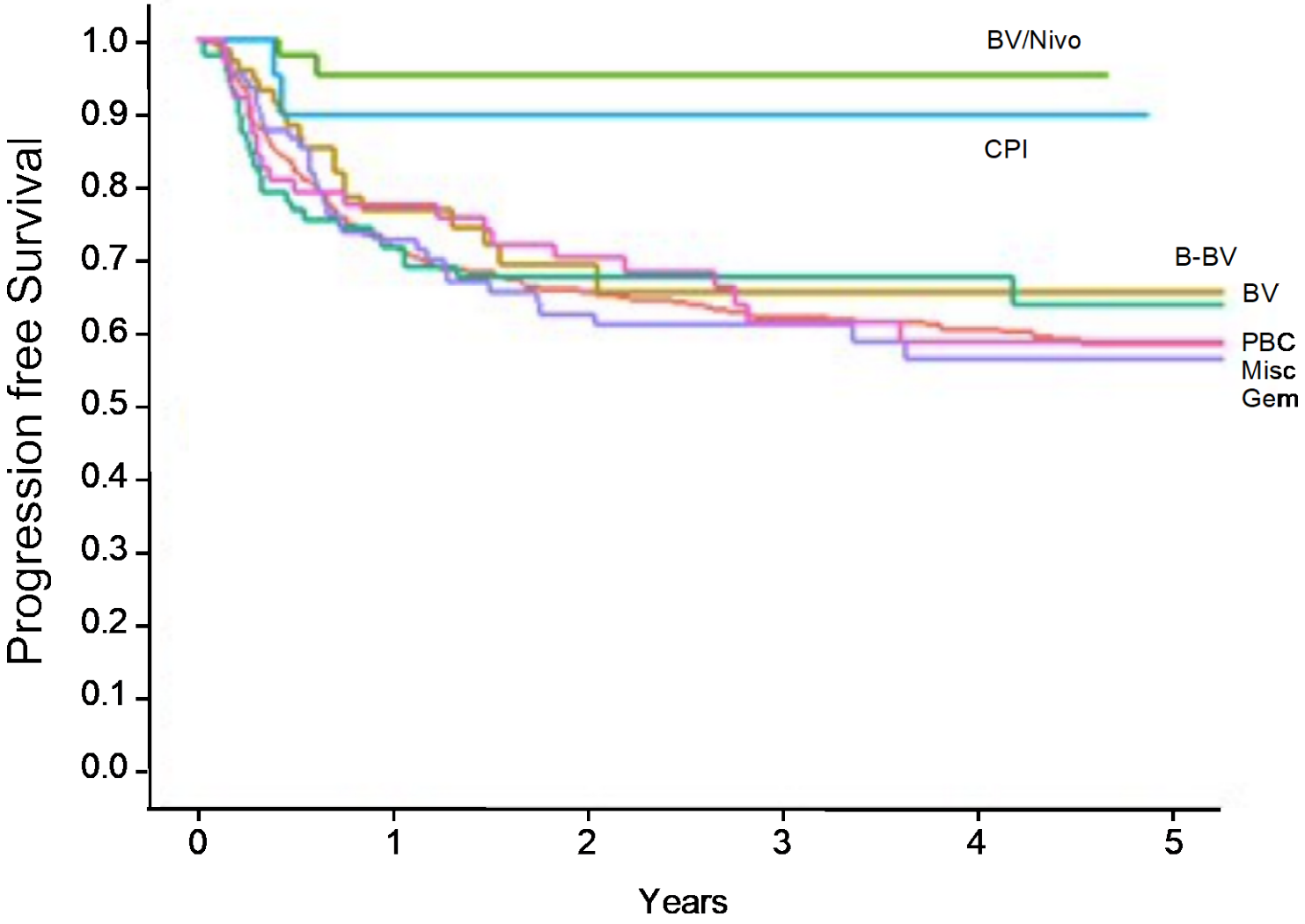
- Study design
  - Retrospective outcome study
  - Consecutive R/R cHL who underwent ASCT at 12 institutions
  - Compare salvage regimens used before ASCT
    - Platinum-based chemotherapy (ICE, DHAP, ESHAP 2
    - Brentuximab bendamustine (BBV)
    - Brentuximab nivolumab (BV/Nivo)
    - Brentuximab vedotin (single agent)
    - Gemcitabine base chemotherapy
    - Checkpoint inhibitor alone
    - Misc

878 Brentuximab & Nivolumab Salvage Regimen for Relapsed/Refractory Classic Hodgkin Lymphoma

Treatment	# Received	ORR	CR
Platinum based	553	79%	49%
B-BV	69	92%	80%
BV/Nivo	48	86%	67%
BV	65	62%	34%
Gemcitabine base	49	Similar to Platinum based	
Checkpoint inhibitor	4	Similar to Platinum based	
Misc	63	Similar to Platinum based	

No significant difference in patient characteristics between groups

878 Brentuximab & Nivolumab Salvage Regimen for Relapsed/Refractory Classic Hodgkin Lymphoma



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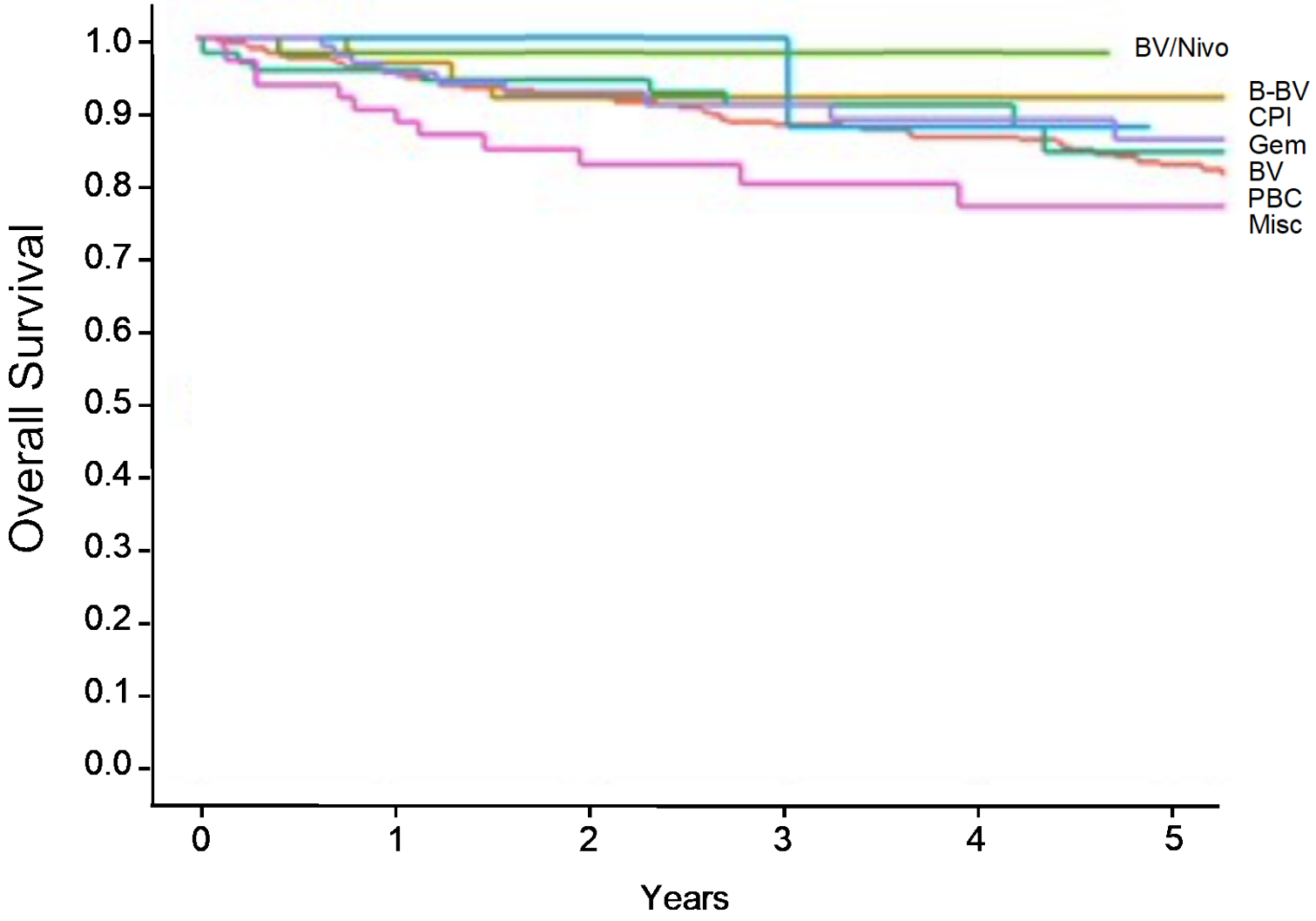

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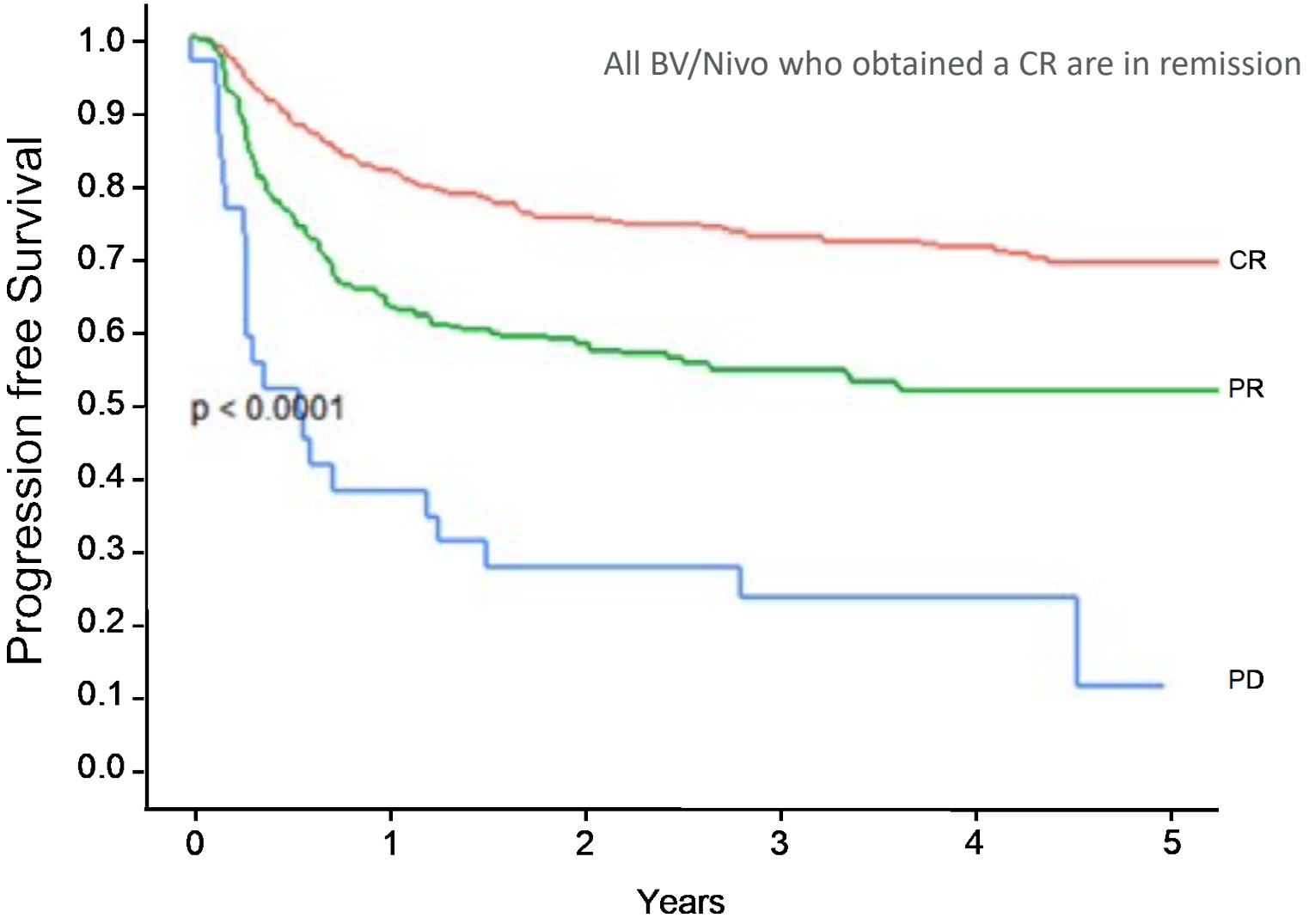

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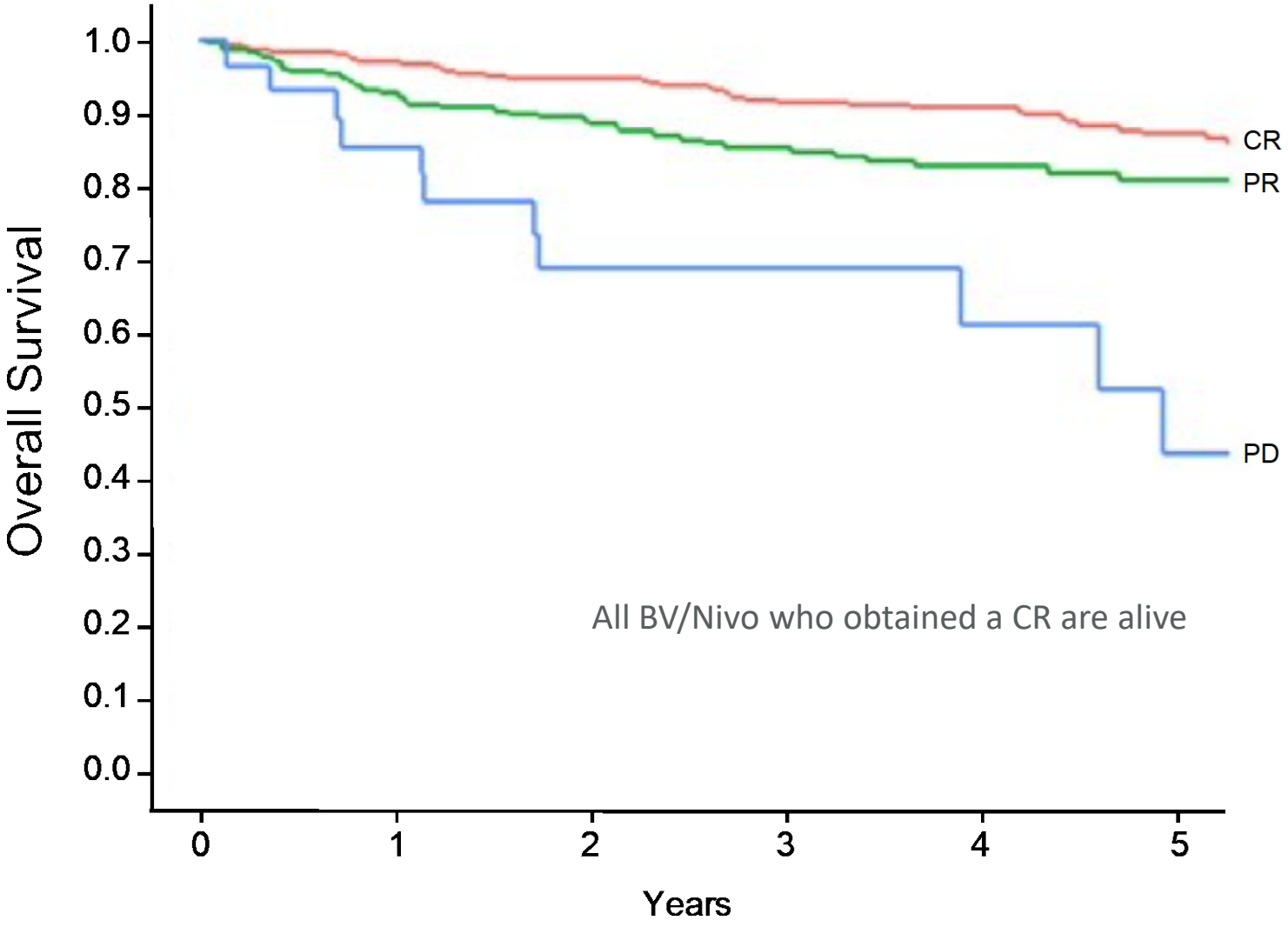

Thank You