Updates in Treatment of Elderly Patients with Non-Hodgkin Lymphoma

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knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

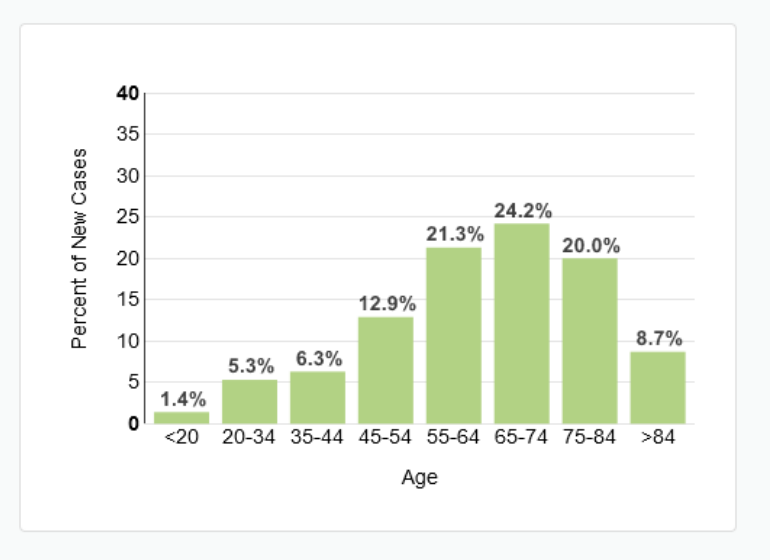
Disclosures

Roles	Relationship	Company/ies
Advisory Board	Advisor	Legend, Epizyme, TG therapeutics, Kite Pharma, Novartis, LOXO-Lilly, Janssen, BMS-Juno, Seattle Genetics
Research Funding	Researcher	Miltenyi Biotec, LOXO-Lilly Oncology
Consulting	Consultant	Miltenyi Biotec, Lilly Oncology, Incyte
Scientific Advisor Board	Member/Founder	Tundra Therapeutics

Managing cancer in elderly patients

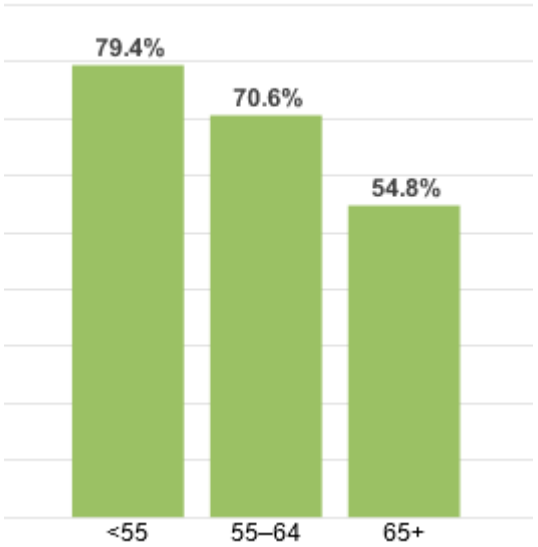
Diffuse Large B-cell Lymphoma

- Aggressive form of B-cell non-Hodgkin Lymphoma
- Most common form of lymphoma in adults in the United States
- Median age of presentation is 66 years
- Treated with curative intent chemotherapy, standard of care regimen is R-CHOP chemotherapy



Outcomes in Older Patients

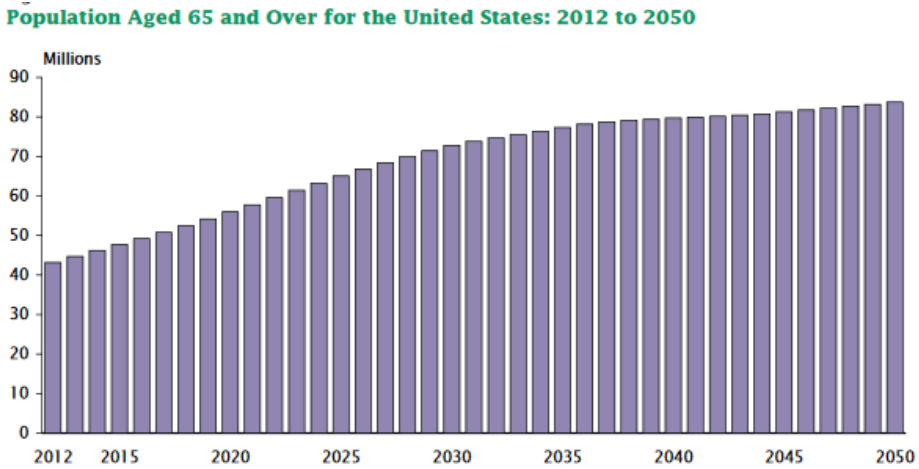
- 5-year survival outcomes decreases with age
- Challenges to delivering curative intent treatment
  - 60-70% of older patients present with DLBCL with at least comorbid condition complicating treatment
  - Specific drugs are challenging to administer
    - Vincristine: Neuropathy can be challenging in older frail patients, especially those with co-existing neuropathy (e.g. diabetic patients)
    - Adriamycin: Higher risk of cardiotoxicity among older patients and cannot administer



5-year Survival outcomes by Age

US Demographics

- Aging population, by 2050 the population of adults 65+ will double to 83 million from 43 million

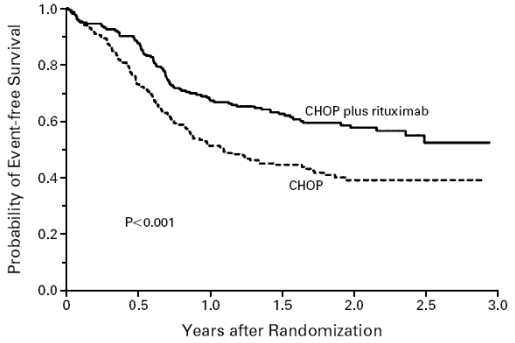


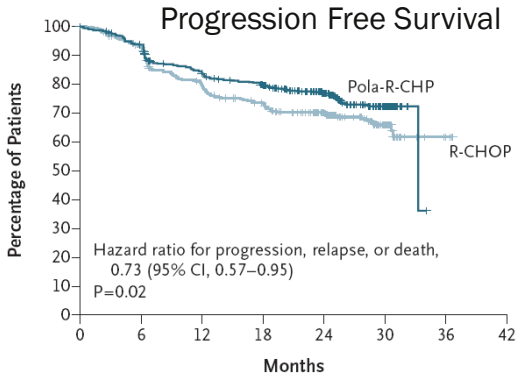
Nirav Shah
>65 years old
2050

https://www.census.gov/library/publications/2014/demo/p25-1140.html

Current Treatment Algorithms

- Standard R-CHOP 21 for 6 cycles is the current optimal treatment for patients with DLBCL.
- Long-term PFS ~60-70% for all comers
- Initial trial for R-CHOP approval in 2002, evaluated the regimen specifically in patients aged 60-80 years
- Pola-R-CHP possibly new standard of care (*not FDA approved*) and but limited enrollment to patients up to age 80-years





Coiffier, B. et al. *NEJM 2002.*
Tilly et al. NEJM 2021

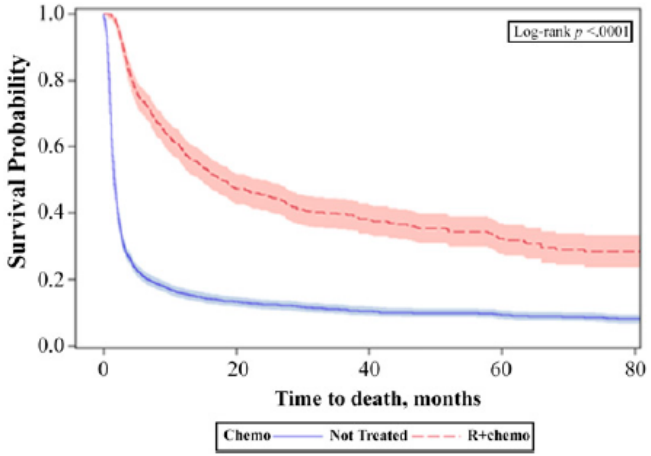
Are older patients getting R-CHOP?

SEER analysis, age>66 years from 2000-2007, among 9333 DLBCL patients, 49% received R+chemotherapy and 23% received chemotherapy alone.

- 23% of patients received no treatment, proportion was higher among those aged > 80 years (33% received no treatment).
- Overall survival is improved in patients who receive treatment versus those who do not

SEER Analysis from 2010-2014

- Evaluated pts≥66 years
- 64% of all treated pts received R-CHOP based chemotherapy
- ≥80 group, this number drops to ~50%



Hamlin, P.A. et al. *The Oncologist, 2014.*
Shaw J. et al. Leukemia & Lymphoma 2019

Do we need anthracycline based therapy?

- SEER analysis among age≥65 years from 1991-1995 found that patients who received doxorubicin survived 2x as long than patients who did not receive anthracycline

  Grann, V.R. et al. *Cancer, 2006.* ***107(7): p. 1530-41.***

- Dose Intensity Matters Too!
  - SEER analysis from 2000-2007 found that less than 6 cycles associated with poor outcomes
  - Several studies have shown that the relative dose intensity (RDI) of R-CHOP chemotherapy impacts survival outcomes. Maintaining RDI>70-90% improves PFS and OS.

  Dlugosz-Danecka, *Cancer Med, 2019.* ***8(3): p. 1103-1109.***

Outcomes with Non-Anthracycline Tx

- Outcomes poorer with non-anthracycline based therapy
- Phase II study of Bendamustine-Rituximab as frontline tx for DLBCL in patients≥80 years
  - 14 patients
  - Median progression free survival 7.7 months
  - 6 patients had a durable remission

Weidmann, E. *Ann Oncol, 2011.* ***22(8): p. 1839-44.***

No. of patients	Institution/ location	Age (y)	% of patients	IPI	3-Year OS (%)	
					Anthracycline-containing regimen	Anthracycline-free regimen
207	MDACC	≥80	54	≥3	63	25
141	Mexico	≥65	61	≥3	63	52
72	Emory University	≥65	25	≥4	59	38
128	Switzerland	≥60	49	≥3	—	—
378	Portugal	≥60	55	≥3	—	—
103	Netherlands	≥75	35	≥2*	—	—
73	OHSU	≥75	49	≥3	68	54
154	MGH	≥75	—		—	—
476	VA system	≥80	49	≥2*	28.1 mo (median)	13.1 mo (median)

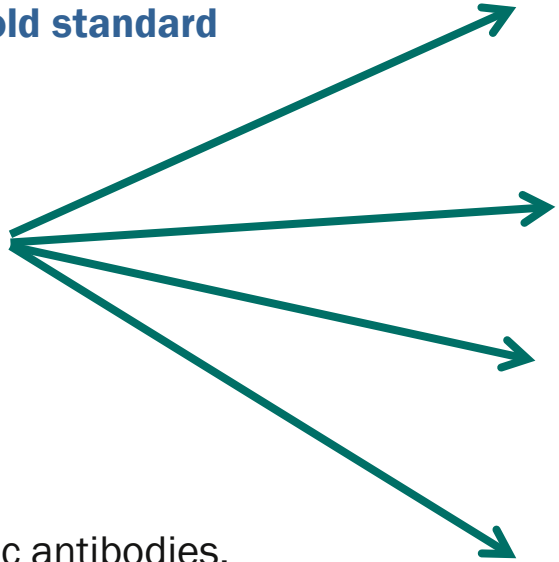
3-year OS rate of 63% for anthracycline treated patients versus 44% of anthracycline free regimens

Lin, R.J., *Blood, 2017.* ***130(20): p. 2180-2185.***

Treatment of Elderly DLBCL

Anthracycline remains gold standard

Elderly DLBCL: Tx Options



R-CHOP 21 for normal EF
R-CEOP or R-CVGP for abnormal EF

Split-Dose R-CHOP
(WON clinical trial)

R-miniCHOP

Other non-curative intent treatments: Rituxan alone, Benda-Rituxan, R-CVP

Evolving Options: Bispecific antibodies, targeted antibodies, and CAR-T cells

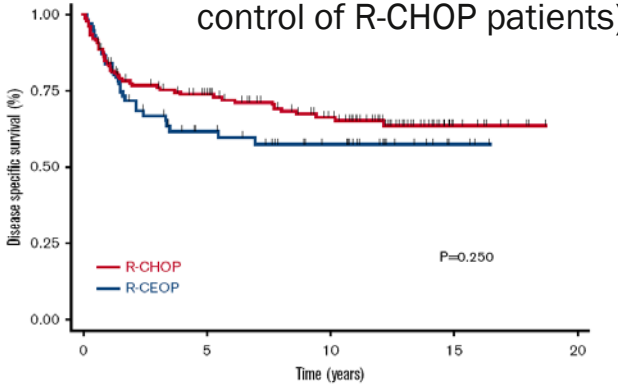
H/o Cardiac Dysfunction: R-CEOP

- Patients with low EF, h/o CHF, or recent MI, may want to consider non-anthracycline based chemotherapy
- R-CEOP (substitute etoposide for Adriamycin)
  - Etoposide given at 50 mg/m2 IV on Day 1 and 100 mg/m2 PO on Day 2 and Day 3
  - 10-year disease-specific survival: 58%

Table 3. Survival outcomes at 5 and 10 years for R-CEOP vs R-CHOP

	R-CEOP		R-CHOP		
	5-y %	10-y %	5-y %	10-y %	*P*
TTP	53	53	69	62	.089
DSS	62	58	74	67	.251
OS	47	30	65	49	.002

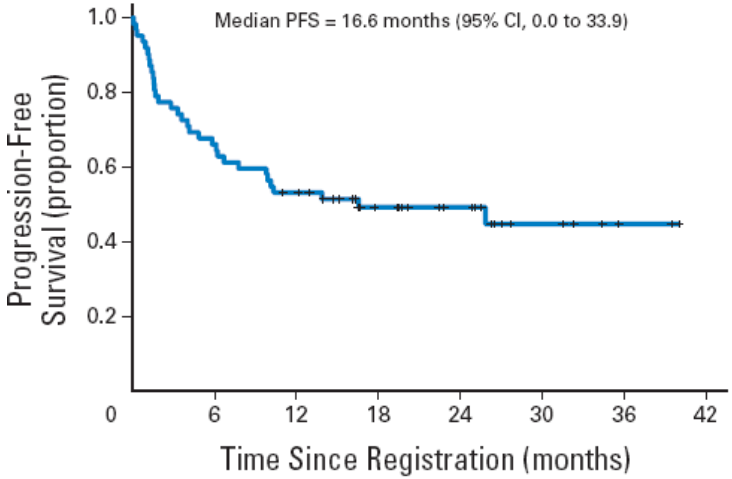
Disease Specific Survival (compared to matched control of R-CHOP patients)



Moccia et al. Blood Advances 2021)

H/o Cardiac Dysfucntion: R-GCVP

- Phase II clinical trial of R-GCVP chemotherapy in patients with cardiac comorbidity
- Median age 76.5 years, N=62 patients, 44% with low EF, remainder with borderline EF and cardiac comorbid condition
- 6 cycles of R-GCVP every 21 days with standard CVP dosing and gemcitabine on Day 1, Day 8 (escalated dosing 750 mg/m^2 →875 mg/m^2, 1000 mg/m^2
- ORR: 62%=CR 39% & PR 23%
- 2 year OS was 56%, major cause of death was relapsed NHL

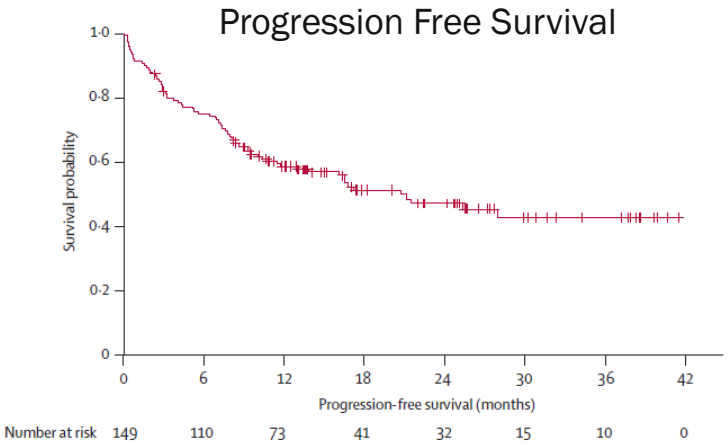


Fields, P.A., *J Clin Oncol, 2014.* ***32(4): p. 282-7.***

R-miniCHOP

Phase II study with 150 patients >80 years of ~50% dose reduction in all drugs in R-CHOP in older patients with comorbid conditions with DLBCL

Rituximab 375 mg/m^2
Cyclophosphamide 400 mg/m^2
Doxorubicin 25 mg/m^2
Vincristine 1 mg
Prednisone 40 mg/m^2 Days 1-5



POLAR BEAR Trial

R-miniCHOP vs R-miniCHP-Pola

Median age 83 years
Median PFS 21 months, 2-year PFS=47%
33 patients died of lymphoma progression
12 deaths attributed to treatment

Peyrade, F., et al. (2011). Lancet Oncol **12(5): 460-468**

Spilt-Dose R-CHOP

Split-dose R-CHOP regimen
Each cycle is 28 days and consists of one A treatment on day 1, and one B treatment on day 15 for up to 6 cycles.

Day 1 (A part of cycle)
- Rituximab 375 mg/m2 IV
- Cyclophosphamide 375 mg/m2 IV
- Doxorubicin 25 mg/m2 IV
- Vincristine 1 mg IV
- Prednisone 50 mg (days 1-5) by mouth

Day 15 (B part of cycle)
- Cyclophosphamide 375 mg/m2 IV
- Doxorubicin 25 mg/m2 IV
- Vincristine 1 mg IV
- Prednisone 50 mg (Days 15-19) by mouth

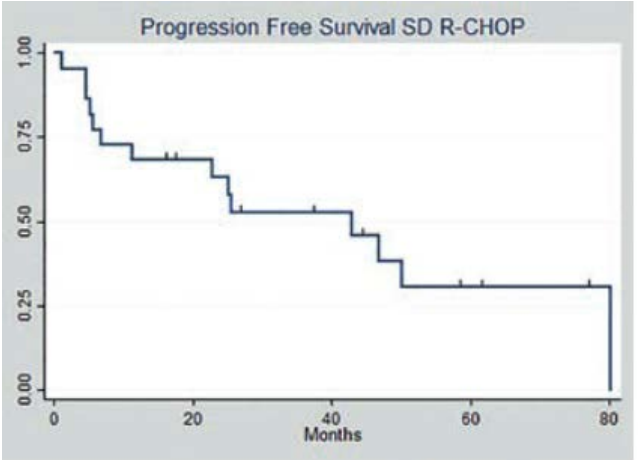
- ❑ Same cumulative dosage of R-CHOP 21 given over 24 weeks instead of 18 weeks
- ❑ Intermediate option between R-Mini CHOP and R-CHOP 21
- ❑ With neulasta and 50% dose reduction, minimal neutropenia

Split-Dose R-CHOP

Variable	Patients (N=22)
Median Age	81 years (60-90)
Diagnosis	
de novo DLBCL	13 (59%)
transformed DLBCL	9 (41%)
Female	16 (73%)
Elevated LDH	16 (73%)
Decreased Albumin	10 (45%)
Did not complete therapy	10 (45%)
Disease Stage≥3	15 (68%)
IPI≥3	14 (64%)
Charlson Comorbidity Index≥2	10 (45%)

Clinical Outcomes

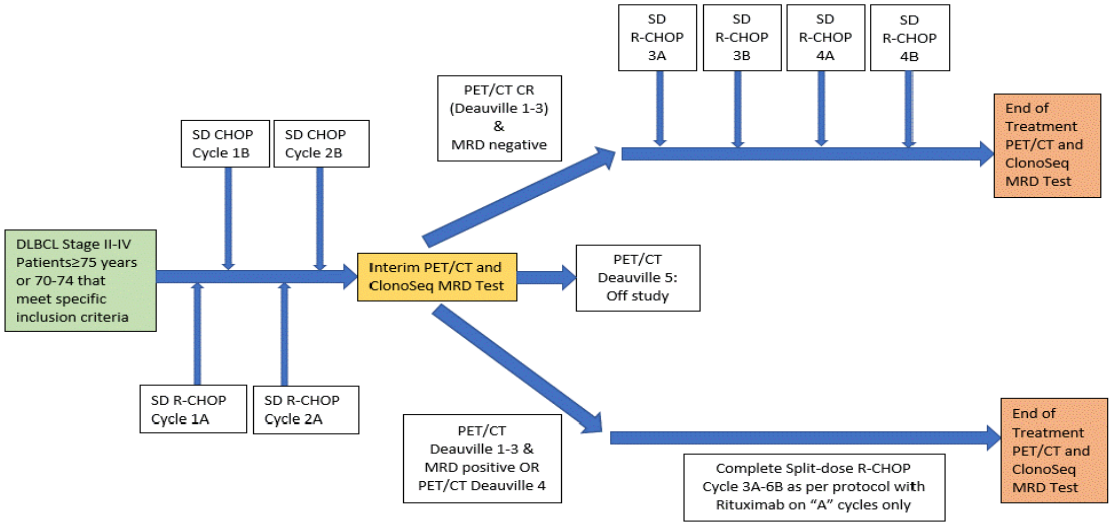
Median OS 47 months
Median PFS 26 months
Complete Response Rate=55%
2-year PFS=~60%



Shah, N.N., et al. *Journal of Community and Supportive Oncology*. Epub 30 Nov 2016;14(ll):450-456.

Phase II WON Clinical Trial

- Evaluate efficacy of split-dose R-CHOP in treatment naïve patients with DLBCL or transformed DLBCL
- Additionally use interim PET/CT and MRD testing (clonoSEQ) to allow truncation of therapy in patients with interim CR

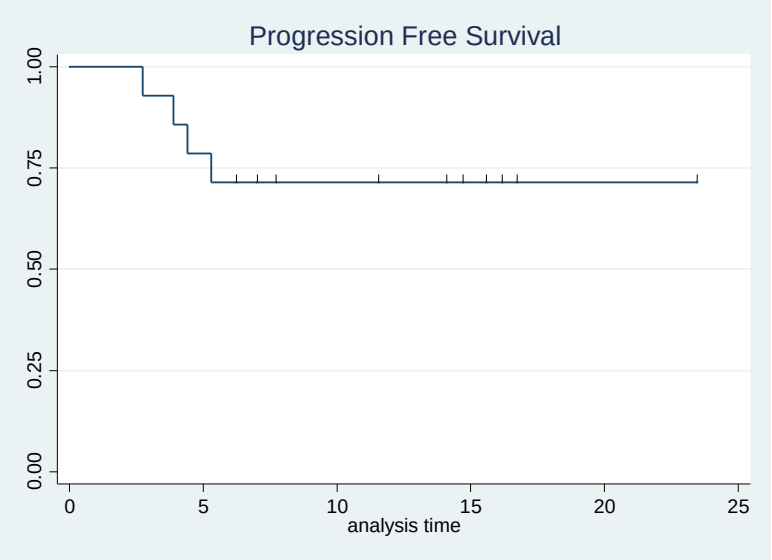


66% cumulative R-CHOP dose

100% cumulative R-CHOP dose

Interim Data

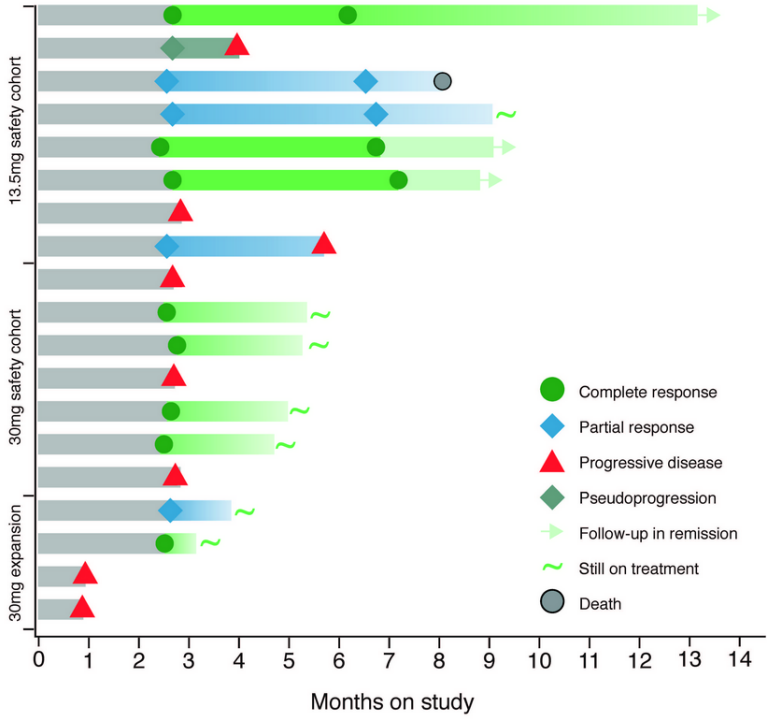
- 14 patients completed treatment
  - Median age 81 years
  - 10 patients achieved CR at end of treatment
  - 4 patients with progressive disease
  - 5 patients with interim MRD and PET negative disease proceeded with abbreviated therapy with no relapses to date
  - Met interim futility endpoint with >7 CR patients in first 16 patients
  - Only 2 deaths—1 due to PD, 1 due to PD+COVID
  - Relapse remains largest problem



Single Agent Bispecific Antibody

- Phase 1/2 trial of Mosunetuzumab CD20/CD3 bispecific antibody as single agent frontline therapy for patients age≥80 years or patients 60-79 years of age with comorbid conditions or impairment in ADLs
- 19 patients treated, median age 84 years
- 47% had CRS, all Grade 1
- 1 patient with Grade 2 ICANS
- 8 patients discontinued treatment due to PD between C2-C6
- ORR was 58% (11/19 patients) with CR rate of 42%

Figure: Duration of response and time on study by Mosun dosing cohorts.



Olszewki et al. ASH 2020

More Targeted Approaches to Come

EPCORE DLBCL-3 study

- Epcoritmab (subcutaneous CD20/CD3 bispecific antibody) with or without lenalidomide as first-line therapy for anthracycline ineligible DLBCL.

LOTIS-9 Phase II Clinical Trial

- Loncatuximab (CD19 antibody drug conjugate) + Rituximab for unfit/frail patients with treatment naïve DLBCL ineligible for R-CHOP chemotherapy

Relapsed DLBCL

- Chemotherapy Regimens
  - Rituximab-Gemcitabine-Oxaliplatin
    - Studied in older transplant ineligible patients, median age 63 years old
    - 46 patients, ORR 83%, CR 50%, 2-year EFS was 43% and 2-year OS 66%

El Gnaoui, T., et al.,. *Ann Oncol, 2007.* ***18(8): p. 1363-8.***

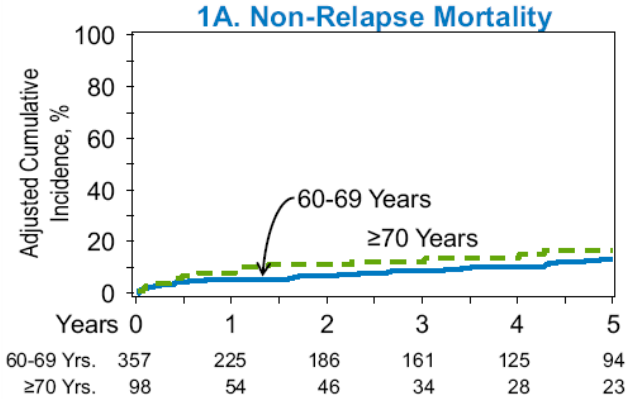
  - Bendamustine-Rituximab-Polatuzumab
    - Recently approved regimen in transplant ineligible patients, median age 67 years
    - Pola-BR with a higher CR Rate 40% vs 17.5% compared to BR alone, median PFS 9.5 vs 3.7 months

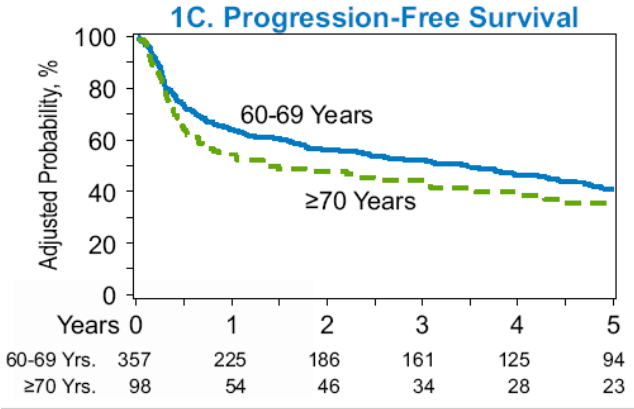
Sehn, L. H., et al. (2020). Journal of Clinical Oncology **0(0): JCO.19.00172.**

  - Other options
    - Lenalidomide-Rituximab
    - Ibrutinib (improved ORR in non-GCB phenotype)

Autologous Transplant

- CIBMTR analysis of patients undergoing auto-HCT comparing patients aged 60-69 years versus age≥70 years
- 103 patients ≥70 years (70-79 years)
- No difference in non-relapse mortality or progression free survival between the two age groups.
- 5-year PFS 60-69 years=52% versus ≥70 years=44%, p=0.16



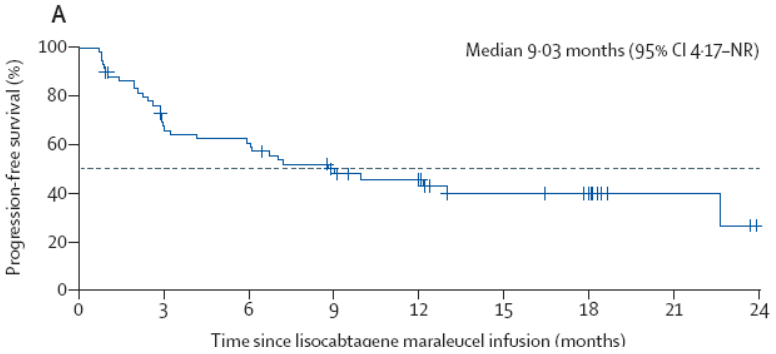


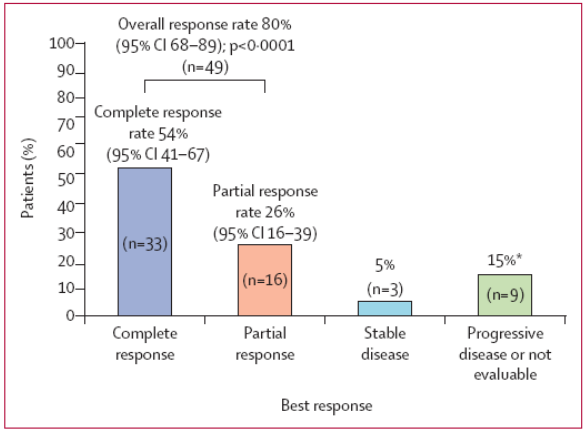
Munshi P…Hamadani, M. TCT 2022

CAR-T cell Therapy

- CAR-T cell therapy with increased utilization in older patients
- **Phase II PILOT Trial: Patients with relapsed DLBCL who were deemed to be transplant ineligible, were given lisocabtagene maraleucel CD19 CAR T-cells as a second-line treatment**
  - 61 treated patients
  - Median age: 74 years (53-84 years)
  - 84% received R-CHOP as frontline treatment
  - Overall Response Rate: 84%
  - CRS 38%, mostly Grade 1-2
  - ICANS in 31%, mostly Grade 1-2
  - No treatment related deaths

Progression Free Survival



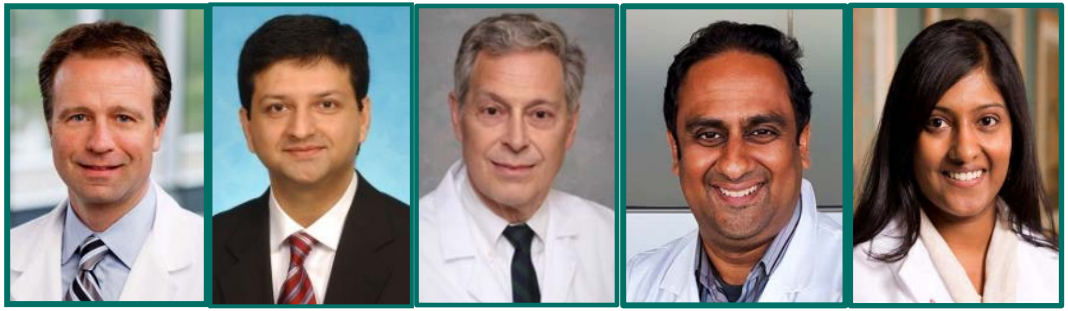


Sehgal, A.R., et al. *Lancet Oncology, 2022*

Summary

- Age is a number, and it alone should not be used to dictate treatment for patients with DLBCL
- Anthracycline based chemotherapy should be offered to all healthier patients independent of age
- Modified regimens for frontline DLBCL include R-miniCHOP, split-dose R-CHOP, or other regimens designed to minimize specific toxicities (e.g., no anthracycline for patients with h/o cardiac toxicities)
- The main cause of death in DLBCL patients remains relapse of disease (not toxicities of chemotherapy)
- Novel agents and immunotherapy offer high response rates with low toxicity profile but unclear curative intent outside of CAR-T as single agent

MCW Lymphoma Team



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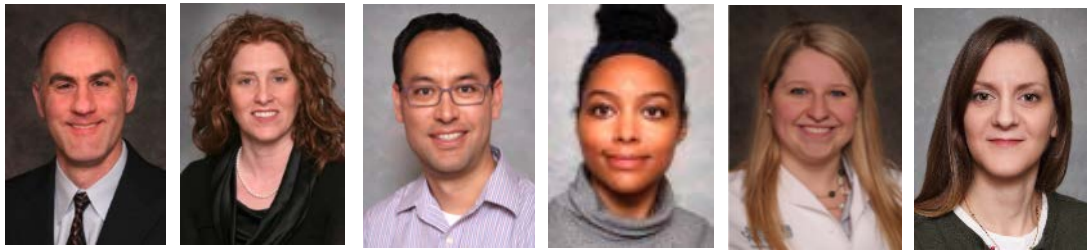

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And: Pharmacists, BMT coordinators, Inpatient nurses, radiology, many other specialists…

Questions