Treating Frail Adults With Common Malignancies:
Best Evidence to Personalize Therapy

Treating for Cure or Palliation: Difficult Decisions for Older Adults with Lymphoma

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Disclosures

- Speaker honoraria: BMS

Agenda

- Aging and lymphoma
- Immunosenescence and antitumoral immune response
- Evasion mechanisms of immune response in lymphoma
- Tailoring therapy in older patients with lymphoma
- Efficacy and safety of immunotherapy in older patients with lymphoma

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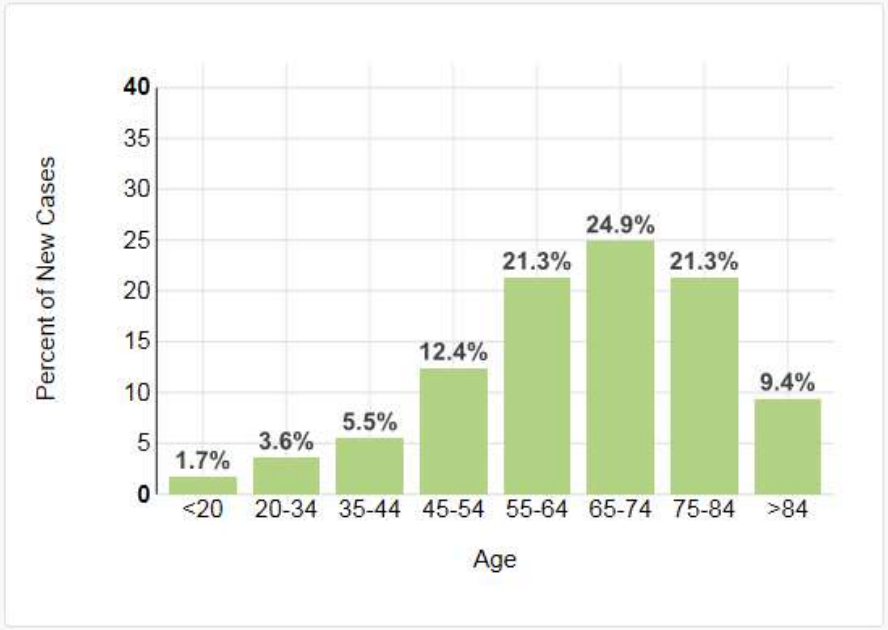
Higher incidence of NHL in older people

Percent of New Cases by Age Group: Non-Hodgkin Lymphoma



Non-Hodgkin lymphoma is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

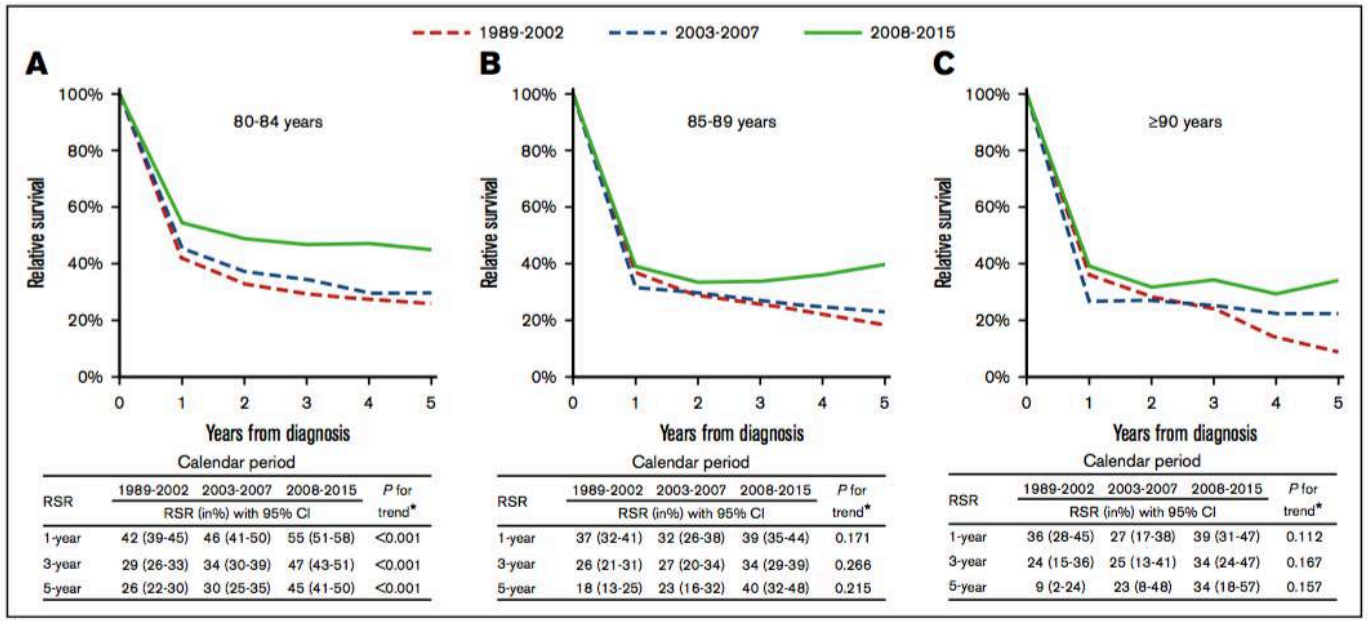
67

SEER 18 2010-2014, All Races, Both Sexes

https://seer.cancer.gov/statfacts/html/nhl.html

Improvement of outcome in older DLBCL patients

Treatment and relative survival in very elderly patients with DLBCL in The Netherlands: a population-based study, 1989 to 2015



Calendar period

RSR	1989-2002	2003-2007	2008-2015	P for trend*
	RSR (in%) with 95% CI			
1-year	42 (39-45)	46 (41-50)	55 (51-58)	<0.001
3-year	29 (26-33)	34 (30-39)	47 (43-51)	<0.001
5-year	26 (22-30)	30 (25-35)	45 (41-50)	<0.001

Calendar period

RSR	1989-2002	2003-2007	2008-2015	P for trend*
	RSR (in%) with 95% CI			
1-year	37 (32-41)	32 (26-38)	39 (35-44)	0.171
3-year	26 (21-31)	27 (20-34)	34 (29-39)	0.266
5-year	18 (13-25)	23 (16-32)	40 (32-48)	0.215

Calendar period

RSR	1989-2002	2003-2007	2008-2015	P for trend*
	RSR (in%) with 95% CI			
1-year	36 (28-45)	27 (17-38)	39 (31-47)	0.112
3-year	24 (15-36)	25 (13-41)	34 (24-47)	0.167
5-year	9 (2-24)	23 (8-48)	34 (18-57)	0.157

Dinmohamed AG et al. Blood Advances 2017;1:1839-1841

Specific Entities of Lymphoma in the Elderly

- Age-Related Molecular Specificities in DLBCL[1]
  - Median age of occurrence of GC-DLBCL is 8 years younger than ABC-DLBCL[2]
  - More unfavorable genetic features: higher BCL2 expression, high genomic complexity[3]

- EBV DLBCL of the Elderly
  - "DLBCL of the elderly" will be replaced by EBV+ DLBCL, NOS[4]
  - New entity "EBV+ mucocutaneous ulcer", associated with age-related immunosenescence[4]

1. Sarkozy C et al. Curr Oncol Rep. 2015;17(7):32
2. Mareschal S et al. Haematologica. 2011;96(12):1888-90
3. Klapper W et al. Blood. 2012;119:1882–7
4. Swerdlow SH et al. Blood. 2016;127(20):2375-2390

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Immunosenescence

A) Host related

Age[1]

Chronic inflammation. Example: CMV[2]

B) Disease related

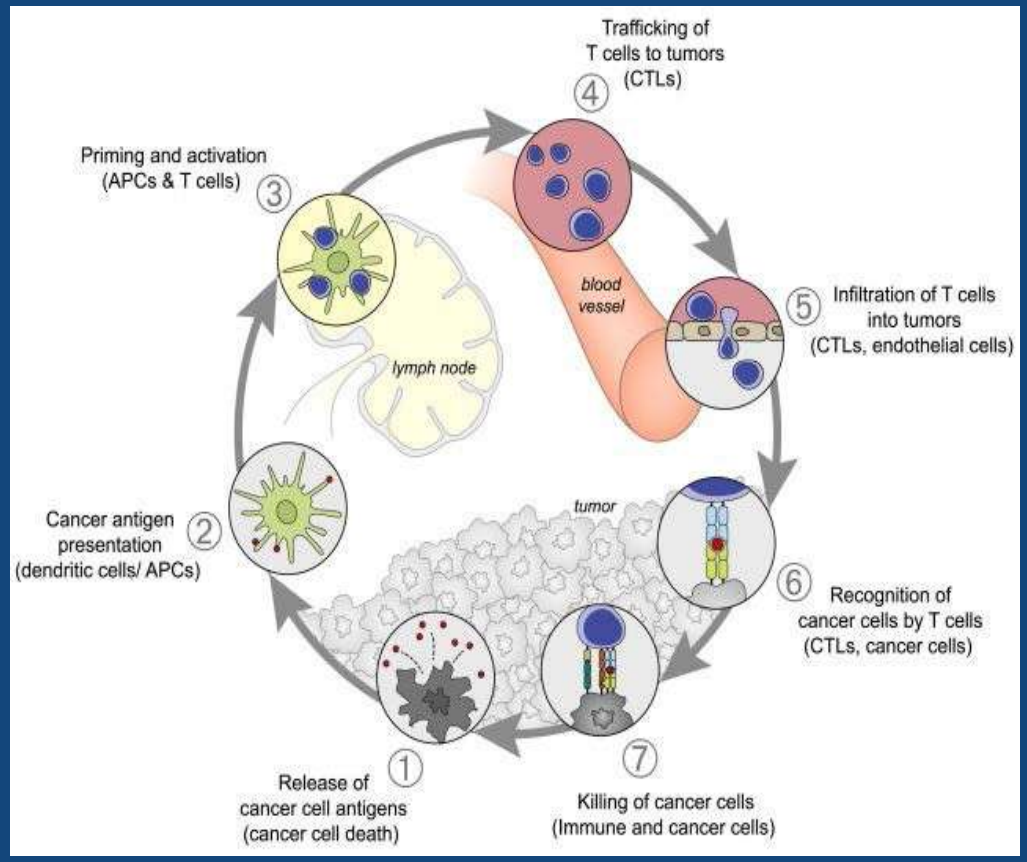
Impairment in antigen presentation. Example: PMBCL

Immunosupressive phenotype. Example: HL, PMBCL, PCNSL, PTL

T-cell exhaustion. Example CLL[3-4]

1. Nikolich-Zugish J. Nature Immunology 2018; 19:10-19
2. Caruso C et al. *Immunity & Ageing* 2009, **6**:10
3. Gassner FJ et al. Br J Haematol 2015;170(4):515-22
4. Jimenez I et al. Blood 2017; 130:1713

The cancer-immunity cycle



Chen D, Mellman I. Immunity 2013;39(1):1-10

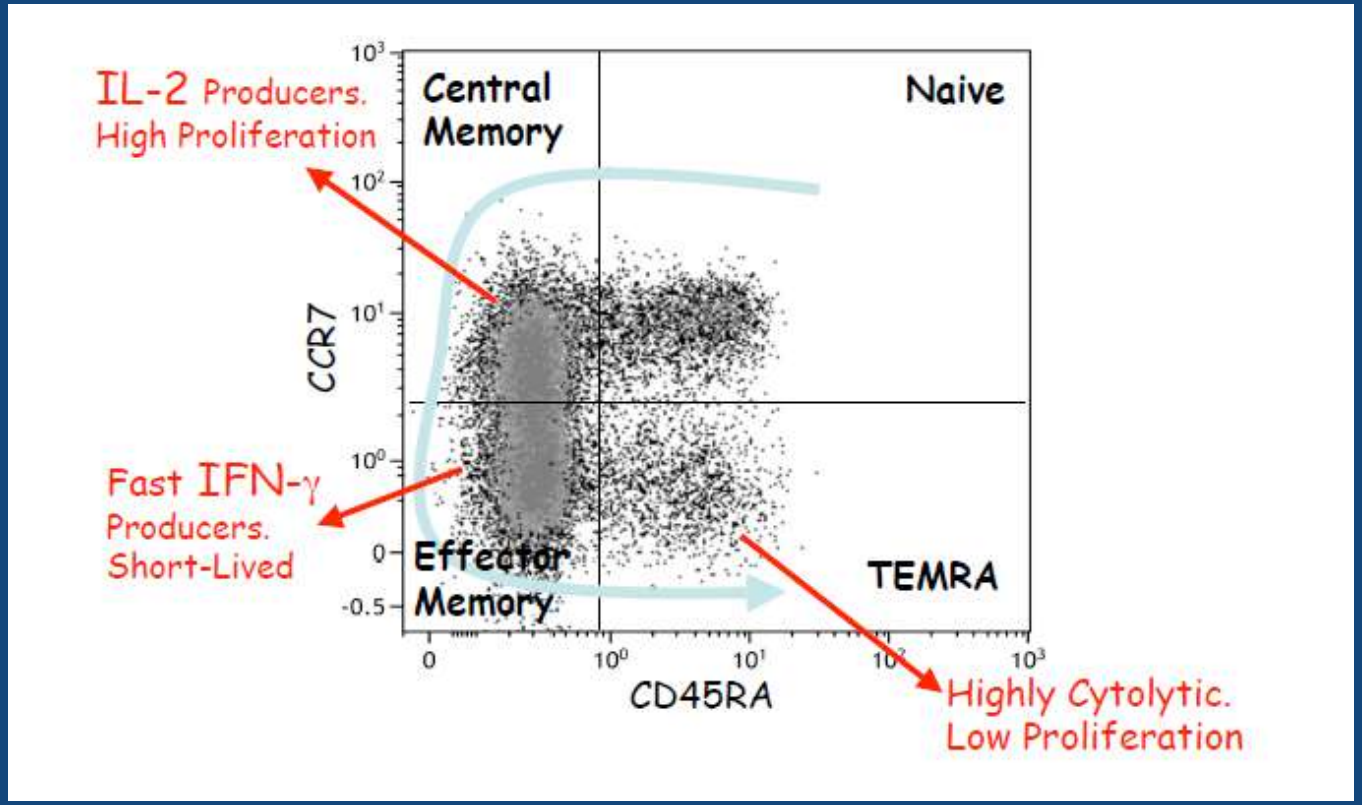
Impairment of the cancer-immunity cycle with age

Summary of major age-associated changes in immune cell function that might impact ICIs.

Type of cells	Alterations with aging
Dendritic cells	• Decreased number of cells [35–41] • Impaired TLR signaling [42] • Decreased phagocytic and migratory function [43] • Down-regulation of CD80 and CD86 [37,45] • Decreased secretion of IFN-α [40,44–48]
CD4 + T cells	• Decreased TCR diversity [62] • Impaired function of naïve CD4 + T cells [63] • Decreased CD28 expression [64–66] • Decreased CD40 ligand expression [64,65]
CD8 + T cells	• Decreased lymphocyte production [51–55] • Decreased CD8+ naïve T cell pool [71] • Decreased TCR diversity [63] • Increased late stage cells with decreased CD28 expression [74–76] • Decreased clonal expansion [77] • Higher expression of CD57 [80,81] • Increased PD-1 expression [68–70] • Increased sensitivity to apoptotic signals [73] • Lower levels of perforin and granzyme [70]
T regulatory cells	• Increased number of CD4 + T regulatory cells [76,99–102] • Higher suppressive activity [76,99–102] • Increased number of CD8 + T regulatory cells [103]
MDSC	• Age-associated increase in numbers in both tumor stroma and circulation [117]
M2 Macrophages	• Controversial but suggestion of increased M2 polarization with age [121–123]

Elias R et al. J Geriatr Oncol. 2017;8(3):229-235

How to assess immunosenescence?



Mahnke YD et al. Eur J Immunol 2013;43(11):2797-2809

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Evasion mechanisms of immune response in lymphoma

- Alterations in 9p24.1 PD-L1/PD-L2[1]
- Inactivating mutations/deletions of B2M (MHC class I)[2]
- Inactivating mutations of CIITA (MHC class II)[3]

1. Green MR et al Blood. 2010;116(17):3268–77
2. Roemer MGM et al. Cancer Immunol Res 2016; 4(11):910.
3. Roberts RA et al. Blood. 2006;108(1):311-8

Overexpresion of PD-L1 in lymphoma

- Alterations in copy number
  - Frequent in HL[1], PMBCL[1], PCNSL[2], PTL[2]
- Chromosomal traslocations
  - Less frequent, but recurrent in HL[3], PMBCL[4], PCNSL[2] y PTL[2]
- Viral infections: EBV+[5,6]
  - HL, PTLD, DLBCL, PBL

1. Green MR et al Blood. 2010;116(17):3268-77
2. Chapuy B et al. Blood. 2016;127(7):869-81
3. Roemer MGM et al. J Clin Oncol 2016;34(23):2690
4. Twa DD et al. Blood. 2014;123(13):2062-5.
5. Green MR et al. Clin Cancer Res. 2012;18(6):1611-8.
6. Bi XW et al. J Hematol Oncol. 2016;9(1):109.

Is there any difference in overexpresion of PD-L1 in elderly DLBCL patients?

	9p24.1 Normal	%	9p24.1 Gain	%	9p24.1 High Gain	%	P-value
Age							0.115
<60	62	35	8	53	4	67	
>60	116	65	7	47	2	33	
COO							
GCB	98	67	4	36	2	33	0.039
ABC/non-GCB	49	33	7	64	4	67	
Unclassified	13		2				
Missing	18		2				

- No differences in 9p24.1 gain among younger vs older patients
- 9p24.1 gain was associated with ABC subtype

Wang Y et al. ASH 2017

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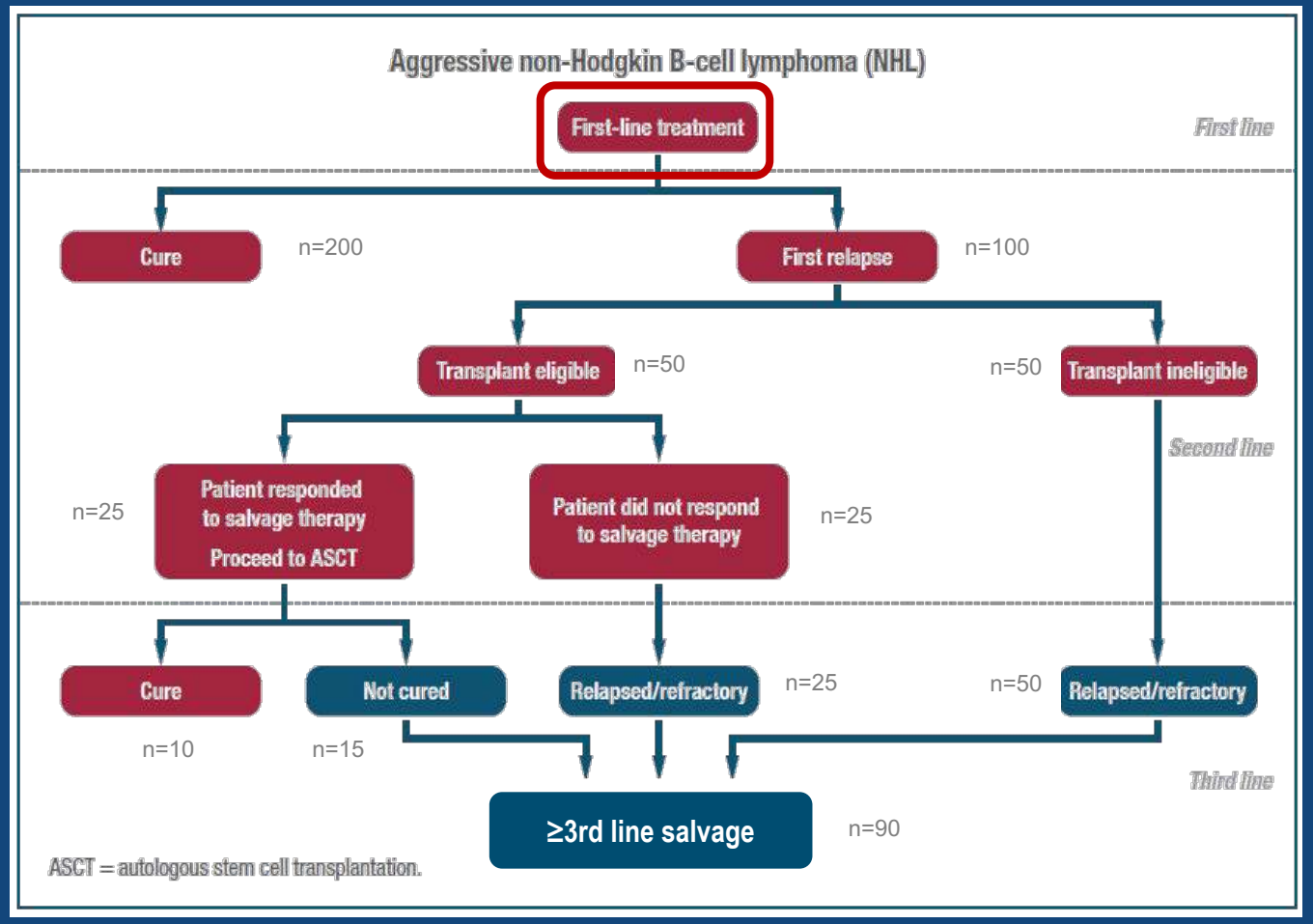
Treatment algorithm for aggressive B-cell NHL



Adapted from: Friedberg JW. Hematology Am Soc Hematol Educ Program. 2011

Practical Assessment in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology

Assessment	Tool
Predict chemotherapy toxicity	CARG, CRASH
Estimate (noncancer) life expectancy	ePrognosis
Functional assessment	IADL
Comorbidity assessment	CIRS-G, CCI
Screening for falls	How many falls have you had in the previous 6 months (or since your last visit)?
Screening for depression	GDS
Screening for cognitive impairment	Mini-COG
Screening for malnutrition	weight loss/body mass index

Mohile SG et al. J Clin Oncol 2018; May 21:JCO2018788687

SIOG guidelines on DLBCL in the elderly: Impact of prognosis, comorbidities, geriatric assessment[1] and approach to therapy[2]

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

Comorbidity	Treatment agents
Cardiovascular	Anthracyclines
Renal dysfunction	Platinum derivates
Neuropathy	Platinum derivatives, vinca alkaloids, lenalidomide
Diabetes	Prednisone
Pre-existent marrow compromise (prior chemotherapy, radiation)	Any myelosuppressive agents
Dementia	All therapies

Therapy	n	Median age, years (range)	Efficacy, CR rate		P value
			RCHOP	CHOP	
CHOP vs RCHOP21	399	69 (60-80)	76%	63%	0.005
CHOP vs RCHOP14	1222	69 (60-80)	78%	68%	0.007
CHOP vs RCHOP21	632	69 (60-80)	77%	76%	NS
			RCHOP21	RCHOP14	
RCHOP21 vs RCHOP14	602	70 (60-80)	74%	71%	NS
RCHOP21 vs RCHOP14	1080	61 (19-88)	63%	58%	NS

1. Morrison VA et al. J Geriatr Oncol. 2015;6(2):141-52
2. Morrison VA et al. Ann Oncol. 2015;26(6):1058-68

DLBCL patients who may benefit from a curative treatment

Patient characteristics	N	%
Total number of evaluable patients	252	
Male	100	40
Age, years; median (range)	83 (80-100)	
Older than 85	59	23
ECOG 0-1	147	58
R-IPI		
Intermediate risk (1-2)	99	41
High risk (3-5)	145	59

Patient characteristics	N	%
CIRS<6	126	50
First line treatment		
R-CHOP	108	43
Others	144	57
Rituximab in 1st or subsequent lines	147	58
Anthracyclines in 1st or subsequent lines	130	51

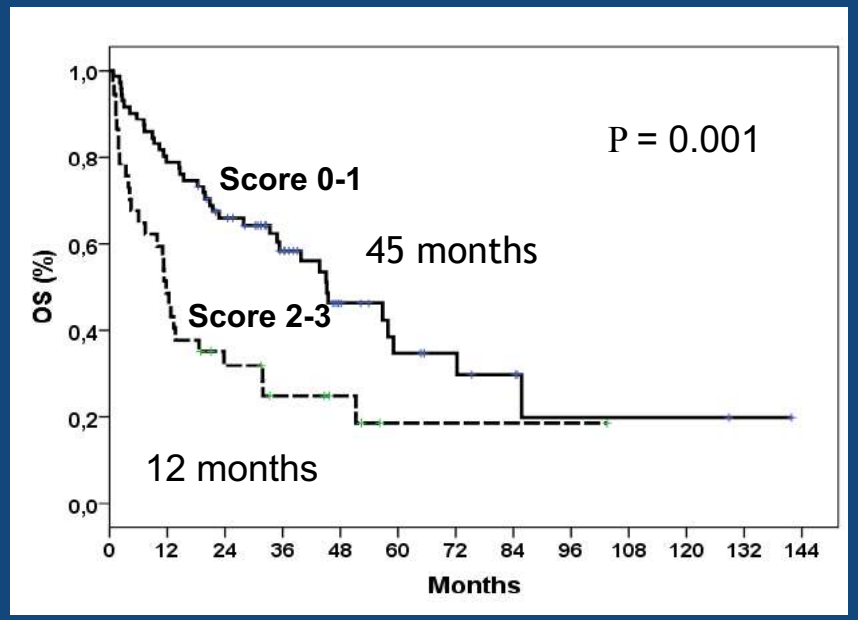
Pardal E et al. Am J Hematol 2018 Apr 15

DLBCL patients who may benefit from a curative treatment

Multivariate analysis for survival restricted to patients treated with R-CHOP at full or reduced doses

Prognostic factor	PFS	P	OS	P
	RR (IC 95%)		RR (IC 95%)	
Age		0,137	0,53 (0,28-0,99)	0,049
< 86 years				
≥ 86 years				
CIRS score	0,53 (0,33-0,83)	0,01	0,52 (0,31-0,86)	0,01
< 6				
≥ 6				
R-IPI	0,59 (0,36-0,95)	0,032	0,57 (0,34-0,96)	0,033
Int risk (1-2)				
High risk (3-5)				

Overall survival of patients treated with R-CHOP at full or reduced doses according to prognostic factors



Pardal E et al. Am J Hematol 2018 Apr 15

CGA to support treatment decisions in older patients with lymphoma

Table I. Definition of three geriatric risk categories according to age, comorbidities and functional abilities of daily living.

	CGA category		
	Fit	Unfit	Frail
ADL	6	5*	≤4*
IADL	8	6–7*	≤5*
CIRS-G	No comorbidity score 3–4 and <5 comorbidities score 2	No comorbidity score 3–4 and 5–8 comorbidities score 2	≥1 Comorbidity score 3–4 or >8 comorbidities score 2
Age		≥80 fit	≥80 unfit

ADL, activity of daily living; IADL, instrumental activity of daily living; CIRS-G, Cumulative Illness Rating Score for Geriatrics; CGA, comprehensive geriatric assessment.
*Number of residual functions.

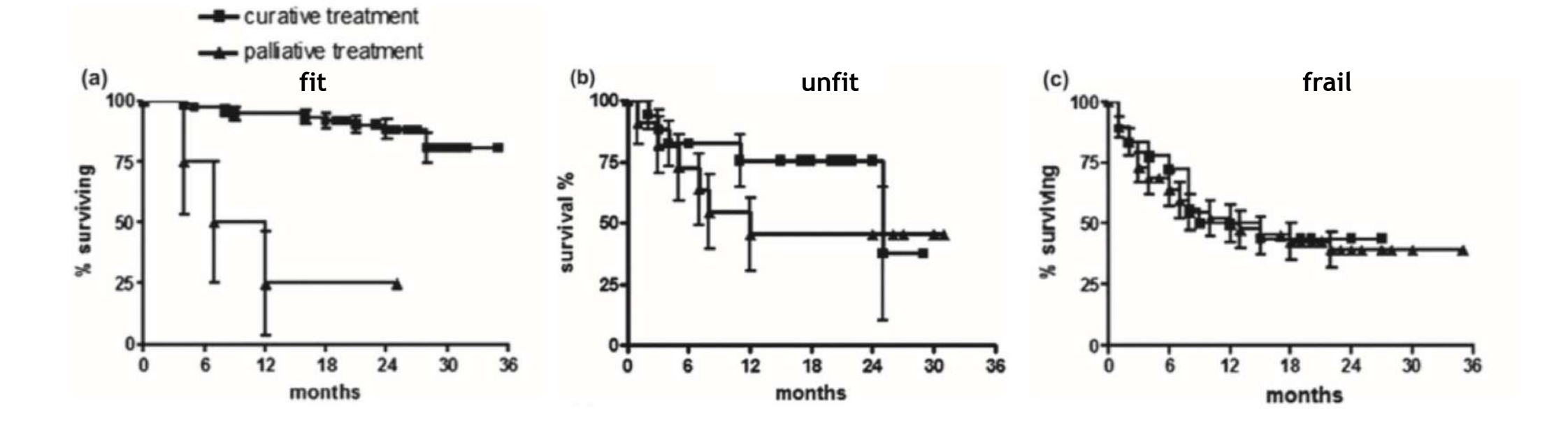
Table IV. Overall survival time according to patient and treatment characteristics (univariate and multivariate Cox regression analysis).

Variables	Univariate HR (95% CI)	*p*-Value	Multivariate HR (95% CI)	*p*-Value
Age < 80 vs. ≥ 80 years	2.67 (1.61–4.44)	0.0002		
Stage I–II vs. III–IV	1.59 (0.92–2.74)	0.09		
IPI (intermediate-low/low vs. intermediate-high/high)	3.72 (1.80–7.68)	0.0003	4.60 (1.35–15.64)	0.008
CGA	5.61 (2.95–10.64)	0.0001	3.69 (1.09–12.51)	0.03
ADL (≤5 vs. 6)	0.3 (0.17–0.51)	0.0001		
IADL (≤6 vs. ≥7)	0.24 (0.14–0.41)	0.0001		
CIRS-G grade 2 (<5 vs. ≥5)	2.89 (1.04–8.03)	0.04		
CIRS-G grade 3–4 (0 vs. ≥1)	2.14 (1.22–3.73)	0.007		
Curative vs. palliative treatment approach	0.27 (0.16–0.46)	0.0001		
Treatment dose (<70% vs. ≥70%)	0.38 (0.17–0.86)	0.02		

IPI, International Prognostic Index; CGA, comprehensive geriatric assessment; ADL, activity of daily living; IADL, instrumental activity of daily living; CIRS-G, Cumulative Illness Rating Score for Geriatrics; HR, hazard ratio; CI, confidence interval.

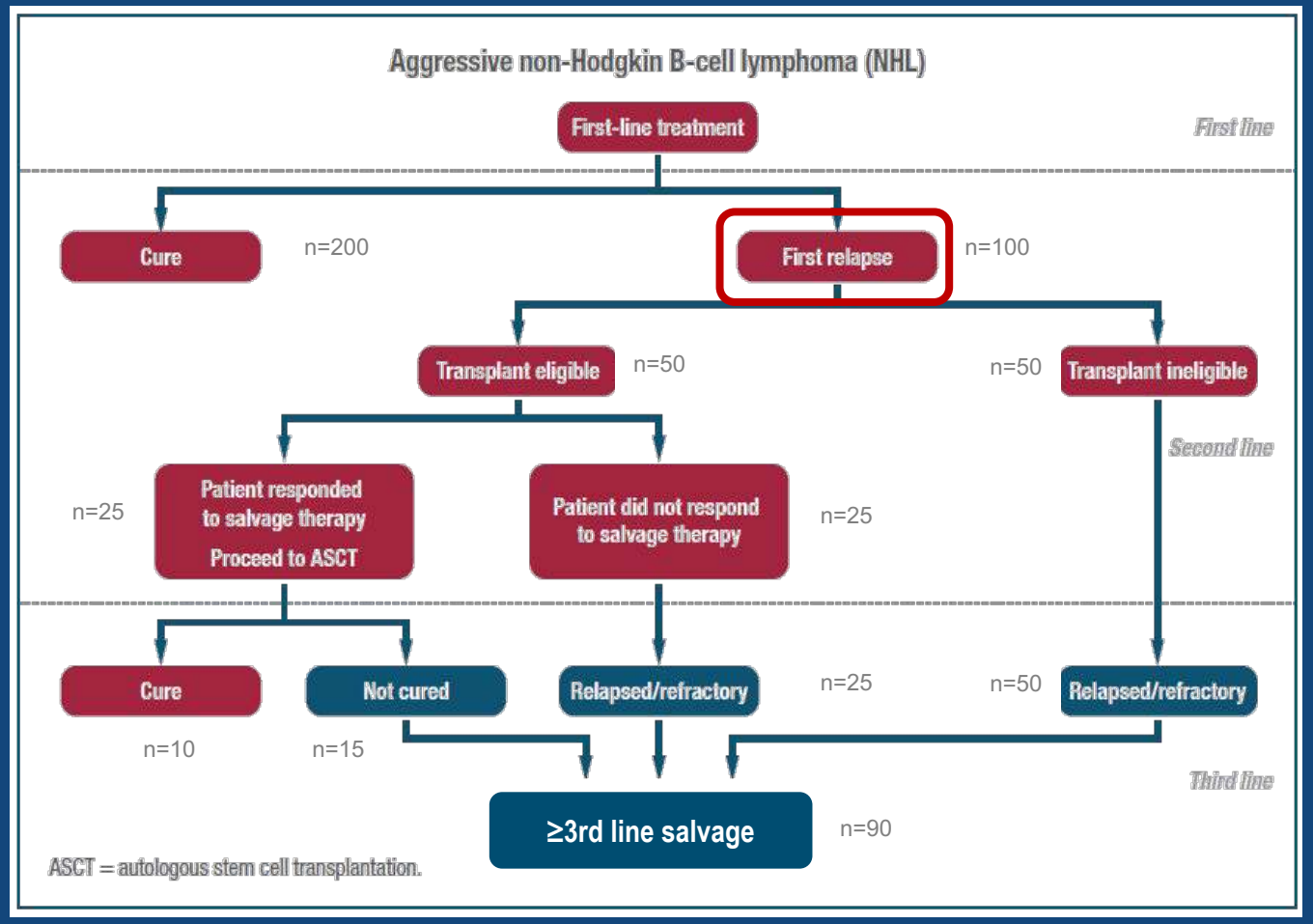
Tucci A et al. Leuk Lymphoma 2015; 56(4): 921–926

OS of fit (a), unfit (b) and frail (c) older patients with DLBCL



Tucci A et al. Leuk Lymphoma 2015; 56(4): 921–926

Treatment algorithm for aggressive B-cell NHL



Adapted from: Friedberg JW. Hematology Am Soc Hematol Educ Program. 2011

Autologous Stem Cell Transplantation in Elderly Lymphoma Patients

Inclusion age criteria, study [reference]	Disease	Setting	No. of patients	Median age, years (range)	OS (year)	PFS (year)	NRM
Age >65							
Hosing et al., 2008 [19]	NHL	Single-center	99	68 (65–82)	61% (3 yr)	NR	8% (2 yr)
Elstrom et al., 2011 [14]	Lymphoma	Single Center	21	71 (69–86)	18 months (median)	8 months (median)	NR
Jantunen et al., 2012 [17]	Mantle cell	Multicenter	79	67 (65–73)	61% (5 yr)	29% (5 yr)	3.8% (100 d)
Schorb et al., 2017 [25]	PCNSL	Multicenter	52	68.5 (65–77)	70.8% (2 yr)	62% (2 yr)	3.8% (100 d)
Age >70							
Andorsky et al., 2011 [26]	Lymphoma	Single Center	17	72 (70–78)	31 months (median)	NR	17.6% (100 d
Hermet et al., 2015 [20]	NHL	Multicenter	81	72 (70–80)	43 months (median)	21 months (median)	5.4% (100 d)

Sun L et al. Oncologist. 2018;23(5):624-630

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PD-1 blockade in HL

Lymphoma	Antibody, dose	Phase; No. of patients	ORR, CR	PFS; OS; duration of response	Rates of all AEs, grade 3-4 AEs	Age, years, median (range)	Older adults (>65 y.o.)
R/R cHL	Nivolumab, 3 mg/kg every 2 weeks	Phase I; n=23	87%, 17%	PFS: 86% at 24 weeks; OS: 91% at 1 year and 83% at 1.5 years; 35% of responders, sustained maintained response	78%, 22%	35 (20-54)	N=0, 0%
R/R cHL that progressed after BV	Pembrolizumab, 10 mg/kg q2w	Phase Ib; n=32	65%, 16%	PFS: 46% at 52 weeks; 70% of responses lasted longer than 24 weeks	97%, 16%	32 (20-67)	N=1, 3%
R/R cHL that failed to respond to ASCT and BV	Nivolumab, 3 mg/kg every 2 weeks	Phase II; n=80	68%, 13%	At 6 months, PFS: 76.9%; OS: 98.7%; at 12 months, median PFS: 10.0 months	99%, 41%	39 (18-72)	N=3, 4%
R/R cHL, progressed after ASCT and/or BV	Pembrolizumab, 200 mg once every 3 weeks, (median No. of treatment cycles: 13)	Phase II; n=210	69%, 22.4%	At 6 months, PFS: 72.4%; OS: 99.5%; 75.6% of patients had a response for ≥6 months	63%; irAEs: 28.6%; IRR: 6.4%.	All patients: 35 (18-76) Cohort 1 (after ASCT/BV): 34 (19-64) Cohort 2 (ASCT ineligible and BV failure): 40 (20-76) Cohort 3 (no BV after ASCT): 32 (18-73)	All patients: n=18, 8.6% Cohort 2: n=15, 18.5% Cohort 3: n=3, 5.0%

Cordoba R. ASCO Educational Book 2018

PD-1 blockade in NHL

Lymphoma	Antibody, dose	Phase; No. of patients	ORR, CR	PFS; OS; duration of response	Rates of all AEs, grade 3-4 AEs	Age, years, median (range)	Older adults (>65 y.o.)
R/R NHL and MM	Nivolumab, 1-3 mg/kg every 2 weeks	Phase Ib; FL: n=10, DLBCL: n=11, other B-NHL: n=10, TNHL:n=23, MM: n=27	FL: 40%,10%; DLBCL: 36%, 18%; other B-NHL: 0%, 0%; T-NHL: 17%, 0%; MM: 4%, 4%	Duration of response: 6.0-81.6 weeks.	All AEs: 63%; (for B-NHL: 71%, 26%)	B-Cell Lymphoma 65 (23-74) T-cell lymphoma 61 (30-81)	Included, but no % reported
R/R PMBCL	Pembrolizumab, 10 mg/kg q2w or 200 mg q3w for up to 2 years	Phase Ib; n=18	41%, 11.8%	Median duration of response and OS were not reached	61%, 11.8%	30 (22-62)	N=0; 0%
R/R CLL with RT and relapsed CLL	Pembrolizumab, 200 mg every 3 weeks for up to 2 years	Phase II; n=25 (transformed DLBCL: n=9, Relapsed CLL: n=16)	RT (transformed DLBCL): 44%, 11%; Relapsed CLL: 0%, 0%	Median OS: 10.7 months for R/R CLL with RT, not reached among patients with prior ibrutinib therapy.	100%, 60%	Total 69 (46-81) RT 69 (46-78) CLL 72 (59-81)	Total* 4 (44%) RT* 9 (56%) CLL* 13 (52%) *>70 y.o.
R/R PCNSL and PTL	Nivolumab, 3 mg/kg iv q2w	R/R PCNSL: n=4, PTL with CNS relapse: n=1.	100%, 80%	3 patients remained free of progression at 13+ to 17+ months.	60%, 20%	64 years (54-85)	N=3, 60%

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Take home messages

- The increasing median age at diagnosis of NHL urges to deliver special health care to older patients
- CGA will allow to identify older patients who are candidates to receive a curative therapy, not only at diagnosis but also at first relapse
- Immunosenescence may play a role in lymphomagenesis and it should be explored before an immunotherapy approach: towards an “Immune Comprehensive Assessment”
- There are very limited data about the efficacy and safety of immunotherapy in older patients with lymphoma, though it seems feasible
- CAR T cells would be a treatment strategy feasible for older patients with R/R B-cell NHL