ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

- KATEDRA ZA ONKOLOGIJO
- SEKCIJA ZA INTERNISTIČNO ONKOLOGIJO

Slovensko Zdravniško Društvo

4. LIMFOMSKA ŠOLA

Zbornik predavanj
na 4. limfomski šoli 15. novembra 2024

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

SZD
Sekcija
za internistično onkologijo

4. limfomska šola/4th school of malignant lymphomas

Petek, 15.11.2024, ob 9.00 uri

Onkološki inštitut Ljubljana, predavalnica C/p

PROGRAM

8.30-9.00 – *registracija udeležencev*

1. Sklop : Limfomi kože - Skin lymphomas 9.00-11.00 – predavanja v angleščini

9.00 – 9.05: Doc. Gorana Gašljević – pozdravni govor in uvod v srečanje
9.05 – 9.35: Prof. John Goodlad – Classification of skin lymphomas
9.35 – 9.50: Doc. Gorana Gašljević – Skin lymphomas in Slovenia 2000-2024: incidence and histologic types
9.50 – 10.05: Prof. Veronika Kloboves Prevodnik – Cutaneous lymphomas in cytology
10.05 – 10.35: Prof. John Goodlad – Cutaneous lymphoma: separating the sheep from the wolves however they are dressed
10.35 – 11.00: Discussion

Coffee break 11.00 – 11.20

Nadaljevanje 1. sklopa 11.20-12.30

11.20 – 11.50: Prof. Mateja Dolenc Voljč - Mycosis fungoides and Sezary syndrome
11.50 – 12.05: Doc. Lučka Boltežar - Systemic therapy of T cell skin lymphomas
12.05 – 12.20: Doc. Lorna Zadravec Zaletel - Radiotherapy in T cell skin lymphomas
12.20 – 12.30: Discussion

Kosilo 12.30-13.20

2. Sklop : Novosti v zdravljenju drobnoceličnih limfomov B 13.20-14.55 – predavanja v slovenščini

13.20 – 13.35: Dr. Milica Miljković - Novosti v zdravljenju limfoma plaščnih celic
13.35 – 13.50: Dr. Aleš Mihelač - Novosti v zdravljenju marginalnoceličnega limfoma
13.50 – 14.05: Dr. Tanja Južnič in dr. Urška Rugelj - Novosti v zdravljenju folikularnega limfoma
14.05 – 14.20: Doc. Matevž Škerget - Novosti v zdravljenju KLL in Waldenstroemove makroglobulinemije
14.20 – 14.40: Prof. Barbara Jezeršek Novaković - Novosti v zdravljenju Richterjeve transformacije KLL v DVCLB
14.40 – 15.00: Discussion
15.00 – Zaključek srečanja – prof. Barbara Jezeršek Novaković

Po prvem sklopu se patologi umaknejo v skupni seminar na Oddelku za radiologijo:
Live-microscopy session:
Participants: dr. Violeta Hosta, dr. Živa Gramc, dr. Živa Ledinek, dr. Biljana Grčar-Kuzmanov, doc. Barbara Gazić, dr. Aleš Rode, dr. Milan Car, prof. Veronika Kloboves-Prevodnik (dr. Anja Jeričević), doc. Gorana Gašljević
Prof. Goodlad: Dealing with epidermotropism: Problems, Pitfalls and Practical Solutions

Prijava na dogodek je obvezna in je možna le preko spletne povezave do 13.11.2024:
https://www.1ka.si/a/48855b1d

Organizacijski in strokovni odbor: doc. dr. Lučka Boltežar, prof. dr. Barbara Jezeršek Novaković, doc. dr. Gorana Gašljević, prof. dr. Veronika Kloboves Prevodnik

Zdravniška zbornica Slovenije bo za udeležbo dodelila **9 kreditnih točk.**
KOTIZACIJE NI.

4. LIMFOMSKA ŠOLA
Zbornik predavanj

Urednik zbornika:
Marko Boc, dr.med.

Recenzija:
prof. dr. Barbara Jezeršek Novaković, dr.med.

Organizator:
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Kraj in leto izida: Ljubljana, 2024

Zborniki šol in ostale publikacije s strokovnih dogodkov so dosegljivi na spletnih straneh OI: www.onko-i.si/publikacije-strokovnih-dogodkov-oi

AVTORJI:
(po abecednem vrstnem redu)

doc. dr. Lučka Boltežar, dr.med.
Ana Čebokli, dr.med.
prof. dr. Mateja Dolenc Voljč, dr.med.
doc. dr. Gorana Gašljević, dr.med.
prof. dr. Barbara Jezeršek Novaković, dr.med.
prof. dr. Veronika Kloboves Prevodnik, dr.med.
Aleš Mihela , dr.med.
Milica Miljković, dr.med.
Urška Rugelj, dr.med.
doc. dr. Matevž Škerget, dr.med.
doc. dr. Lorna Zadravec Zaletel, dr.med.

KAZALO

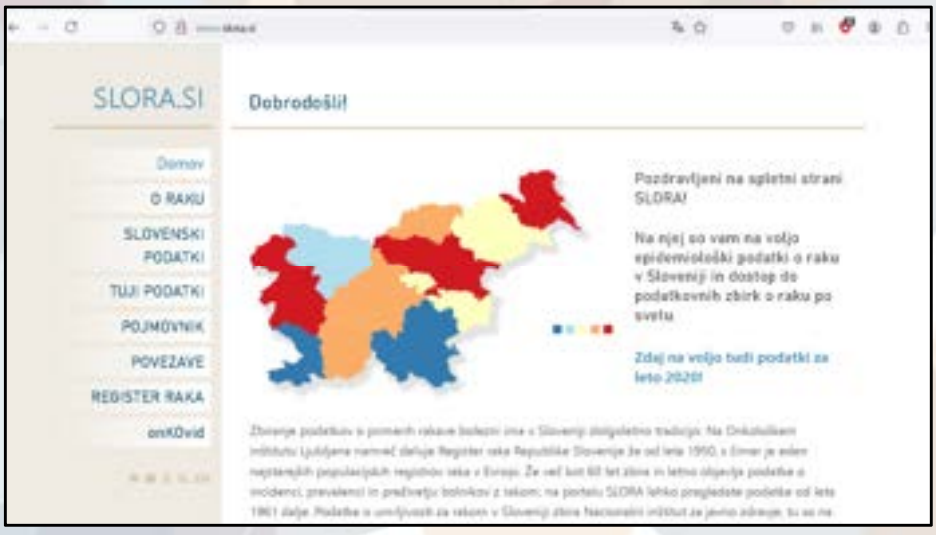
ONKOLOŠKI INŠTITUT LJUBLJANA

INSTITUTE OF ONCOLOGY LJUBLJANA

VERY BASIC EPIDEMIOLOGY OF SKIN LYMPHOMAS IN SLOVENIA 2000-2022 : simplified pathologist‘s view

Gorana Gašljević, Department of Pathology
(Vesna Zadnik & Tina Žagar, Slovenian Cancer Registry)
Institute of Oncology Ljubljana
Ljubljana, 15th Nov 2024

Slovenian Cancer Registry



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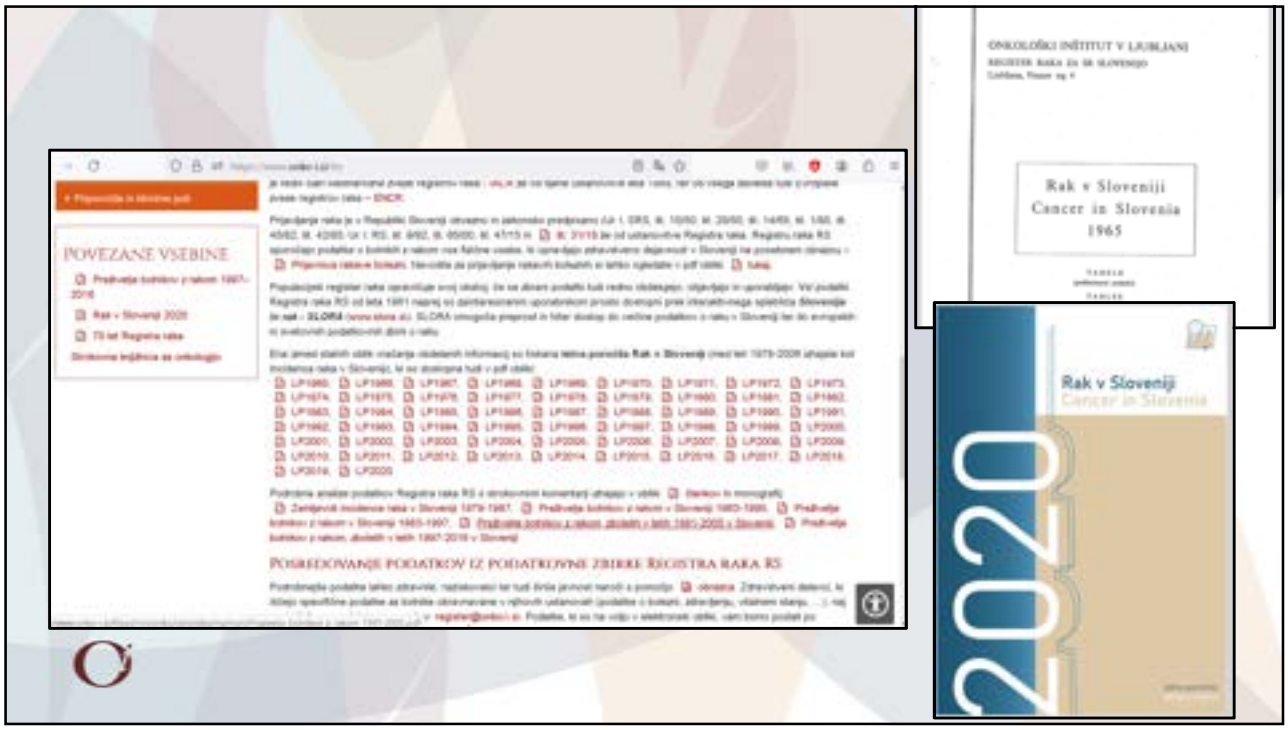


EPIDEMIOLOGY OF PRIMARY CUTANEOUS LYMPHOMAS

- Rare: epidemiological studies are sparse
- Classifications have been evolving over the time – difficut to compare older and recent studies!
  - Early 80s: only MF, SS
  - Kiel classification, Working Formulation
  - 1997 EORTC classification
  - WHO 3rd Ed: CTCL but no CBCL
  - 2005/2008/2016 WHO-EORTC...
- Many cancer registries are based on ICD-10 that do not recognize each subtype of CTCL and CTCB
- Use of different classifications and inclusion not only PCLs but some entities with frequent presentation in skin (ENK/TCL, PBL, ATLL...) or LPDs that are not reportable (EBV MCU, CD4+ SMC LPD, CD8+ A LPD...)
- Publications based on:
  - Cancer registry data (SEER -covers only 50% population!; NCRI,),
  - National registries for cutaneous/systemic lymphomas (GFELC, GOTEL,DDG...)
  - Tertiary care, single center studies (many), regional registries: small cohorts

EPIDEMIOLOGY: DATA SCARCE AND PUBLISHED ONLY RECENTLY

GENERAL CONSIDERATIONS IN THE EPIDEMIOLOGY OF PCLs

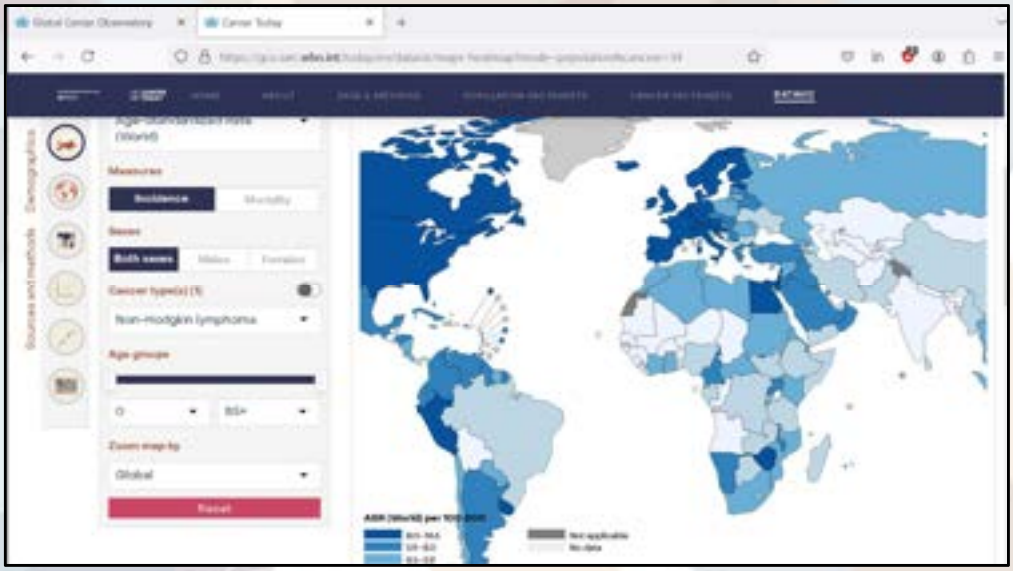
- **Incidence is increasing**
  - Better description of some entities
  - Better recognition by pathologists based on the development of IHC and molecular biology analysis
  - Care centralization and multidisciplinary approach
  - Longer life expectancy

- **PCTCL**
  - MF/SS more prevalent in Europe than in USA
  - ↓of cMF, ↑ of vMF (PR, STMF)
  - Clusters of MF/SS (regional differences) in some regions of USA, Canada, Sweden: increased levels of environmental toxins (benzen, trichloracetylen)?
  - Racial and etnics differences for MF
  - Socioeconomic differences: ? Higher incidence in higher socioeconomical groups
  - EBV and HTLV-1 associated: South America, Asia
  - Genetic predisposition: HAVCR2 gene germline mutation (South America, Asia) – SPLTCL

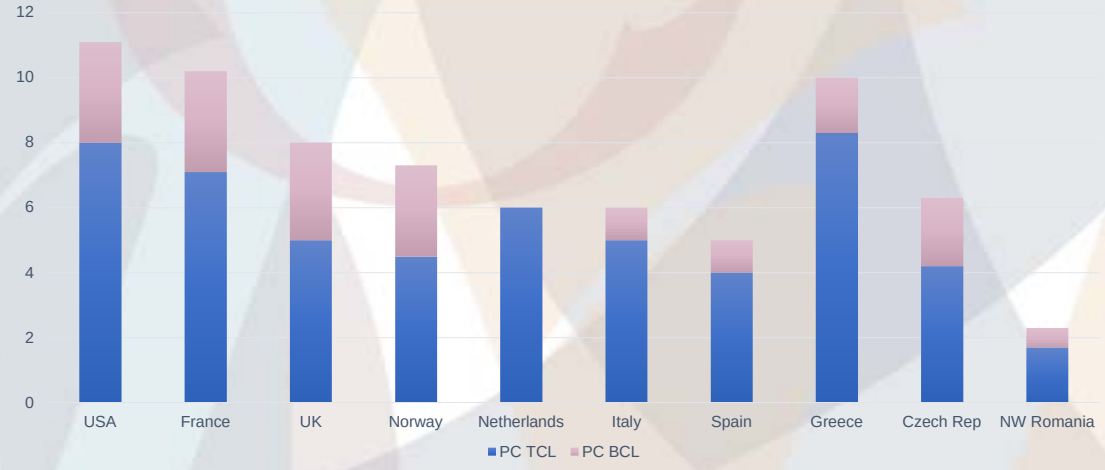
- **PCBCL**
  - SEER: 4/1 000 0000/y
  - Regional differences? (Borrelia burgdoferi, vaccines, arthropode bites, tatoos...)
  - Differences in the incidence of DLBCL LT

Dobos G et al: Br J Dermatol. 2021
Dobos G et al: Presse Med. 2022
Wiesse D et al:Int. J. Environ Res Pub Health 2023
Clough L et al: Cancer 2020
Moon JI et al: Sci Rep 2024
Hristov CA et al: AJH 2023
Martnez-Banaclocha et al: Cancers 2024

GLOBAL CANCER OBSERVATORY NOV 2024; IARC



ESTIMATED CRUDE INCIDENCE OF PCL IN DIFFERENT COUNTRIES ON 1 000 000 / y



Dobos et al: Presse Med 2022
Onghia M et al: Curr Oncol 2023
Bradford at al: Blood 2009; Willson L et al: Clin Lymphoma Myeloma Leuk 2012
McFelly O et al: JEADV 2023; Kalimpou S et al: EJC, 2021
Assaf C et al: J Dtsch Dermatol Ges 2007; Falkenhaim-Lopez et al: Actas Dermosifiliogr 2023
Abbott et al: Br J Dermatol 2013; Bessel et al: Br J Dermatol 2012 ; Fetica B et al: EJC 2019; Ettler J et al:Onkologie 2018;

MATERIALS AND METHODS

- Data on NHLs/LPDs being coded as PCLs 2000-2020 Slovenian Cancer Registry
- List of the patients treated for PCLs at the IOL 2000-2022
- Web.dr: patinets' database at IOL

- **ICD-10 morphology Slo 2000-2020**

ICD-O-3-M	2000-2004	2005-2009	2010-2014	2015-2019	2020	Skupaj
9591	2	3	3	1		9
9597			2	4	1	7
9673			1			1
9680	10	12	12	20	9	63
9690	3	3	5	5	1	17
9691				1		1
9695				1		1
9698	1	1		1	1	4
9699	1	3	14	12	5	35
9700			2	32	7	41
9701		1		1		2
9702	2	1	5	4	3	15
9705		1				1
9708		1			1	2
9709	7	8	14	10		39
9714		4	4	3		11
9718	4	9	9	4	2	28
9719			1			1
9726				1		1
9727		1				1
9735						0
9823	1		1	3		5
Skupaj	31	48	73	103	30	285

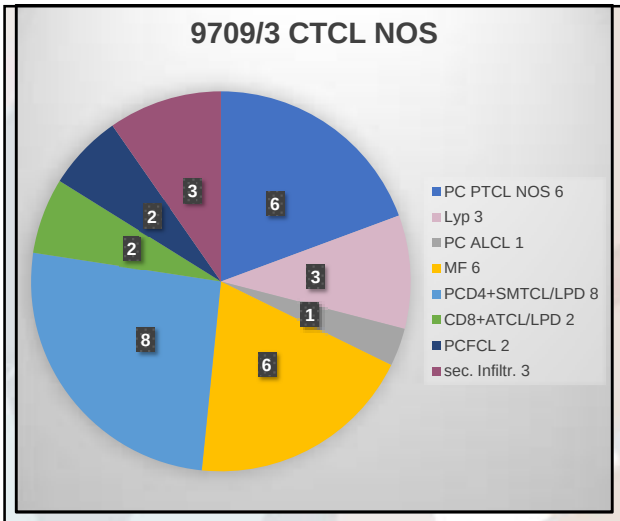
- **Patients treated for PCL at IOL 2000-2022**

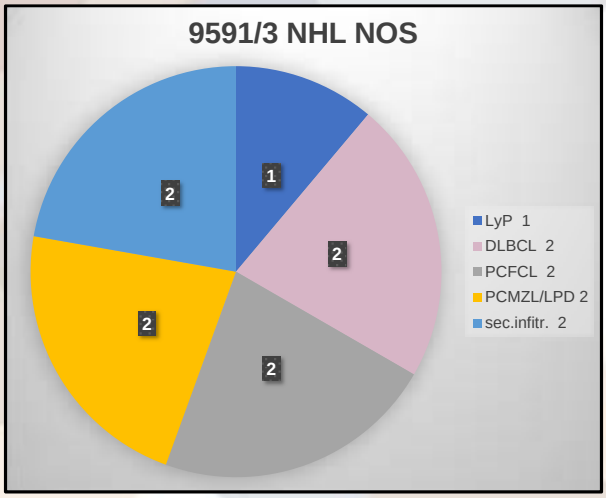
obravnavani na OIL

ICD-O-3-M	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	Skupaj
9591	2	3	3	1		9
9597			2	4	1	7
9673			1			1
9680	10	9	12	19	16	66
9690	3	3	5	5	1	17
9691				1		1
9695				1		1
9698	1	1		1	2	5
9699	1	3	14	12	12	42
9700			1	17	4	22
9701		1		1		2
9702	1	1	5	4	6	17
9705		1			1	2
9708		1			1	2
9709	7	6	12	5	1	31
9714		4	4	2	1	11
9718	4	9	9	4	2	28
9719			1			1
9726				1		1
9727		1				1
9735					2	2
9823	1		1	2		4
Skupaj	30	43	70	80	50	273

COMPLETE LIST OF THE PATIENTS TREATED FOR PCLs
OIL 2000 - 2022

	Priimek	Ime	spol	Datum rojstva	popis OI	datum ugotovitve	ICD-O-3-M	Malignost	Gradus	dg OIL	dg drugi	
2			Ž	10.03.1941	7200/16	15.09.2016	9680	3	6	DLBCL LT		
3			M	06.12.1948	6024/05	01.06.2005	9718	3	5		LyP	
4			Ž	03.12.1936	6955/22	03.10.2022	9735	3	6	DLBCL LT		
5			M	30.04.1942	8289/08	29.09.2004	9718	3	5	LyP		
6			M	26.10.1932	1183/20	13.02.2020	9698	3	6	PCFL		
7			M	19.07.1943	471/19	25.01.2019	9597	3	6	PCFL		
8			Ž	17.11.1979	1848/11	14.02.2011	9709	3	5		PC PTCL, NOS	
9			M	28.03.1937	7086/18	24.08.2018	9680	3	6	DLBCL		
10			M	14.03.1975	6052/06	20.06.2006	9591	3	9	LyP		
11			M	09.07.1968	5989/20	11.08.2020	9699	3	6	PCMZL		
12			M	02.02.1934	2506/10	15.04.2010	9718	3	9		PC ALCL	
13			Ž	06.05.1927	8136/07	07.09.2007	9680	3	6		DLBCL	sek inf kože
14			M	19.02.1959	8019/16	20.10.2016	9700	3	9	TFH,AI type		sek inf kože
15			M	15.02.1953	112/22	16.06.2020	9700	3	5		MF	
16			Ž	25.09.1971	4808/22	21.12.2021	9699	3	6		PCMZL	
17			M	17.11.1938	1000/10	03.02.2010	9718	3	5	LyP		
18			M	29.11.1974	5999/17	15.06.2016	9690	3	6	PCFL		
19			M	29.07.1939	5770/22	21.07.2022	9680	3	6	DLBCL LT		
20			Ž	12.06.1925	2937/22	08.04.2022	9680	3	6	DLBCL LT		
21			M	20.09.1937	2537/16	22.04.2016	9591	3	6	PCFL		
22			Ž	14.10.1934	337/66	05.08.2002	9709	3	5	LyP		
23			Ž	19.05.1930	275/10	15.12.2009	9727	3	9			AML sek inf
24			Ž	20.05.1952	5555/17	26.07.2017	9718	3	5	LyP		
25			M	23.12.1967	4936/22	10.06.2022	9700	3	5		MF	





EXCLUSION OF THE SECONDARY SKIN INFILTRATION

- 56 (21%) wrongly reported diagnoses (systemic diseases reported to be cutaneous)

	2000-2004	2005-2009	2010-2015	2015-2019	2020-2022	sum
DLBCL	7	2	4	4	7	24
FL		3	1			4
MZL	1		2		2	5
PTCL NOS		2	4	1	2	9
nTFHL		1	2	2	1	6
ALK-ALCL			2		1	3
CLL/SLL		1		2		3
MCL			1			1
AML			1			1
						56

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
PCFCL (**9597/3**, 9690/3, 9691/3, 9695/3, 9698/3)	4	1	4 4	4 8	3 3	11 20
DLBCL LT/NLT (9680/3) PBL (9735/3)	6	8	8 1	15 1	9	46 2
PCMZL/LPD (9699/3)	0	5	12	12	10	39
MF (9700/3)	3	3	2	32	7	47
SS (9701/3)		1		1		2
PC ALCL/LyP (9718/3; 9718/1) ALK+ALCL (9714/3)	6	9 4	9 4	5 2	1 1	30 11
PCγδ				1		1
SPLTCL			1	1		2
ENK/TCL, NT (9719/3)				1		1
PTCL NOS (9702/3)	3	3	4	2	2	14
CTCL NOS (9709/3)				6	4	10
	22	35	49	90	40	236

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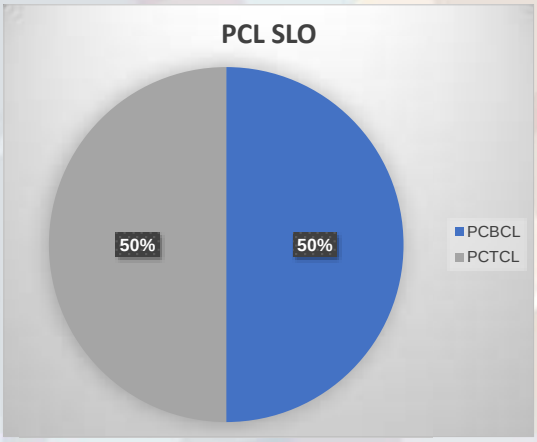
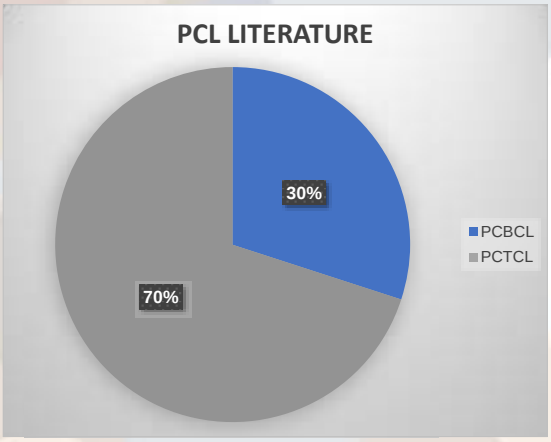
RESULTS

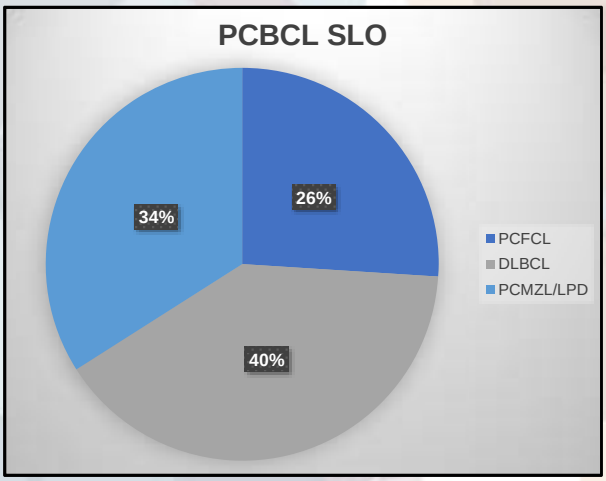
- Dobos G. Et al: Dobos et al: Presse Med 2022
- Dobos G et al: Cancers 2020
- Dobos G et al: Br J Hem 2021
- D'Onghia M et al: Curr Oncol 2023

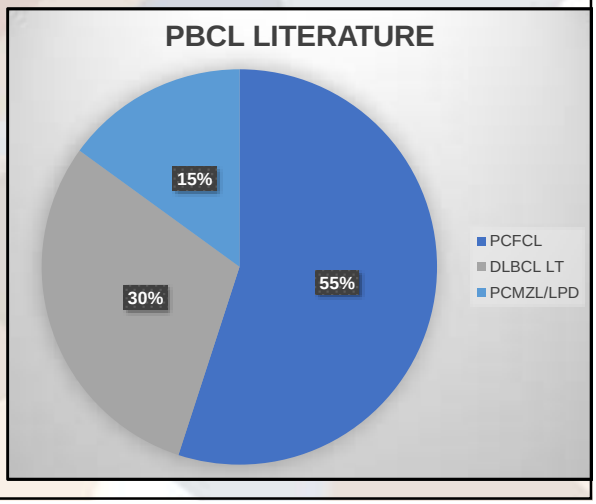




PCBCL

- Dobos G. Et al: Dobos et al: Presse Med 2022
- Dobos G et al: Cancers 2020
- Dobos G et al: Br J Hem 2021
- D'Onghia M et al: Curr Oncol 2023
- Hristov AC et al: AJH 2023
- Martinez-Banaclocha N et al: Cancers 2024





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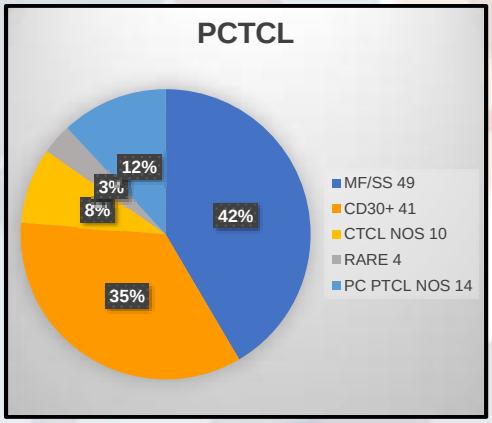
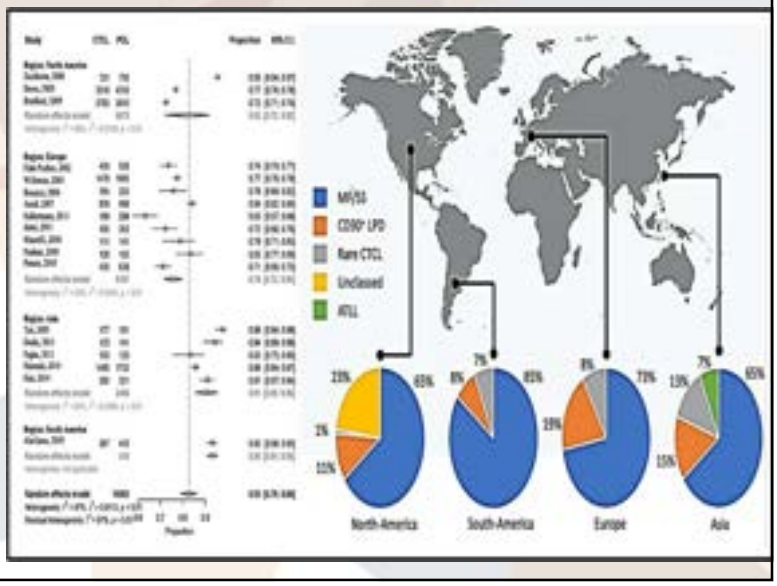
PCTCL

Dobos G et al: Epidemiology of Cutaneous T-Cell Lymphomas: A Systematic Review and Meta-Analysis of 16,953 Patients; Cancers 2020





	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
PCFCL (**9597/3**, 9690/3, 9691/3, 9695/3, 9698/3)	4	1	4 4	4 8	3 3	11 20
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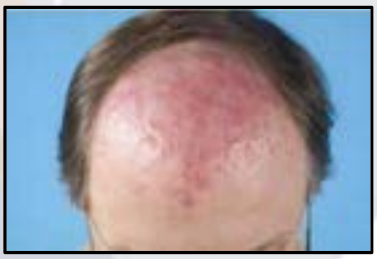
PCMZL/LPD (9699/3)	0	5	12	12	10	39
MF (9700/3)	3	3	2	32	7	47
SS (9701/3)		1		1		2
PC ALCL/LyP (9718/3; 9718/1) ALK+ALCL (9714/3)	6	9 4	9 4	5 2	1 1	30 11
PCγδ				1		1
SPLTCL			1	1		2
ENK/TCL, NT (9719/3)				1		1
PTCL NOS (9702/3)	3	3	4	2	2	14
CTCL NOS (9709/3)				6	4	10
	22	35	49	90	40	236

PCFCL



Source: Senff N et al; Blood 2008

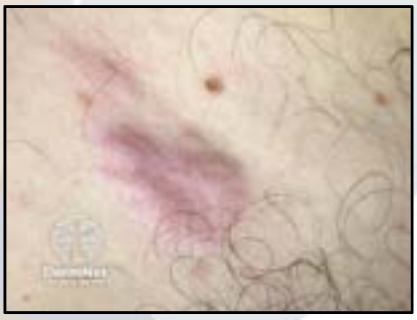
- The code 9597/3 is effective from 2010 (SEER)
- Before: 9690/3 (9691/3, 9695/3, 9698/3)
  9709/3
- accounts for 10% of all primary cutaneous lymphomas and 50% of CBCL

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
PCFCL (9597/3, 9690/3, 9691/3, 9695/3, 9698/3)	4	1	4	8	3	20
			4	4	3	11

- Incidence: 0.9 cases per 1,000,000 individuals per year but steadily increasing
- In 20 yrs period approximately 40 cases would be expected

https://seer.cancer.gov/
https://medilib.ir/uptodate/show/4718
Vitiello P et al: Front Oncol 2020
Willemze R et al: Blood 2019
Dobos G et al: Presse Med 2022

PCMZL (LPD)



Source:https://dermnetnz.org/topics/cutaneous-marginal-zone-lymphoma

- The code 9699/3 is effective from 2001 (SEER)
- 1992-2000: 9710/3
  9711/3
  9715/3
- accounts for 2–7% of all primary cutaneous lymphomas

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
PCMZL/LPD (9699/3)	0	5	12	12	10	39

- Incidence: 0.8 cases per 1,000,000 individuals per year but steadiliy increasing
- In 20 yrs period approximately 32 cases would be expected

https://seer.cancer.gov/
https://www.uptodate.com/contents/primary-cutaneous-marginal-zone-lymphoma
Vitiello P et al: Front Oncol 2020
Willemze R et al: Blood 2019
Dobos G et al: Presse Med 2022

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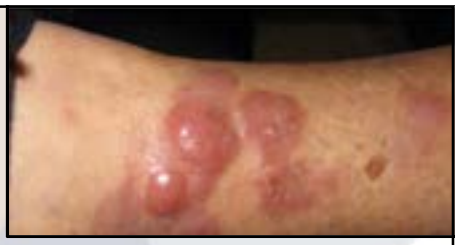
PCDLBCL-LT



Source: https://www.semanticscholar.org/paper/Primary-cutaneous-diffuse-large-B-cell-lymphoma%2C-of-Patsatsi-Kyriakou/ed36fb43a33ed4a1ae5b24750c0eca707563229d

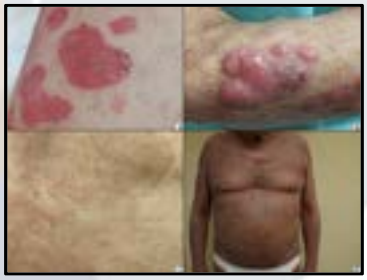
- Code 9680/3 is effective from 2001 (SEER)
- Accounts for 3-4% of all cutaneous lymphomas and 10-20% of PCBCLs

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
DLBCL LT/NLT (9680/3)	6	8	8	15	9	46

- incidence 0.6-0.7/ 1 000 000/y
- In 20 yrs period approximately 30-35 cases would be expected

https://seer.cancer.gov/
https://www.uptodate.com/contents/primary-cutaneous-diffuse-large-Bcell-lymphoma
Arjyal L et al: Blood 2019
Moustafa AM et al: JCO 2020
Bradfort T et al: Blood 2009

MF



Source: Pileri A et al: Cells 2021

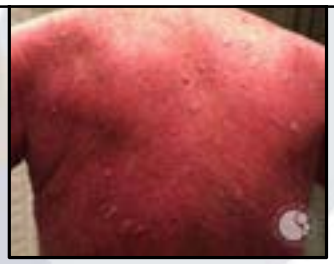
- Code 9700/3 reportable for cases diagnosed 1978 and later (SEER)
- Comprises 55-60% of CTCL in USA and 70-73% in Europe

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
MF (9700/3)	3	3	2	32	7	47

- Incidence 6/1 000 000/y
- Proportion of MF variants is increasing, classical MF decresing
- Approximately 60 cases in 20 yrs would be expected

Vitiello P et al: Front Oncol 2020
Willemze R et al: Blood 2019
Dobos G et al: Presse Med 2022
Dobos G et al: Cancers 2020

SS



Source: https://imagebank.hematology.org/referenc
case/133/sezary-syndrome

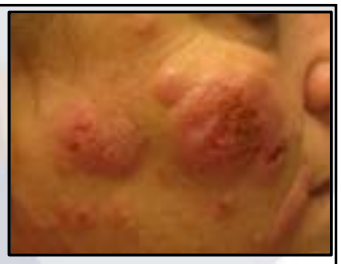
- Code 9701/3 reportable for cases diagnosed 1978 and later (SEER)
- annual incidence rate 1/10,000,000/y ; stabile
- represents 3% of all cutaneous lymphomas.

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
SS (9701/3)		1		1		2

- In 20 yrs period at least 5 cases would be expected

Vitiello P et al: Front Oncol 2020
Willemze R et al: Blood 2019
Dobos G et al: Presse Med 2022
Dobos G et al: Cancers 2020

CD30 + PCL (PC ALCL, LyP)



https://link.springer.com/chapter/10.1007
/978-3-319-17217-0_10

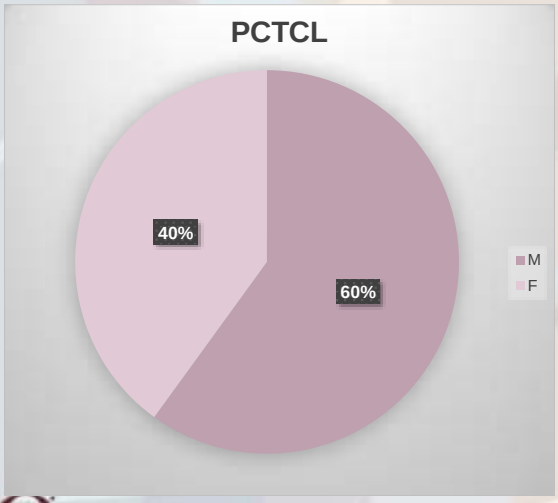
- 9718/1: Lymphomatoid papulosis effective 2010 and later (SEER)
  Reportability: This neoplasm is not reportable
  incidence 1.2 – 1.9/1 000 000/y
- 9718/3: PC ALCL
  Effective 2001 and later
  Reportable: for cases diagnosed 2001 and later

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022	SUM
PC ALCL/LyP (9718/3; 9718/1)	6	9	9	5	1	30
ALK+ALCL (9714/3)		4	4	2	1	11

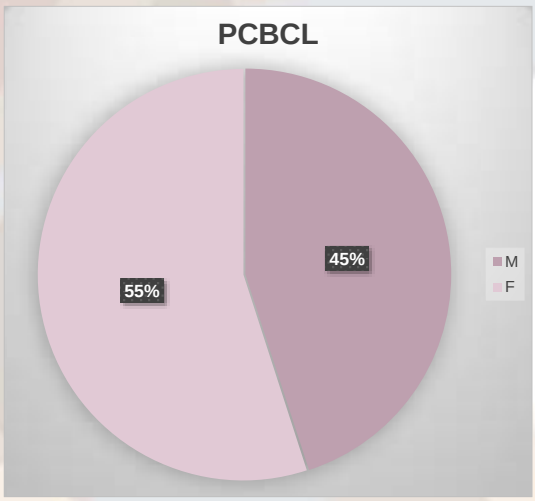
accounts for approximately 9% of cutaneous lymphomas
overall incidence rate was found to be 0.12/1,000,000 /y
in 20 yrs approximately 10 cases would be expected

Deb P et al: NAJMS 2024
Dobos G et al: Cancers 2020
Willemze et al: Blood 2019
Sanchez GC et al: Blood 2019

PCL & SEX: M vs F

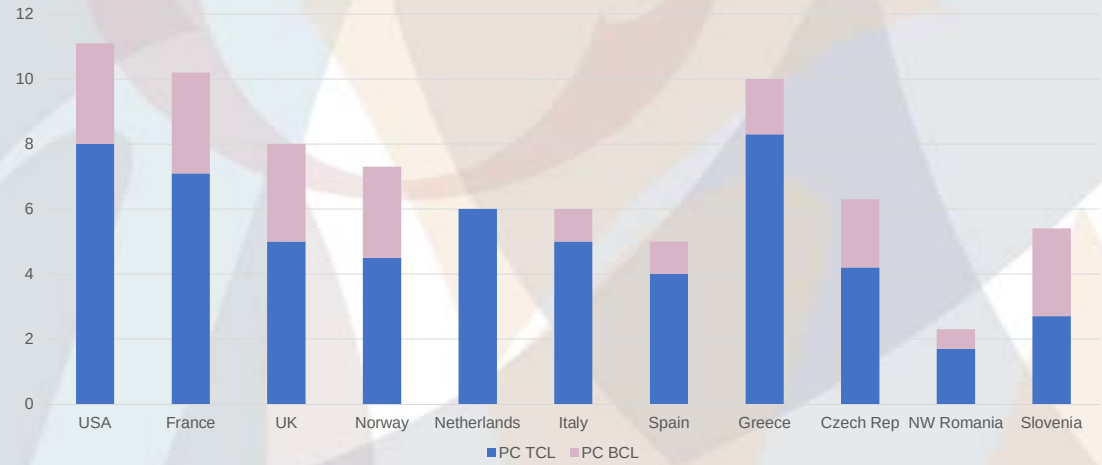


M: MF, SS, CD30+
F: SPLTCL, PTCL NOS, CTCL NOS



F: DLBCL LT, PC MZL
M: PC FCL

ESTIMATED CRUDE INCIDENCE OF PCL IN DIFFERENT COUNTRIES ON 1 000 000 / y



Dobos et al: Presse Med 2022
Onghia M et al: Curr Oncol 2023
Bradford at al: Blood 2009; Willson L et al: Clin Lymphoma Myeloma Leuk 2012
McFelly O et al: JEADV 2023; Kalimpou S et al: EJC, 2021
Assaf C et al: J Dtsch Dermatol Ges 2007; Falkenhaim-Lopez et al: Actas Dermosifiliogr 2023
Abbott et al: Br J Dermatol 2013; Bessel et al: Br J Dermatol 2012 ; Fetica B et al: EJC 2019; Ettler J et al:Onkologie 2018;

CONCLUSIONS

- 11-12 cases/year; 5.5/1 000 000/y
- Incidence of PCFCL and PCMZL/LPDis steadily rising in the course of the years
- Falsly low incidence of MF and SS?
- Uneven reporting of MF
- PTCL NOS category is shrinking
- CTCL NOS category will shrink in the future
- Finding out the real incidence of PCL/PCLPD subtypes will remain problematic in the future (lymphomas → LPD)

	2000-2004	2005-2009	2010-2014	2015-2019	2020-2022
PCFCL (9597/3, 9690/3, 9691/3, 9695/3, 9698/3)	4	1	4	4 8	3 3
DLBCL LT/NLT (9680/3) PBL (9735/3)	6	8	8 1	15 1	9
PCMZL/LPD (9699/3)	0	5	12	12	10
MF (9700/3)	3	3	2	32	7
SS (9701/3)		1		1	
PC ALCL/LyP (9718/3; 9718/1)	6	9	9	5	1
ALK+ALCL (9714/3)		4	4	2	1
PCγδ				1	
SPLTCL			1	1	
ENK/TCL, NT (9719/3)				1	
PTCL NOS (9702/3)	3	3	4	2	2
CTCL NOS (9709/3)				6	4
	22	35	49	90	40

TAKE A HOME MESSAGES

- Not all lymphomas presenting with skin infiltrates are primary cutaneous lymphomas - heavy emphasis is placed on clinical features and staging when making a certain diagnosis!
- Majority of PCLs have their own ICD-10 codes: please use them thoroughly
- PC LPDs (..../1) are not reportable and Slovenian Cancer registry does not register them

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Cutaneous Lymphomas in Cytology

Veronika Kloboves Prevodnik
Institute of Oncology Ljubljana, Slovenia

Primary cutaneous lymphomas

- Heterogeneous group of skin-based NHLs lacking extracutaneous manifestations
- The second most common form of extranodal lymphomas
- T-cell >> B-cell
- Cytopathology: FNAB, scrapes

- **T-cell lymphomas (75%)**
- MF/SS (most frequent)
- Primary cutaneous CD30+ lymphoproliferative disorders
  - ALCL
  - Lymphomatoid papulosis
  - Large cell transformation of MF
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma nasal type
- Rare types of PC TCL
- Increased risk of other malignances
  - (NHLs, melanoma, lung and bladder ca.)

- **B-cell lymphomas**
- Primary cutaneous MZL
- Primary cutaneous FL
- Primary cutaneous DLBCL, leg type
- EBV+ mucocutaneous ulcer
- Intravascular large B-cell lymphoma

- Indolent lymphomas
- Histologically: diffuse infiltrates in the dermis

Mycosis fungoides and Sezary syndrome

(Considered as a separate entities due to the difference in clinical behavior and cell of origin)

	Mycosis fungoides (MF)	Sezary syndrome (SS)
Definition	Primary cutaneous T-cell lymphoma clinically characterized by the sequential evolution of patches, plaques and tumors	Neoplasm of T lymphocytes defined by the triad of erythema, generalized lymphadenopathy, and presence of clonally related neoplastic T cells (Sezary cells) in the skin, lymph nodes and peripheral blood
Tumor cells	Clonal small to medium- sized mature T-cells with hyperchromatic, hyper-convoluted (cerebriform) nuclei	Sezary cells: Blood: Large atypical lymphocytes with cerebriform nuclei Lymph nodes and tissues: Medium sized cells with irregular contours and deep clefts
Immunophenotype	Early-stage MF: CD45+, CD3+, CD5+, CD7d+ or loss, CD2+, TCRβ+, CD4+, CD8-, CD30+or-, PD1+/-, Advanced-stage MF: loss of CD2, CD5, TCRβ+, diminition of CD4, partial expression of CD30 MF with cytocoxic phenotype (CD8+ and/or TCR γ/δ) is well recognised.	CD3+, CD4+, CD8- Frequent loss of CD2, CD5, CD7 and/or CD26 PD1+, CLA+, CCR4+, CCR7+, TCRαβ+, CD27, ICOS+, CXL13-/+, CD158k+/-, NKp46+/-
Spread of the disease	Lymph nodes, visceral organs, bone marrow	Other organs in the body, including the lymph nodes, liver , spleen, and bone marrow
Transformation	Presence of more than 25% of large lymphoid cells or of aggregates of large cells in dermal infiltrates	/
Clinical coarse	Indolent	Aggressive

TNMB staging of MF and SS (ISCL and EORTC)

Category	T/N/M/B stage		Substage (if applicable)	
Blood	B0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sezary) cells)	B0a	Clone-negative
			B0b	Clone-positive
	B1	Low blood tumor burden: ≥ 5% of peripheral blood lymphocytes are atypical (Sezary cells), but criteria for B2 are not met	B1a	Clone-negative
			B1b	Clone-positive
	B2	High blood tumor burden, Sezary cell count ≥ 1000 /μL: clone-positive (1000 /μL = $1x10^9$/L)		

!

The role of cytopathology

- **Samples**
  - Peripheral blood
  - Enlarged lymph nodes (FNAB)
  - Nodules in tumor stage of MF (FNAB)
- **Aim**
  - Staging
  - Guide site selection for excisional lymph node biopsy
  - Material for ancillary testing of skin nodules and parenchymal lesions
  - Morphological evidence of large-cell transformation

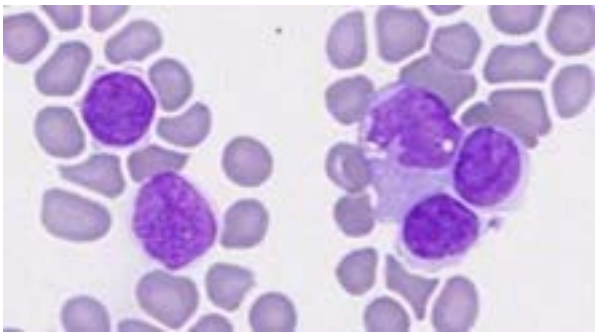
- **Diagnosis**
  - Cell morphology
  - Flow cytometry
  - TCR gene rearrangement studies (BIOMEDII)

Peripheral blood examination in MF & SS

- Standardized procedure based on
  - Cell morphology (Sezary cells)
  - Flow cytometry results
  - Clonality testing (Biomed II)
- Aim
  - Diagnosing peripheral blood involvement
  - Staging (B0, B1, B2)
  - Monitoring of treatment response
  - Confirmation of the disease progression

Morphological features of Sezary cells in peripheral blood smears

- Large atypical lymphocytes
  - Abnormally shaped deeply grooved nucleus with nuclear convolutions (cerebriform nucleus)

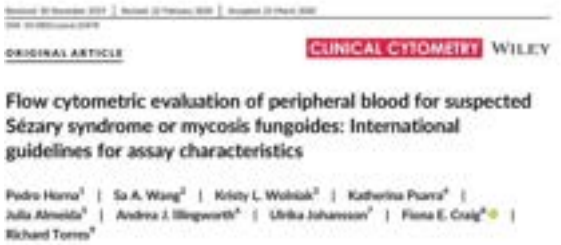


Peripheral blood smear

Flow cytometry

International guidelines

Clinical Cytometry, 2022



ORIGINAL ARTICLE

CLINICAL CYTOMETRY WILEY

Flow cytometric evaluation of peripheral blood for suspected Sézary syndrome or mycosis fungoides: International guidelines for assay characteristics

1) Minimal number of of six antibodies specific for MF or SS
2) Analysis template for reliable detection of abnormal T-cells
3) Gating strategies for reliable differentiation between abnormal and normal T-cells
4) Calculation and reporting abnormal cells concentration in blood

K1). Minimal number of antibodies

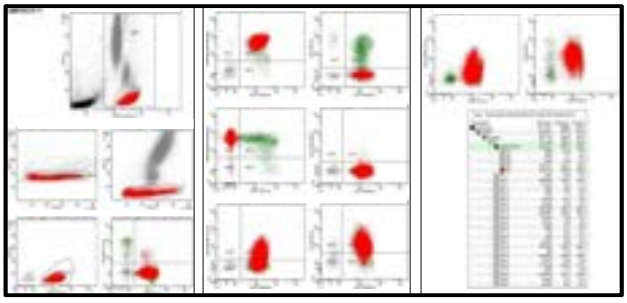
- **Six antibodies: CD3, CD4, CD7, CD8, CD26, CD45** are recommended as a minimum to be combined in one tube
- **Additional antibodies** in combination with CD3, CD4, CD7 and CD26 should be used in the same tube
  - CD5 and CD2 for CD3dim+ cases
  - CD164 and PD-1
  - CD38 (absence)
  - CD45RO, CD45RA

Tubes	FITC	PE	PerCP-Cy5,5	APC	PE-Cy7	APC-Cy7	V-450	V-500	BV605
1.	κ	λ	CD19	CD5	CD56	CD20	CD3	CD45	CD10
2.	CD57	CD2	CD5	CD7	CD56	CD8	CD3	CD45	CD4
3.	CD52	CD30	CD5	TCRαβ	TCRγδ	CD8	CD3	CD45	CD4
4.	CD4	CD26	CD5	CD7	CD27G	CD8	CD3	CD45	CD10
5.	CD27	CD197	CD45RA	HLADR	CD45RO	CD8	CD3	CD45	CD4

K2). Analysis template

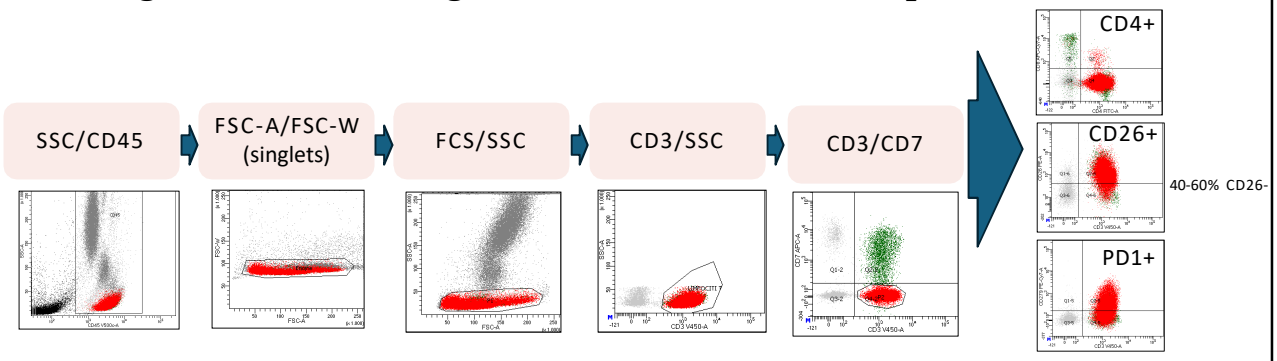
- Detection of T-cells even when they lack staining for CD3 or CD45
- Demonstration of a phenotype that is not characteristic of normal T-cells

- **IOL:** Template analysis for five tube 10-color antibody panel which allows identification of
  - CD3-or CD45-Sezary cells,
  - Lymphoma cells with atypical immunophenotype i.e. CD8+ and/or TCR γ/δ+...



K3). Gating strategies

- In agreement with the guidelines and individual experience



K4). Interpretation of the flow cytometric results

- Calculation of the absolute Sezary cell count (CD4+, CD7-, CD26-)
  - **Direct enumeration**
  - **Dual-platform method** (calculating the lymphocyte subset counts: cells/µL from flow cytometry-derived percentages multiplied by the whole blood cell count)
- Diagnostic criteria:
  - Absolute Sezary cell count: ≥ 1000 /µL (0,001/L)
  - CD4:CD8 ratio > 10
  - Expanded CD4+ population with abberant immunophenotype
    - CD4+/CD7- ≥ 40%
    - CD4+/ CD26- ≥ 30%

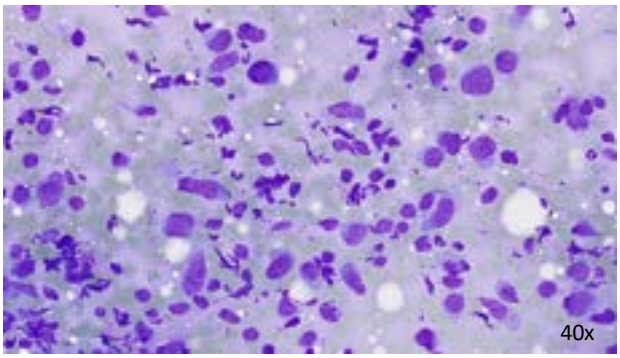
Gene rearrangement studies

- Performed concurrently with flow cytometry
- Sezary cells in blood
  - Clone-negative
  - Clone-positive

Cytology of cutaneous lymphomas other than MF and SS

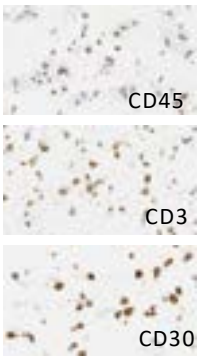
- Patients who come to FNAB clinic because of undefined tumors in the skin
- Staging
- Progression of the disease
- Materiel for molecular studies

65-year-old male
FNAB of skin lesion in the chin



ICC:

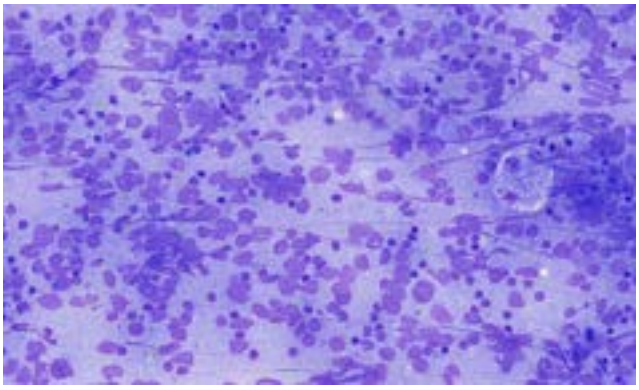
- CK AE1/AE3 -
- S100 -
- Sox100 +
- CD45 +
- CD20-.
- CD3+,
- CD30+



FNAB: CD30+ lymphoprolipherative disease

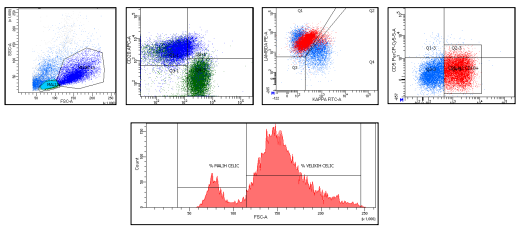
Histology: Primary cutaneous ALCL

51-year-old male
FNAB of skin lesion in the back



- **Large cells-**
- CD20+,
- CD19+,
- **Lambda+**
- **CD10+,**
- FMC7-,
- CD23-
- CD5-

- **Small cells:**
- CD20+,
- CD19+,
- Kappa/Lambda: polytypic
- CD10-,
- FMC7-,
- CD23-/+
- CD5-

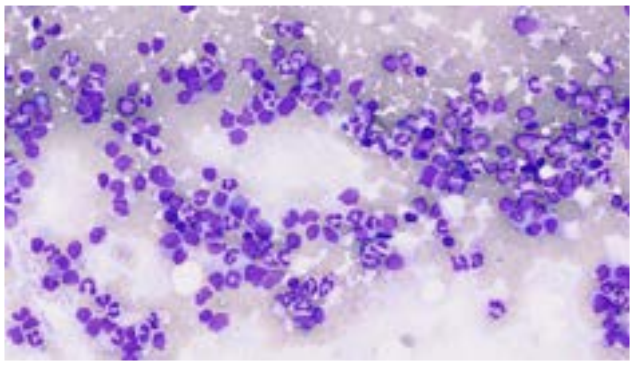


FNAB: Large B-cell lymphoma

Histology: Primary cutaneous DLBCL, leg type

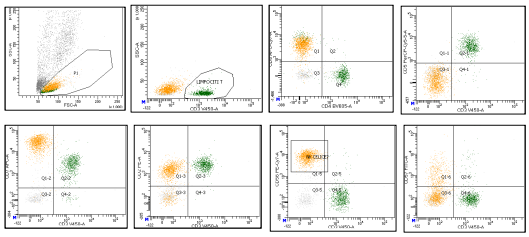
76-year-old male

- ***treated for subcutaneous panniculitis like T-cell lymphoma***
- ***FNAB of skin lesion in right cheek clinically suspicious for recurrent lymphoma***



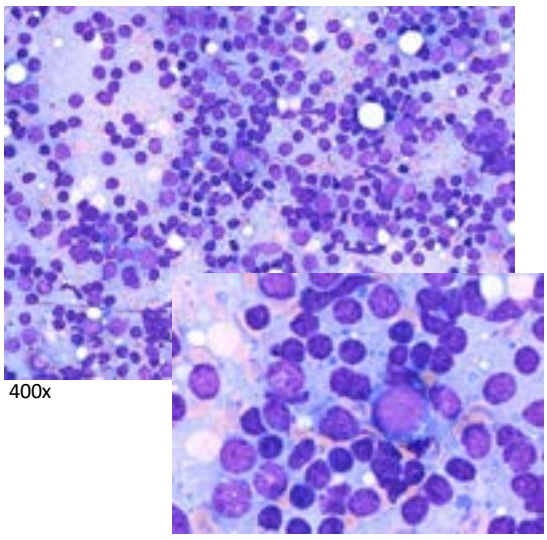
FNAB: Recurrent T-cell lymphoma (signed out suspicious)

- Lymphoma cells
- CD3-
- CD8+
- CD5-
- CD7++
- CD2 d+
- CD56+
- CD57-/+

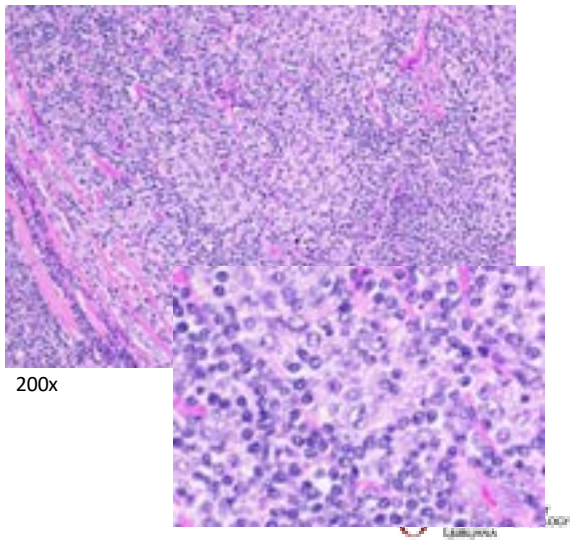


87 -year-old male

- ***treated for CLL for 21 years***
- ***FNAB of skin lesion in the left side of the neck***

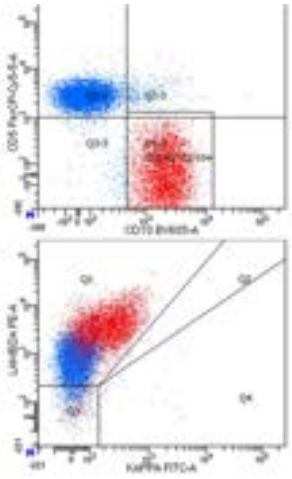


400x

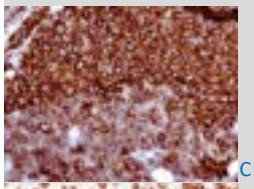


200x

Flow cytometry:



CLL: CD20 dim+, lambda dim+, CD5+, CD23+, FMC7-,
FL: CD20 bright+, lambda +, CD10+, FMC7+,

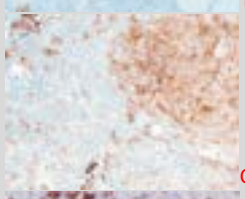

CD20

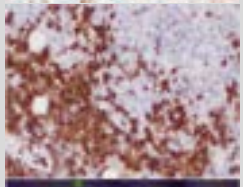

CD5

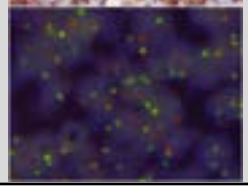

CD23


LEF-1


Bcl-6


CD10+


Bcl-2


t(14;18)

FNAB and histology diagnosis:

Composite lymphoma: CLL & FL G3

Conclusions

- The determination of Sezary cell count in peripheral blood is accurate method at OIL and is in accordance with the international guidelines
- Cutaneous lymphomas can be diagnosed by cytopathological examination if the cytology sample contain enough cells for morphological evaluation, flow cytometric immunophenotyping and PCR based clonality analysis
- Excisional biopsy and histological examination is necessary for accurate classification of cutaneous lymphomas

Mycosis fungoides and Sézary syndrome

Mateja Dolenc-Voljč
Dermatovenerološka klinika UKC Ljubljana
Medicinska fakulteta UL

4. limfomska šola
Ljubljana, 15. november 2024

WHO-EORTC Classification of Cutaneous T-cell Lymphomas *Willemze R et al. Blood 2019; 133: 1703-14*	
Mycosis fungoides MF variants: pagetoid reticulosis, folliculotropic MF, granulomatous slack skin	**60%**
Sézary syndrom	**5%**
CD30+ T-cell lymphoproliferative disorders Lymphomatoid papulosis Primary cutaneous anaplastic large cell lymphoma	25%
Subcutaneous panniculitis-like T-cell lymphoma	10%
Rare subtypes	
Primary cutaneous gamma-delta T-cell lymphoma	
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	
Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder	
Primary cutaneous peripheral T-cell lymphoma, unspecified	

Latzka E et al. Eur J Cancer 2023; 113343
Goodlad JK, Cerroni L et al. Wirchows Archiv 2023;482:281-98

"

Overview

- Risk factors
- Clinical characteristics
- Diagnostic approach
- Updated treatment recommendations (focus on dermatological treatment)

Risk factors for MF and SS

- Continuous activation of skin T helper lymphocytes → malignant transformation of a specific clone
- UV radiation: workers exposed to sunlight have a higher risk of MF
- Occupational and environmental exposure to chemicals: aromatic halogenated hydrocarbons, pesticides
- Drugs (antiepileptics?, calcium channel blockers?, angiotensin-converting enzyme inhibitors?, hydrochlorothiazide?)
- Genetic predisposition (rare reports of familiar MF, detection of specific HLA class II alleles)
- Immunosuppression
- Chronic inflammatory skin diseases (atopic dermatitis, eczema, psoriasis)?

Bonin S et al. Exp Mol Pathol 2010; 89: 46-50
Licht P et al. Biofilms and Microbiomes 2024;10:74
Wohl Y et al. Curr Probl Dermatol 2007:35:52-64
Hristov AC et al. Am J Hematol 2023; 98:193-209
Morales-Suarez VMM et al. J Occup Environ Med 2006;48:390-3

Skin microbiome in cutaneous T-cell lymphoma

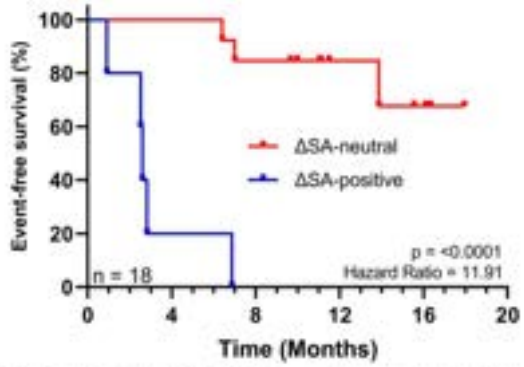


Fig. 8 | Event-free survival Kaplan-Meier curves. Patient Enrolment started in September 2020 and was completed in April 2021. The follow-up period lasted until May 2022. The Log-rank test was used to determine differences between survival curves (1 degree of freedom).

- Increased prevalence of *S. aureus* skin and nasal colonisation in patients with CTCL
- Event-free survival significantly higher in *S. aureus* neutral patients
- *S. aureus* colonization can contribute to secondary infections and disease progression

Licht P et al. Biofilms and Microbiomes 2024;10:74

Mycosis fungoides

Incidence of cutaneous T-cell lymphoma has been increasing

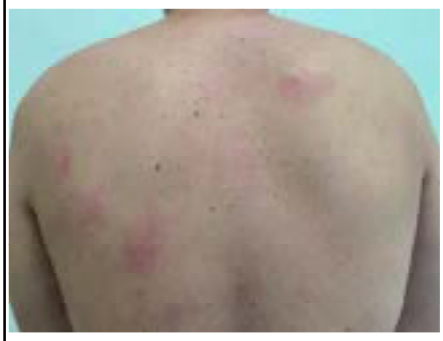
- MF incidence: 5-10 per million persons
- Male to female ratio 2 : 1
- MF can occur at any age
- Incidence increases significantly with age:
  - median age at diagnosis 55 - 60 years
  - 4-fold increase in patients older than 70 years
- Highest incidence reported among African-Americans: younger age of onset, female predominance, worse prognosis
- Less prevalent in Asian and Hispanic populations

Vermeer M. Br J Dermatol 2021:184:990-1003
Hristov AC et al. Am J Hematol 2023; 98:193-209

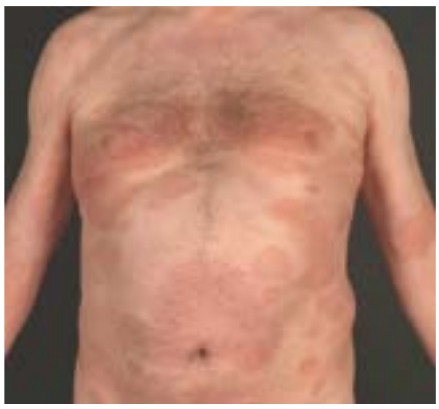
Clinical manifestations of mycosis fungoides

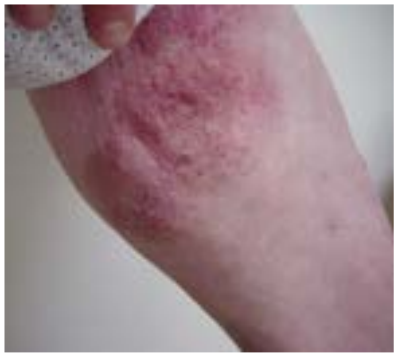
MF – „classic“ skin lesions

- About 70 to 75% of patients with MF present with the „classic form“ of the disease, with patches and plaques



Erythematous patches



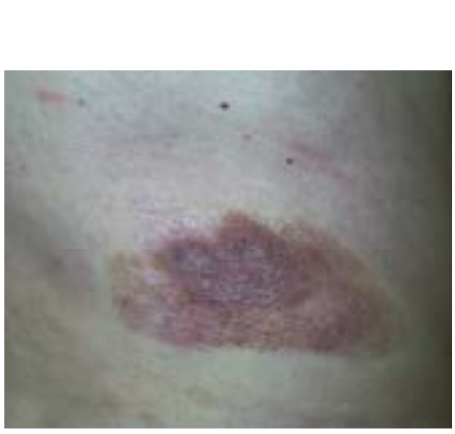
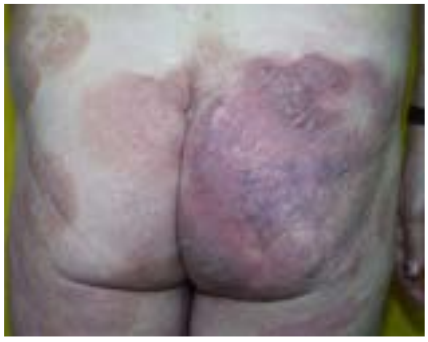
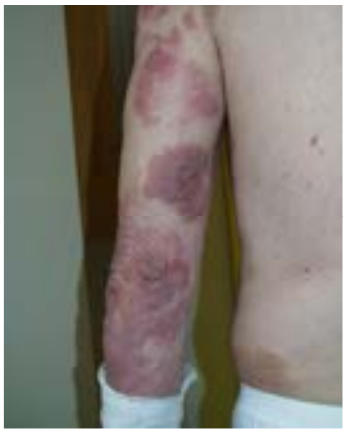


Patches and plaques

Figures: author‘s source

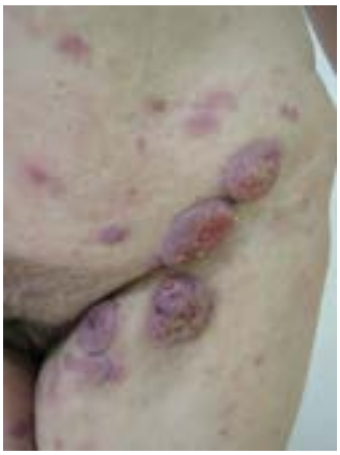
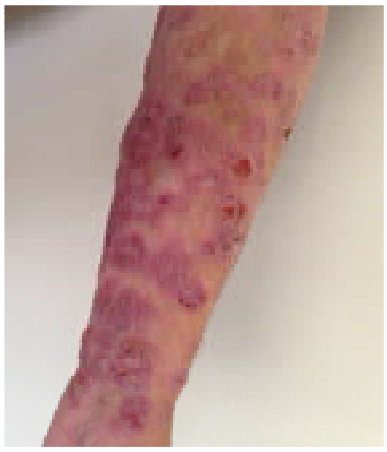
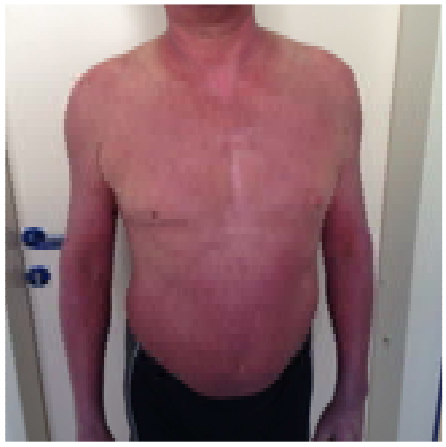
MF – patches, plaques

- Localisation on sun-protected skin sites, „bathing suit-like“ distribution

Figures: author‘s source

MF – tumors, erythroderma

Tumors

Erythroderma

Figures: author‘s source

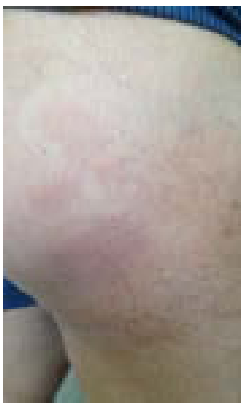
MF potential of progression

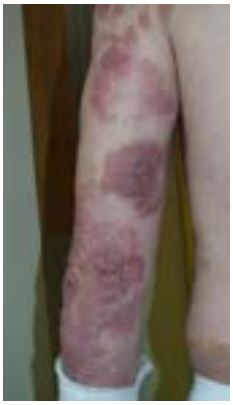
Macules

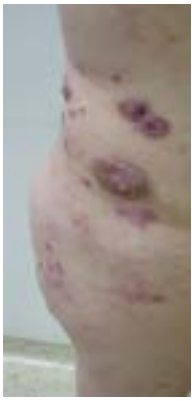
Plaques

Tumors

Erythroderma







Low-grade lymphoma

Progression from macules to plaques and tumours can take many years or decades

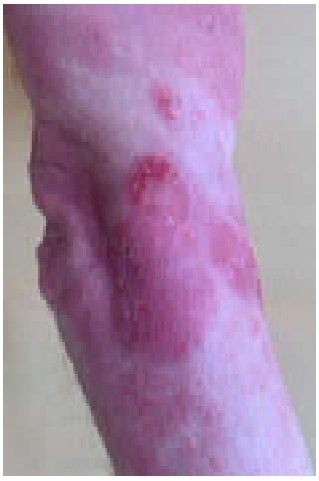
Progression to lymph nodes, blood and internal organs in up to 30% of patients

Wilcox RA. Am J Hematol 2016;91:151–65
Song SX, et al. Am J Clin Pathol 2013;139:466–90
Mazzeo E, et al. Rep Pract Oncol Radiother 2013;19:77–91

Figures: author's source

MF variants (subtypes)

Pagetoid reticulosis



Figures: author's source

Folliculotropic MF

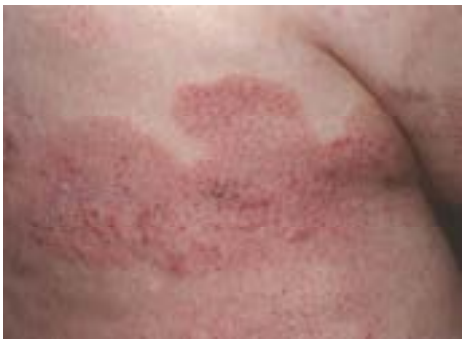


Figure: Prof. Cerroni L. Skin Lymphoma 2014

Granulomatous slack skin

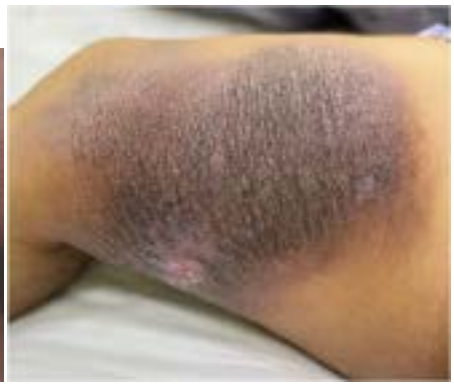


Figure: Mitwalli H et al. JAAD Case Reports 2023;33:30-2

MF – atypical manifestations

- About 20 to 25% of patients with MF present with atypical clinical manifestations

Poikilodermic MF

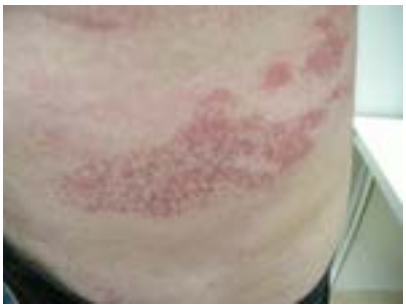
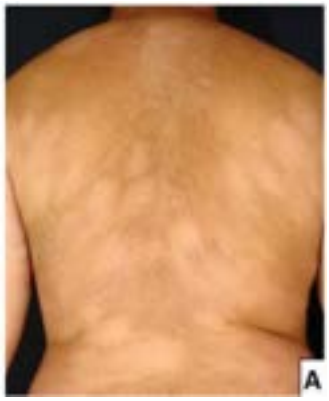


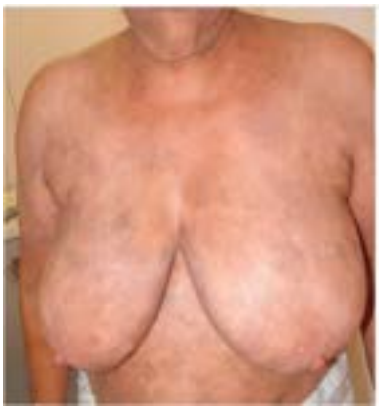
Figure: author's source

Hypopigmented MF



Furlan FC et al. An Bras Dermatol 2013

Hyperpigmented MF



Pavlovsky L et al. JAAD 2012

Atypical clinical presentation

Tinea pedis-like MF
mimicking mycosis fungoides

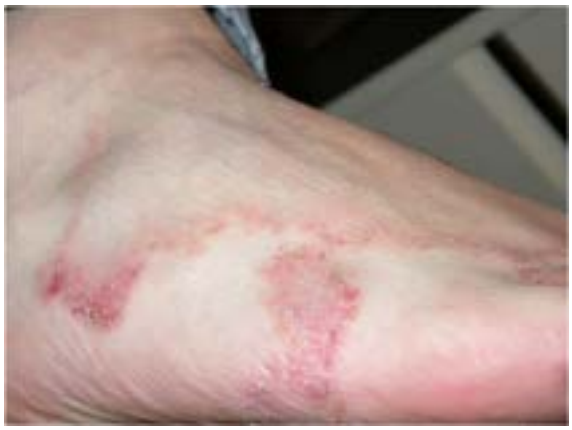


Figure: Lebas E et al. Dermatol Ther (Heidelb) 2021

Syringotropic MF
mimicking dyshidrosiform dermatitis

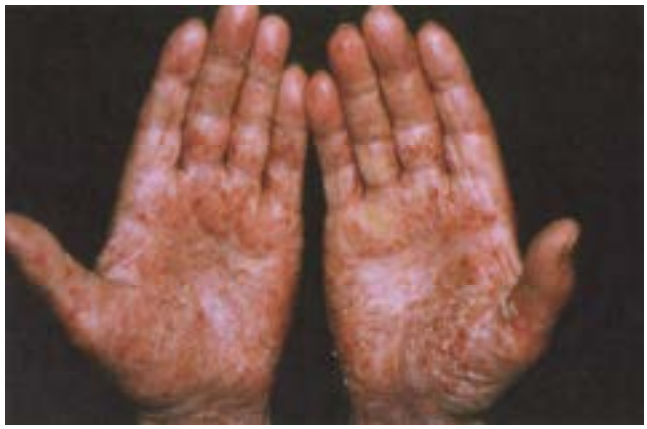
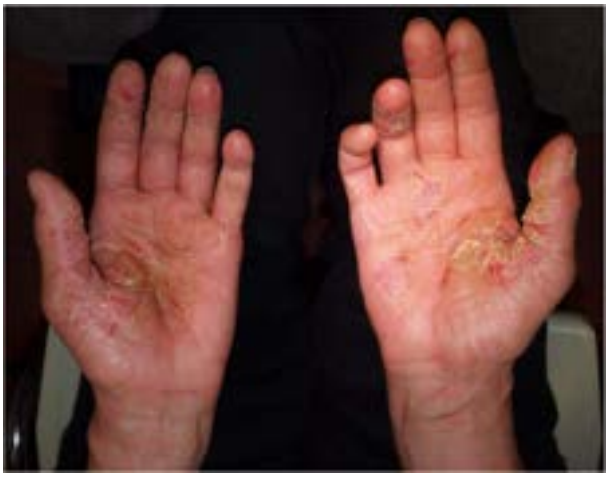


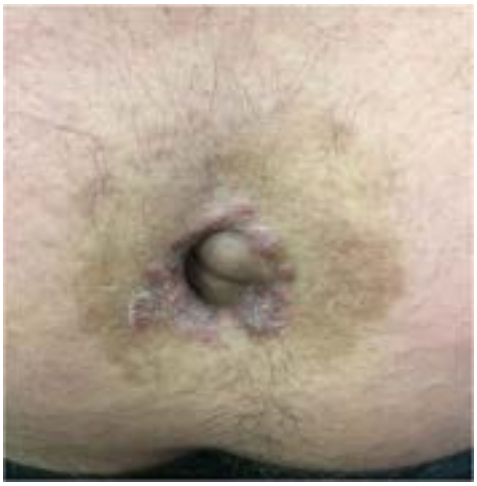
Figure: Cerroni L. Skin Lymphoma 2014

Atypical clinical presentation

MF mimicking palmar keratoderma



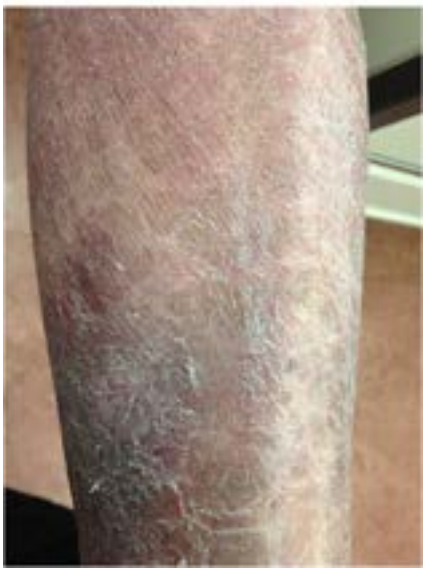
MF mimicking umbilical psoriasis inversa



Lebas E et al. Dermatol Ther (Heidelb) 2021

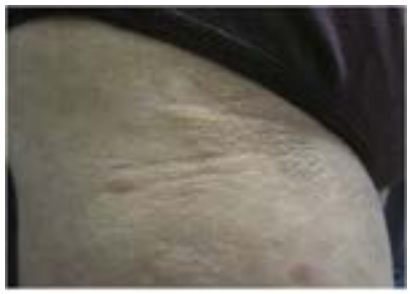
Atypical clinical presentation

MF mimicking ichthyosis



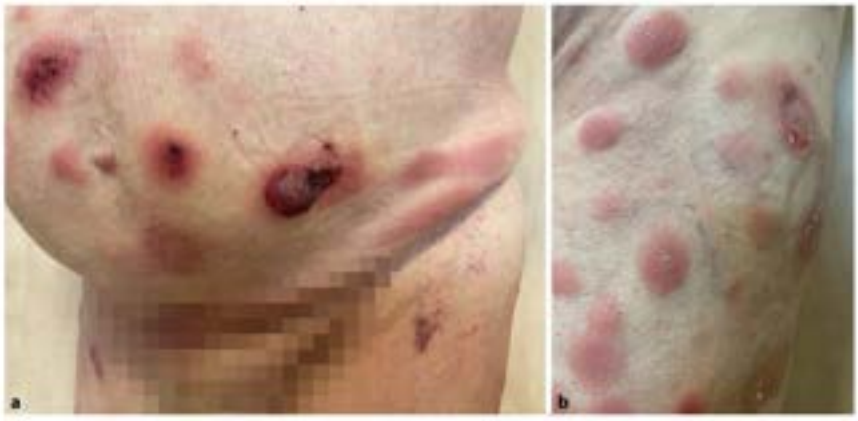
Lebas E et al. Dermatol Ther (Heidelb) 2021

Acanthosis nigricans-like MF



Kim DJ et al. JAAD Case Reports 2021;16:144-8

MF presenting with bullous lesions



Gerdes AL et al. Dermatologie (Heidelb.) 2024; doi: 10.1007/s00105-024-05399-4

MF – mimicking other skin diseases

- Acne
- Acanthosis nigricans
- Angular cheilitis
- Atopic dermatitis
- Drug eruption
- Dyshidrosis
- Erythema annulare centrifugum
- Erythema multiforme
- Folliculitis decalvans
- Infections (erysipelas, tinea, gangrene)
- Inflammatory linear verrucous epid. nevus
- Keratosis lichenoides chronica
- Keratosis punctata palmaris
- Lichen sclerosus
- Morphea
- Necrobiosis
- Pellagra
- Perioral dermatitis
- Pityriasis alba
- Pityriasis lichenoides
- Psoriasis inversa
- Psoriasis vulgaris
- Pyoderma gangrenosum
- Reticular erythematous mucinosis
- Rosacea
- Sarcoidosis
- Sarcoma
- Seborrheic dermatitis
- Teleangiectiasia
- Urticaria
- Varicous eczema
- Vitiligo

Lebas E et al. Dermatol Ther (Heidelb) 2021; 11: 1931-51

Atypical clinical presentation

Dermatol Ther (Heidelb) (2021) 11:1931–1951
https://doi.org/10.1007/s13555-021-00625-6

REVIEW

A Comprehensive Update of the Atypical, Rare and Mimicking Presentations of Mycosis Fungoides

Eve Lebas · Patrick Collins · Joan Somja · Arjen F. Nikkels

Increasing number of MF mimicking other dermatoses has been reported

Differential diagnosis

- MF can display a wide variety of clinical features
- Diagnosis of early-stage MF can be difficult, clinically and histopathologically

- MF should always be in the differential diagnosis for persistent patches or plaques unresponsive to usual therapies
- Low threshold for skin biopsy is a key to early diagnosis

Olsen EA et al. JAAD 2024; 90: 257-260

Staging evaluation of mycosis fungoides

TNMB classification of Mycosis fungoides - Staging

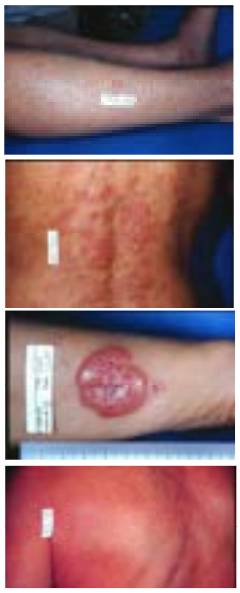
Trautinger et al. *EJC* 2017; 77 : 57-74
Olsen E et al. *Blood 2007*; 110: 1713-22

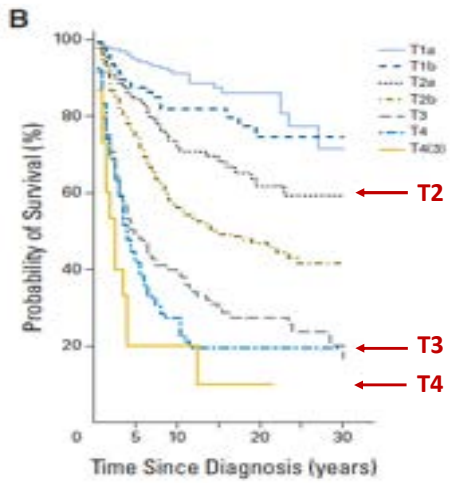
Stadij	Skin	Lymph nodes	Internal organs	Blood	
IA	T_1: limited patches/plaques < 10% skin surface T_{1a} – patches T_{1b} – patches, plaques, papules	N_0	M_0	$B_{0,1}$	Early stage disease 2/3
IB	T_2: generalised patches/plaques > 10% skin surface T_{2a} – patches T_{2b} – patches, plaques, papules	N_0	M_0	Risk of progression <50% over 20 years	
IIA	T_1, T_2	N_1: enlarged lymph nodes, neg. histopathology	M_0	$B_{0,1}$	
IIB	T_3: tumors 1 or more tumors > 1 cm	N_0, N_1	M_0	$B_{0,1}$	Advanced stage disease 1/3
III A/B	T_4: erythroderma erythema > 80% skin surface	N_0, N_1	M_0	Risk of progression 50% within 5 years	
IVA 1/2	T_1- T_4	N_2, N_3 pos. histopathology	M_0		
IVB	T_1- T_4	N_0-N_3	M_1	B_{0-2}	

MF - Survival by skin stage

T (skin)	
T1	**Limited** patch/plaque **< 10%**
T2	**Generalized** patch/plaque **≥ 10%**
T3	**Tumors**
T4	Generalized **erythroderma**

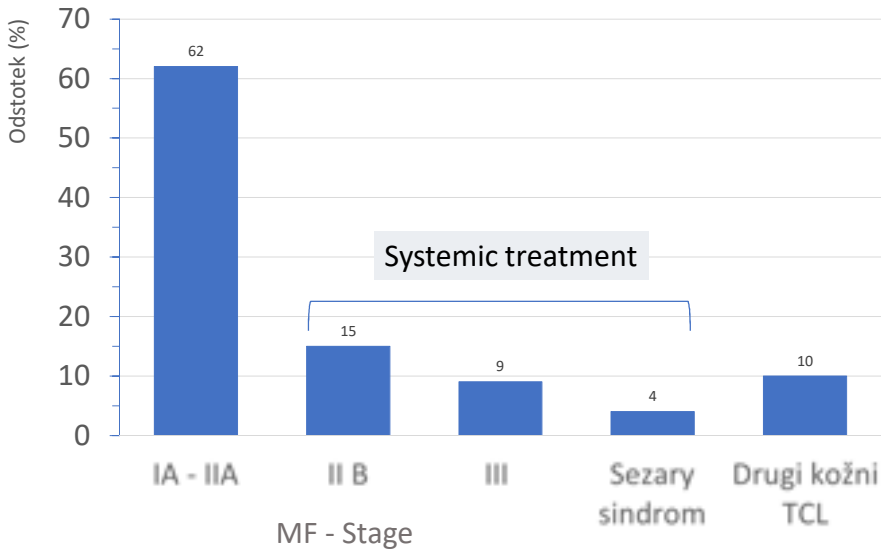
Patients with skin tumors and erythroderma generally progress earlier and have worse prognosis





Agar NS et al. J Clin Oncol 2010; 28: 4730-9
Olsen EA et al. Blood 2007; 110: 1713-22

Patients with T-cell lymphoma treated at the Department of Dermatovenereology in Ljubljana (2018-2023, N = 160)



Sézary syndrome

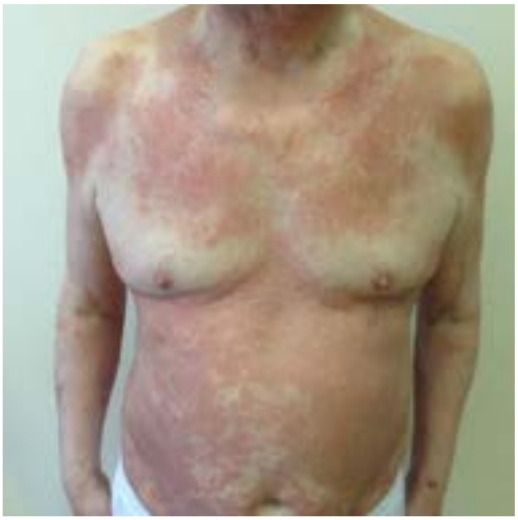
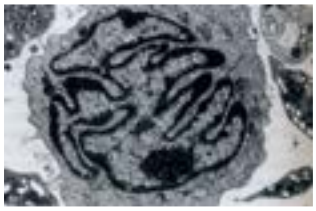


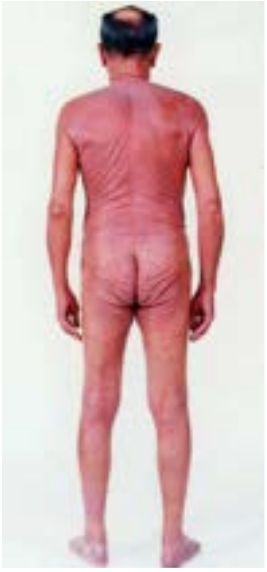
Figure: author's source

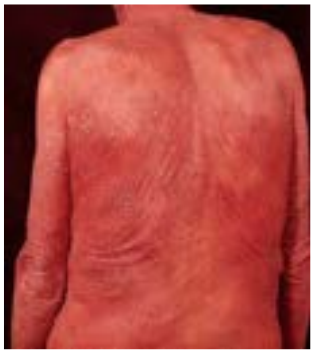
- Incidence: 1 per million
- 5-year survival: 24%
- Average time of survival: 2–3 years
- SS is efined as a triad of:
  - generalized erythematous patches/plaques or erythroderma
  - generalised lymphadenopathy
  - leucocytosis: > 1000 Sézary cells/mL



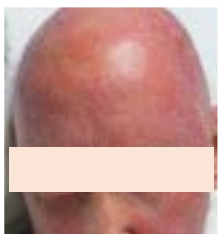
Sézary syndrome

Erythroderma

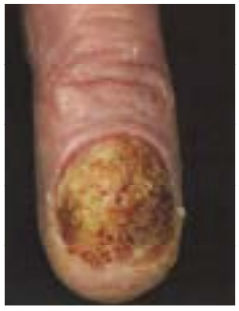


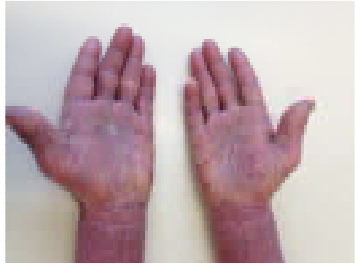


Alopecia

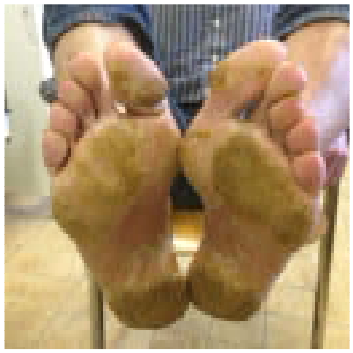


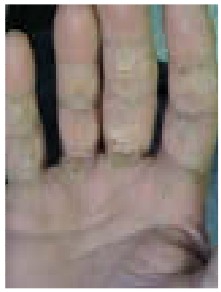
Onychodystrophy





Palmoplantar hyperkeratosis





Diagnosis of MF/SS

Clinical presentation

Histopathology

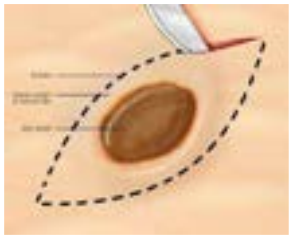
Immuno-phenotyping

Clonality

Skin biopsy

- Excisional biopsy or at least 4 mm punch biopsija
- Recommended from two or more lesions
- Most indurated area if only one biopsy

- Topical corticosteroids can diminish or eliminate neoplastic T cells and typical histopathological findings for 2 to 4 weeks
- Repeated skin biopsy may be needed



Wilcox AR. *Am J Hematol* 2015;9:73-76
Cerroni L. Skin Lymphoma, 2014

Histopathological examination

- Lymphocytic infiltrate in the upper dermis
- Epidermothropism
- Atypic lymphocytes
- Vacuolar interface dermatitis
- Papilar dermal fibrosis

- Histopathological features may be unspecific in early-stage MF
- Vary between patients and in a single patient in different lesions (influence of topical and systemic therapy)
- Late-stage: loss of epidermotropism

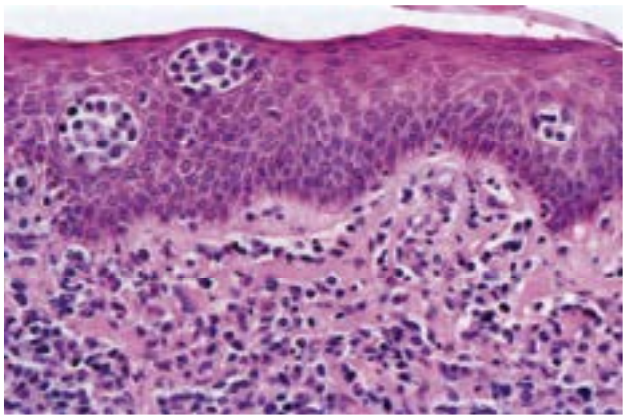


Figure: Prof. Cerroni L. Skin Lymphoma 2014

Immunohistochemistry

Mycosis fungoides

- Predominance of T-cell markers CD4+, CD8-, CD3+
- Loss of one or more of T-cell markers: CD7 > CD5 > CD2
- Variant immunophenotypes:
  CD4+/CD8+, CD4-/CD8+, CD4-/CD8-

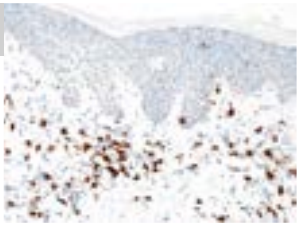
Sézary syndrome

- CD4+, CD8-; CD4/CD8 > 10
- Loss of CD2, CD3, CD5, CD7, CD26
- Loss of CD7 > 40%, CD26 > 80% (specific for SS)
- Expression of PD-1 and TOX

Hristov AC et al. Am J Hematol 2023
Saleh JS et al. Human Pathology 2023;140:75-100
EORTC consensus recomendations: Eur J Cancer 2023

CD4

CD8



CD7

Figures: Prof. dr. Luzar Boštjan

Clonality

- T-cell receptor (TCR) gene rearrangement
- Neither entirely sensitive nor specific
- Often negative result in early-stage MF
- May identify monoclonal T cells in reactive dermatoses

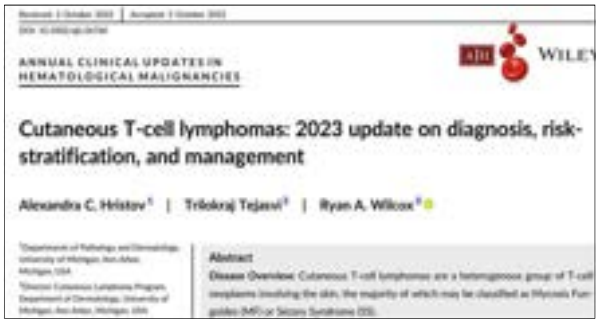
- PCR-based methods
- NGS (next generations sequencing)
  - a newer tool in the evaluation of T-cell clonality
  - not yet widely available
  - more sensitive and/or specific compared to PCR
  - may also identify a clonal T-cell population in reactive skin conditions

Saleh JS et al. Human Pathology 2023;140:75-100

Updated treatment recommendations


European Journal of Cancer

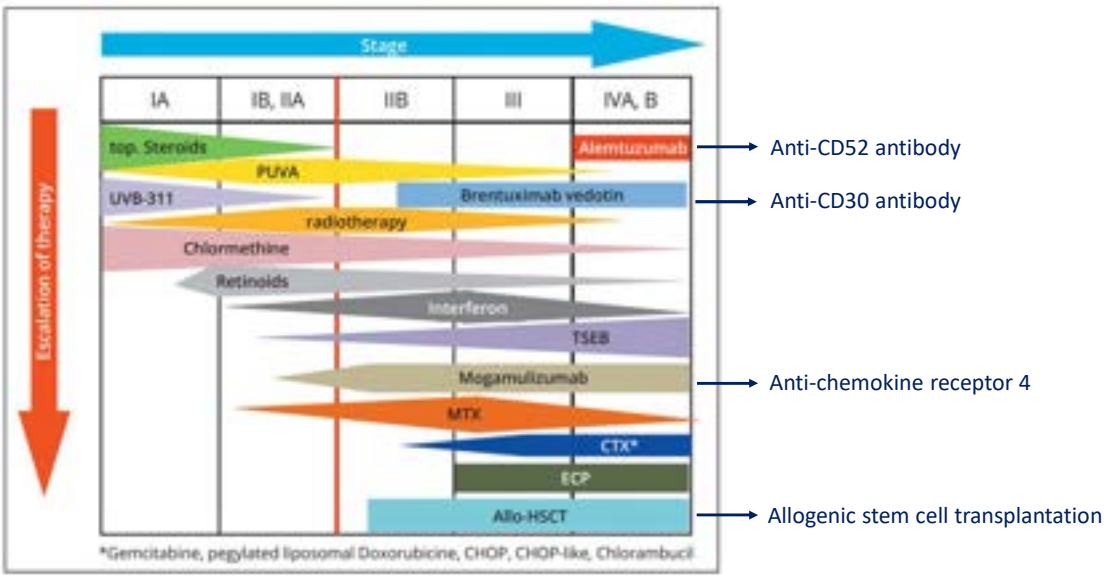
EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2023


ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES

Cutaneous T-cell lymphomas: 2023 update on diagnosis, risk-stratification, and management

Alexandra C. Hristov | Triłokraj Tejasvi | Ryan A. Wilcox

Treatment recommendations



Stranzenbach R. *Ital J Dermatol Venereol* 2021; 156: 534-44

Treatment recommendations

Multidisciplinary treatment approach

Team	Treatment
Dermatologists	Topical treatment
	Phototherapy (Nb-UVB, PUVA)
	Retinoids (acitretin, bexaroten)
	Interferon alpha (peg-IFN-α 2a)
	Metotrexate
Radiation oncologists	Radiotherapy
Oncologists	Brentuximab
	Alemtuzumab
	Mogamulizumab
	Chemotherapy
Transfusionists Blood Transfusion Centre of Slovenia	Extracorporeal photopheresis
	TSEB (total skin electron beam)
Pathologists, haematologists, other specialists (treatment side effects)	

First-line treatment of MF stages IA, IB and IIA

Stage	Skin directed therapy	
T1 Limited patches/plaques < 10% skin area T2 Generalised patches/plaques > 10% skin surface N_{0-1}, M_0, B_{0-1}	Expectant policy (watch and wait)	stage IA
	Topical corticosteroids	-
	Topical chlormethine	-
	Nb UVB	patches, thin plaques
	PUVA	thicker plaques
	Localised radiotherapy	localised lesions pagetoid reticulosis

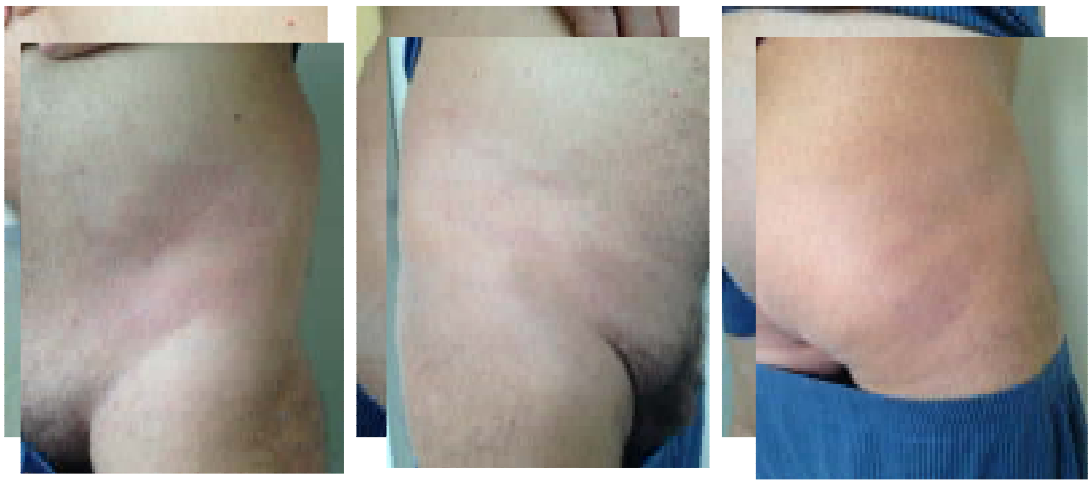
Latzka J et al. Eur J Cancer 2023:113343

Topical treatment

- Corticosteroids – 3 to 5 days weekly, of low potency in macules
- Chlormethine (nitrogen mustard) (Ledaga^{R}) – limited experiences
- Tacrolimus 0,1% ointment – used off label, in combination with topical corticosteroids

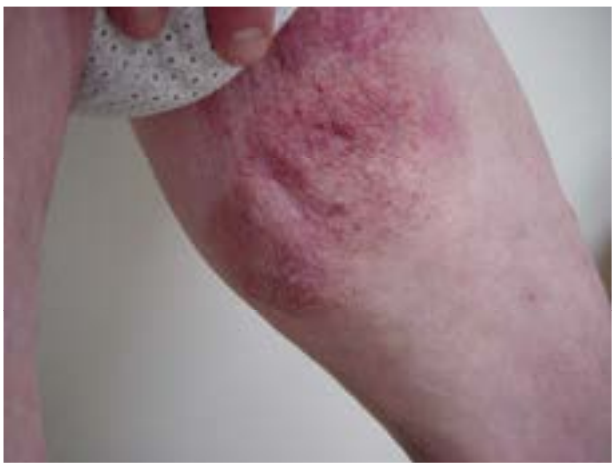
- Carmustine
- Bexarotene gel

Mycosis fungoides, stage IA – UVB phototherapy

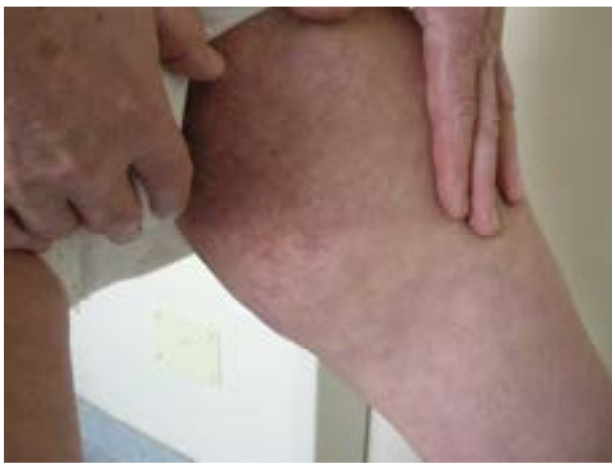


Figures: author's source

MF, stage IIB – PUVA and acitretin



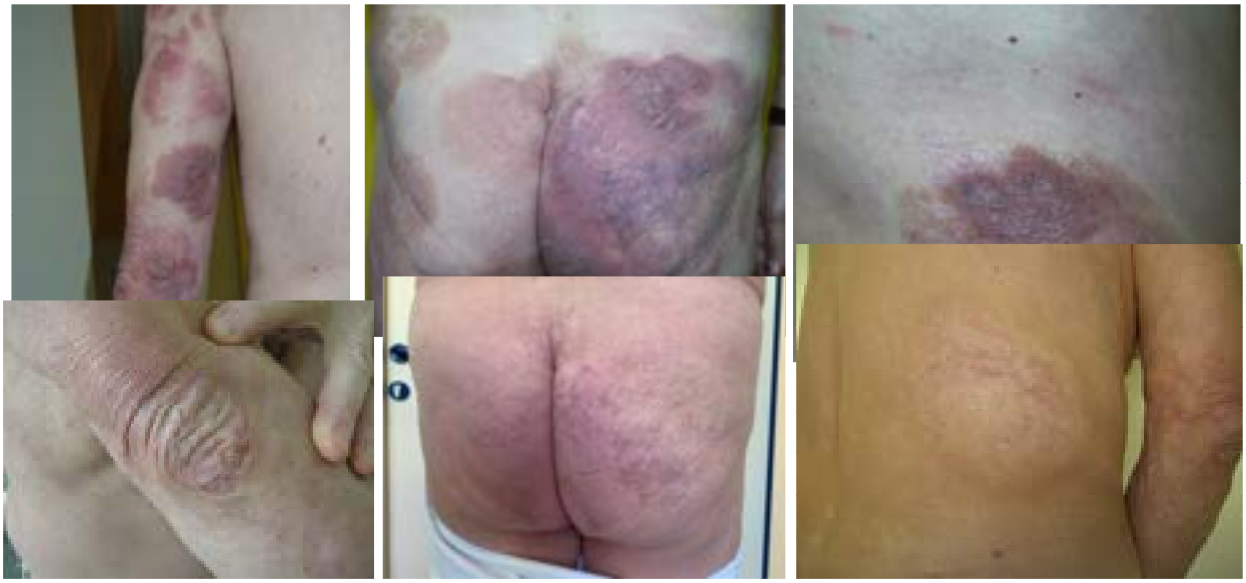
2009



2021

Figures: author's source

MF, stage IIB – PUVA and acitretin and radiotherapy



Figures: author's source 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE | RETRACTED

Treatment of Cutaneous T-Cell Lymphoma by Extracorporeal Photochemotherapy

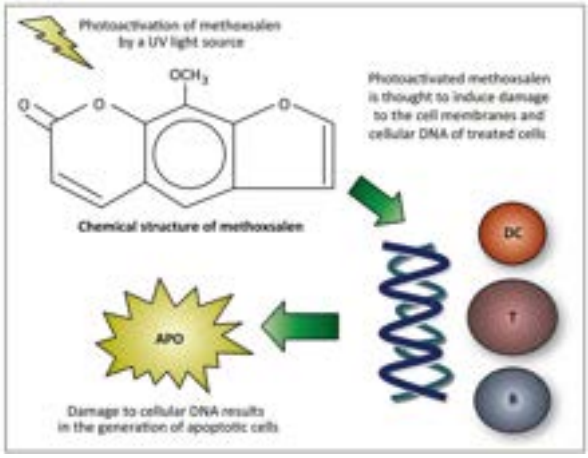
Authors: Richard Edelson, M.D., Carole Berger, Ph.D., Francis Gasparro, Ph.D., Brian Jegasothy, M.D., Peter Heald, M.D., Bruce Wintroub, M.D., Eric Vonderheid, M.D., +12, and Liliane Laroche, M.D. Author Info & Affiliations

Published February 5, 1987 | N Engl J Med 1987;316:297-303 | DOI: 10.1056/NEJM198702053160603

VOL. 316 NO. 6

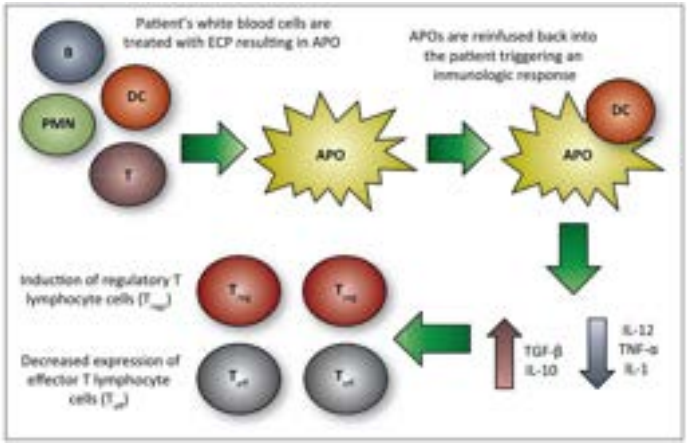
ECP induces cell apoptosis

8-methoxy-psoralen induces damage to the cell membranes and cellular DNA of treated cells



Chiesa-Fuxench ZC et al. PR Health Sci J 2010;29:337-47

ECP induces long-term immunologic response



- Increased production of anti-inflammatory cytokines: IL10, beta-transforming growth factor
- Pathological balance between Th1 and Th2 is restored, with a shift from Th1 to Th2 cytokine profile

- Induction of regulatory T cells
- ECP induces immune response against malignant lymphocytes

- Immunomodulatory therapy
- No risk of opportunistic infections

Chiesa-Fuxench ZC et al. PR Health Sci J 2010;29:337-47

Extracorporeal photopheresis

ECP is recommended as the first-line therapy in:

- erythrodermic MF, stages III and IV
- Sézary syndrome

Latzka J et al. Eur J Cancer 2023:113343

ECP treatment for CTCL

Studies	Partial and complete response	Complete reponse
Metaanalysis - 30 studies 1987-2007 689 patients	63% (33 – 100%)	20% (0 – 30%)
Metaanalysis 19 studies More than 400 patients	56% Combination with other drugs	15 – 18%
Data from 7 studies 2007 - 2011	42% - 80%	0 – 30%
Sézary syndrome	43%	10%

- In at least 60% improvement of the disease (partial or complete remission)
- Influence of ECP on the survival has not been evaluated

Knobler R. JEADV 2020; 34:2693–2716
Zic JA. Dermatol Ther 2003; 16: 337–346
Scarisbrick JJ et al. Br J Dermatol 2008; 158: 659–678

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GUIDELINES

European dermatology forum – updated guidelines on the use of extracorporeal photopheresis 2020 – part 1

R. Knobler,[1,*] P. Arenberger,[2] A. Arun,[3] C. Assaf,[4] M. Bagot,[5] G. Berlin,[6,7] A. Bohbot,[8] P. Calzavara-Pinton,[9] F. Child,[10] A. Cho,[11] L.E. French,[12] A.R. Gennery,[13] R. Gniadecki,[14] H.P.M. Gollnick,[15] E. Guenova,[16,17] P. Jaksch,[18] C. Jantschitsch,[19] C. Klemke,[20] J. Ludvigsson,[21] E. Papadavid,[22] J. Scarisbrick,[23] T. Schwarz,[24] R. Stadler,[25] P. Wolf,[26] J. Zic,[27] C. Zouboulis,[28] A. Zuckermann,[29] H. Greinix[30]

[1]Department of Dermatology, Medical University of Vienna, Vienna, Austria
[2]Third Faculty of Medicine, Charles University, Prague, Czech Republic
[3]FRCPath, The Rotherham NHS Foundation Trust, Rotherham, UK
[4]Department of Dermatology and Venerology, Helios Klinikum Krefeld, Krefeld, Germany
[5]Hospital Saint Louis, Université de Paris, Paris, France

GUIDELINES

European dermatology forum: Updated guidelines on the use of extracorporeal photopheresis 2020 – Part 2

R. Knobler,[1,*] P. Arenberger,[2] A. Arun,[3] C. Assaf,[4] M. Bagot,[5] G. Berlin,[6] A. Bohbot,[7] P. Calzavara-Pinton,[8] F. Child,[9] A. Cho,[10] L.E. French,[11] A.R. Gennery,[11] R. Gniadecki,[12] H.P.M. Gollnick,[13] E. Guenova,[14] P. Jaksch,[15] C. Jantschitsch,[7] C. Klemke,[16] J. Ludvigsson,[17] E. Papadavid,[18] J. Scarisbrick,[19] T. Schwarz,[20] R. Stadler,[21] P. Wolf,[22] J. Zic,[23] C. Zouboulis,[24] A. Zuckermann,[25] H. Greinix[26]

[1]Department of Dermatology, Medical University of Vienna, Vienna, Austria
[2]Third Faculty of Medicine, Charles University, Prague, Czech Republic
[3]FRCPath, The Rotherham NHS Foundation Trust, Rotherham, United Kingdom

Patients with MF/SS, treated with ECP (since December 2013)

Patient	Leto roj.	Spol	TCL	ECP	Other treatments
CF†	1941	M	MF IV	12/2013-12/2016	metotreksat, kemoterapija (CHOP)
AT†	1955	M	Sézary sy	11/2014 - 07/2015	metotreksat, purinetol, alemtuzumab
MI	1974	F	MF IIIB	04/2015 – 11/2019	interferon
SI†	1947	F	Sézary sy	09/2015 – 08/2017	interferon, metotreksat, purinetol, kemoterapija
KM†	1966	M	Sézary sy	12/2015 – 07/2021 od 01/2022	interferon, metotreksat, purinetol, mogamulizumab
PM†	1958	M	Sézary sy	01/2018 – 08/2018	interferon, metotreksat
SJ	1938	M	MF IIIA	08/2018 – 04/2019	retinoid (acitretin)
CK	1972	M	MF III	10/2018 – 02/2019	acitretin, beksaroten, interferon, mogamulizumab
BD	1946	F	Sézary sy	od 11/2019	metotreksat
ŠF	1947	M	Sézary sy	05/2020 – 06/2023	beksaroten
ŠR	1966	M	Sézary sy	od 09/2021	metotreksat
GM	1951	F	Sézary sy	03/2022 – 01/2024	metotreksat
ŠNS	1941	F	Sézary sy	od 09/2023	metotreksat, mogamulizumab

$!

Patients with MF/SS, treated with ECP

Patient	Leto roj.	Spol	TCL	ECP	Other treatments
JR	1936	M	Sézary sy	09/2014 – 11/2014	np
LA	1941	M	MF	12/2016 – 10/2019	np
ZB	1960	M	Sézary sy	09/2018 – 04/2021	np
ŽB	1974	F	Sézary sy	od 06/2021	np
SM	1964	M	pre-Sézary sy	od 12/2021	np
LJ	1940	F	Sézary sy	12/2021 – 10/2022	np
KK	1961	F	MF	06/2022 – 07/2022	np
MT	1959	M	MF	10/2022 – 12/2022	np
DŠ	1970	M	SS	od 11/2024 –	

Pruritus

- Pruritus is more severe in late-stage MF and in SS
- Topical treatment:
  - emollients
  - topical corticosteroids
- Systemic treatment:
  - antihistamines
  - mirtazapine
  - selective serotonin reuptake inhibitors
  - gabapentinoids
  - naltrexone
  - aprepitant

Latzka J et al. Eur J Cancer 2023:113343

Skin care

- Emollients, moisturizers
- Washing with antiseptics (ulcerated lesions)
  - chlorhexidine baths
  - octenidine dihydrochloride lotion

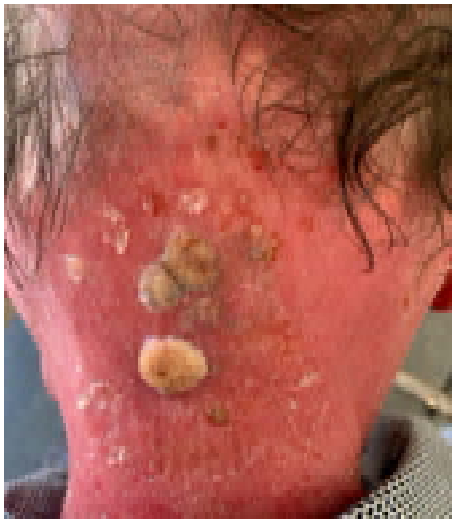
MF - Comorbidities

Higher incidence of secondary malignancies:

- non-Hodgkin lymphomas
- lung cancer
- bladder cancer
- melanoma
- cutaneous squamous cell carcinoma

- Appropriate screening of patients

Goyal A et al. J Am Acad Dermatol 2020; 83: 404-11
Goyal A et al. J Am Acad Dermatol 2020; 85: 1418-28



JAAD Case Reports 2020;6:1288-90

Cutaneous squamous cell carcinoma arising within a mycosis fungoides patch: Case report and review of the literature

Elnara Muradova, MD,[1] Nupur Patel, MD,[2] Pei-Ling Chen, MD,[3] and Lucia Seminario-Vidal, MD, PhD[1,4]
Tampa, Florida

Key words: cutaneous squamous cell carcinoma, cutaneous T cell lymphoma, mycosis fungoides

Photodermatology, Photoimmunology & Photomedicine 2023;39:428-34

ORIGINAL ARTICLE

WILEY

Risk of skin cancers in mycosis fungoides patients receiving PUVA therapy: A real-life experience from a single tertiary center

Pelin Ertop Doğan[1,2] | Bengü Nisa Akay[1] | Seçil Vural[1,2] | Canan Arı[1] | Tuğçe Ertürk Yılmaz[3] | Hatice Şanlı[1]

Figure: author's source

Treatment goals in MF/SS

- To reduce or clear skin lesions
- Induction of long-term remission
- To prevent progression of the disease
- To reduce pruritus
- To improve quality of life

- Multidisciplinary treatment approach can significantly contribute to achieve these goals

Knobler R. *J Eur Acad Dermatol Venereol 2014*

Systemic therapy of T cell skin lymphomas

Asst. Prof. Lučka Boltežar, MD, PhD
Institute of Oncology Ljubljana
15.11.2024

Mycosis fungoides – II B (tumor stage disease)

- Retinoids → D
- Low dose Methotrexate → D
- Gemcitabin monotherapy → O
- Pegilated Liposomal doxorubicin → O
- Brentuximab vedotin → O

National guidelines Institute of Oncology 2023.

Mycosis fungoides – III (erythrodermic disease), IV

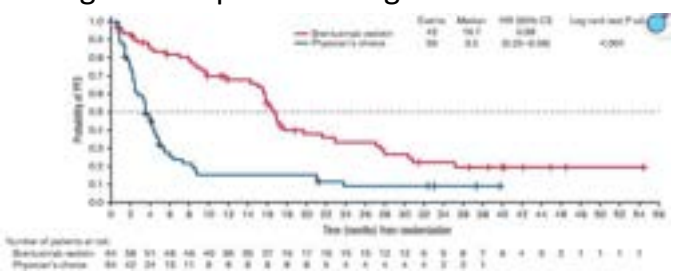
- Gemcitabin monotherapy ✓
- Pegilated Liposomal doxorubicin ✓
- Brentuximab vedotin ✓
- Denileukin diftitox ☒
- Vorinostat and romidepsin (not registred in EU) ☒
- Bortezomib ✓
- Mogamulizumab ✓
- Allogenic stem cell transplant ✓*

Extracorporal photopheresis + …

National guidelines Institute of Oncology 2023.

Brentuximab vedotin

- Randomised controlled phase III trial (ALCANZA) of brentuximab vedotin (/3 weeks, for up to 16 cycles) vs. Conventional therapy (oral methotrexate 5–50 mg once per week or oral bexarotene 300 mg/m^2 once per day, for up to 48 weeks) in MF and primary cutaneous anaplastic large-cell lymphoma
- The primary endpoint was the proportion of patients in the intention-to-treat population achieving an objective global response lasting at least 4 months
- 131 patients (128 ITT), mFU 46m
- ORR 54,7% vs. 12,5% (CR 17,2%, PR 48,4% for brentuximab)
- Med. PFS 16,5m vs 3,5 months



Horwitz SM et al. Blood 2021.

Gemcitabine

- Pretreated patients – report of 39 patients°, 1200mg/m2 D1, D8, D15 /4w for 3-6 cycles
  - ORR 51% (20 of 39 patients) → CR and PR rates were 23% (9 of 39 patients) and 28% (11 of 39 patients), respectively
  - Patients with MF had a CR rate of 16% and a PR rate of 32% compared with a CR rate of 30% and a PR rate of 25% of PTCLU patients
  - Among the CR patients, 7 of 9 were in continuous complete response with a variable disease-free interval (15-120 months)

- As front line treatment – phase II study of 32 patients*, same schedule treatment
  - 7 pts (22%) achieved a CR and 17 (53%) achieved a PR
  - The CR and PR rates were found to be the same for patients with MF and PTCLU
  - The median duration of CR was 10 months (range 4-22 m)

*Marchi E et al. Cancer 2005. °Zinzani PL et al. Ann Oncol 2010.

Bortezomib

- Phase II study of pretreated patients with cutaneous T-cell lymphoma patients or PTCL-NOS with only skin involvement
- Treatment protocol was 1,3 mg/m2 intravenously D1, D4, D8, and D11 every 21 days for a total of six cycles
- 15 were registered, of whom 12 (10 CTCL, all mycosis fungoides, and two PTCLU with isolated skin involvement) were assessable
- The ORR was 67% → 2 (17%) CR and 6 (50%) PR
- Histologically, the responder patients were seven with CTCL and one with PTCLU with isolated skin involvement
- All responses were durable, lasting from 7 to 14 or more months

Zinzani PL et al, J Clin Oncol 2007.

Pegylated Liposomal Doxorubicin

- Phase II study, 19 pts, ORR 84,2% → CR 42,1%, PR 42%, mPFS 19m*
- Prospective study 40mg/m2 /4w, 25 pts, ORR 56% → 5 CR (20%) and 9 PR (36%); the median OS was 43,7 months; For the 14 patients who experienced an objective response, the median PFS after the end of treatment was 5 months°
- EORTC 21012 20mg/m2 D1, D15 /4w, 49 pts, ORR 40,8% → complete clinical response [CCR] 3 pts (6,1%) and PR 17 pts (34,7%); Median PFS was 7,4m and median duration of response (DOR) 6 months˘

*Pulini S et al, Haematologica 2007.°Quereux G et al. Arch Dermatol 2008.˘Dummer R et al, J Clin Oncol 2012.

Mogamulizumab

Randomised controlled phase III trial (MAVORIC) of mogamulizumab (anti CCR4 antibody) vs. Vorinostat in patients with previously treated MF (≥ stage IB) and SS.

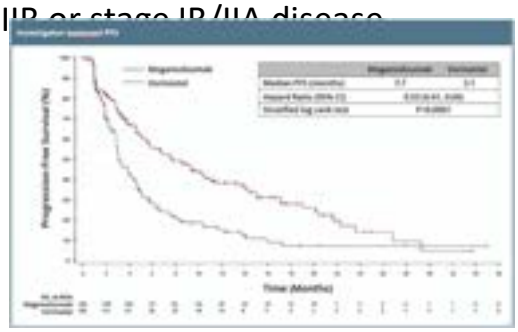
- Responses were higher in patients with blood involvement (stage III or stage IV disease) than those with stage IB or stage IB/IIA disease

Median time to response was 3,3 months

- ORR for MF was 21%,

in Sezary siyndrome 37%

(vorinostat 5%), PFS benefit



Kim YH et al, Lancet Oncol 2018.

Kim YH. The Lancet Oncology, 2018;19(9):1192-1204

Sezary syndrome

- Chlorambucile in combination with prednizone ✓
- Low dose methotrexate ✓
- Gemcitabine ✓
- Pegylated liposomal doxorubicin ✓
- CHOP ✓
- Modified COP ✓
- Alemtuzumab ✓*
- Brentuximab vedotin ✓
- Denileukin diftitox ☒
- Mogamulizumab ✓
- Allogenic stem cell transplant ✓*
- Pembrolizumab ✓

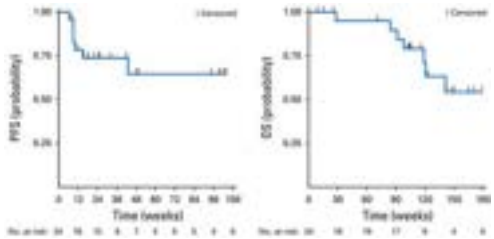
National guidelines Institute of Oncology 2023.

Alemtuzumab

- Phase II study of 22 pts, step up dose to 30mg 3x weekly; ORR was 55% → 32% CR and 23% PR, Sézary cells were cleared from the blood in 6 of 7 (86%) pts, and CR in lymph nodes was observed in 6 of 11 (55%) pts; The effect was better on erythroderma (OR, 69%) than on plaque or skin tumors (OR, 40%) and in patients who had received 1 to 2 previous regimens (OR, 80%) than in those who had received 3 or more prior regimens (OR, 33%), median time to treatment failure was 12m (range 5-32+), 50% infections*
- Low intermediate dose study, 14 pts, max dose 15mg, ORR was 12/14 patients (85,7%) → 3 CR (21,4%); after a median follow-up of 16 months, the median time-to-treatment failure was 12 months, 28,6% infections°
- Single center report of 19 pts, ORR 84% → 9 CR (47%) and 7 PR (37%), med PFS 6 months˘

*Lundin J et al, Blood 2003.°Bernengo MG et al, Haematologica 2007.˘Querfeld C et al, Leuk Lymphoma 2009.

Pembrolizumab



- Phase II study, 24 pts,
pembrolizumab 2mg/mg /3 w up to 24 cycles
- Median 4 prior systemic lines
- The ORR 37% → 2 (8%) CR and 7 (29%) PR
- The med DOR was not reached with a median response follow-up time of 58 weeks
- Immune-related adverse events led to treatment discontinuation in four patients
- A transient worsening of erythroderma and pruritus occurred in 53% of patients with SS (this cutaneous flare reaction did not result in treatment discontinuation for any patient)
- Treatment responses did not correlate with expression of PD-L1

Khodadoust MS et al, J Clin Oncol 2020.

Stem cell transplant

Autologous stem cell transplant → PFS 2 months*; metaanalysis° → superior OS and event free rates with allogenic transplant

*Olavarria E et al, Br J Haematol 2001. °Wu PA et al, Biol Bloow Marrow Transplant 2009.

Author	N. of patients	Age	OS	Progression	NRM
Duvic et al. Hosing et al.	47	51	4-year 51%	4-year PFS 26%	NRM 10% in 1 yr
Duarte et al.	60	46,5	3-year 54% 5-year 46%	5-year PFS 32% 45% progressed in med. 3,8 m	NRM 22% in 7 yrs
Paralkar et al.	12	53	2-year 58%	Med. EFS 5,3 m	16% transplant related; NRM not reported
Lechowicz et al.	129	51 (RIC), 44 (Mya)	1-year 54% 5-year 32%	Risk of progression 50% in 1yr, 61% in 5yrs	NRM 1 yr 19% NRM 5 yr 22%
De Masson et al.	37	44	1-year 65% 2-year 57%	1-year PFS 39% 51% progression in median 10 weeks	22% transplant related; NRM Not reported
Cudilo et al.	16	54	1-year 61% 10-year 54%	1-year DFS 40% 10-year DFS 34%	NRM 43%

Duvic M et al, J Clin Oncol 2010; Hosing C et al, Ann Oncol 2015, Duarte RT et al, J Clin Oncol 2010, Paralkar VR et al, Bone Marrow Transplant 2012, Lechowicz MJ et al, Bone Marrow Transplant 2014, De Masson A et al, Haematologica 2014, Cudillo L et al, Ann Hematol 2018.

%

Treatment	ORR	CR	PR	DOR/PFS
Brentuximab vedotin	54,7%	17,2%	37,5%	mPFS 16,7 months
Gemcitabine → First line → Second line	 75% 51%	 22% 23%	 53% 28%	7pts remission post gem med.34months Med. duration of CR 10 months
Bortezomib	67%	17%	50%	DOR 7 – 14 months
Pegylated Liposomal Doxorubicin	84% 56% 40,8%	42% 20% 6,1%	42% 36% 34,7%	mPFS 19 months mPFS 5 months after EOT mPFS 7,4 months
Mogamulizumab	28%	Skin 42%, blood 48%, lymph nodes 17%, viscera 0%		mPFS 7,7 months
Alemtuzumab	55% 85% 84%	32% 21% 47%	23% 64% 37%	Med. time to treatment failure 12 months mPFS 6 months
Pembrolizumab	37%	8%	29%	Med DOR not reached

%

RADIOTHERAPY IN T-CELL SKIN LYMPHOMAS

Lorna Zadravec Zaletel
Institute of Oncology
Ljubljana

OVERVIEW

- Classification of CTCL
- Indication for radical RT and different radiosensitivity of CTCLs
- role of RT in mycosis fungoides (radical, palliative) and cases
- Total skin electron beam (TSEB) RT

WHO-EORTC classification of CTCL - update

Table 1. Relative frequency and prognosis of primary cutaneous lymphomas included in the 2018 update of the WHO-EORTC classification

WHO-EORTC Classification 2018	Frequency, %*	5-y DSS, %*
CTCL		
MF	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
SS	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30$^+$ LPDs		
C-ALCL	8	95
Lyp	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
Primary cutaneous γ/δ T-cell lymphoma	<1	11
CD8$^+$ AECTCL (provisional)	<1	31
Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder (provisional)	6	100
Primary cutaneous acral CD8$^+$ T-cell lymphoma (provisional)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15

Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. Blood. 2019;133(16):1703-1714

RADIOTHERAPY for CTCL

LOCAL SKIN IRRADIATION

is effective:

- for eradication of uni-lesional disease (radical RT)

  different radiosensitivity !

or

- palliation for multisite disease (palliative RT)

Radical RT in localized disease of different types of CTCL

TYPE OF CTCL	curative RT dose
Primary cutaneous NK/T-cell lymphoma, nasal-type	50 -55 Gy
Subcutaneous panniculitis-like T-cell lymphoma	≥ 40 Gy
Primary cutaneous γ/δ T-cell lymphoma	24 – 30 Gy
Primary cutaneous anaplastic large cell lymphoma	24 – 30 Gy
Fungoid mycosis	24 – 30 Gy

Lena Specht et al. Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group. Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 32e39, 2015

MYCOSIS FUNGOIDES

CLINICAL STAGING OF MF AND SS[†]

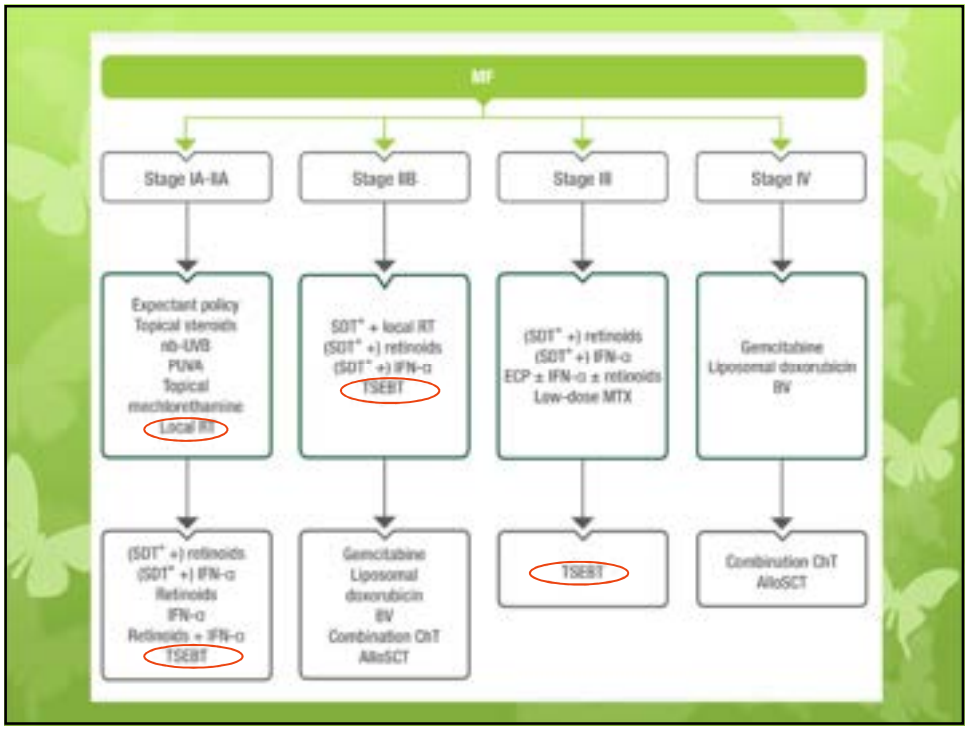
Clinical Stage[‡]	T (Skin)	N (Node)	M (Visceral)	B (Blood Involvement)
IA (Limited skin involvement)	T1 (Patches, papules, and/or plaques covering <10% body surface area [BSA])	N0	M0	B0 or B1
IB (Skin only disease)	T2 (Patches, papules, and/or plaques covering ≥10% BSA)	N0	M0	B0 or B1
IIA	T1–2	N1–2	M0	B0 or B1
IIB (Tumor stage disease)	T3 (One or more tumors [≥1 cm in diameter])	N0–2	M0	B0 or B1
IIIA (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B0
IIIB (Erythrodermic disease)	T4 (Confluence of erythema ≥80% BSA)	N0–2	M0	B1
IVA$_1$ (Sézary syndrome)	T1–4	N0–2	M0	B2
IVA$_2$ (Sézary syndrome or Non-Sézary)	T1–4	N3	M0	B0 or B1 or B2
IVB (Visceral disease)	T1–4	N0–3	M1A or M1B	B0 or B1 or B2
	Large-cell transformation (LCT)[##]			

Olsen EA, et al. Blood 2022;140:419-437

TREATMENT OF MYCOSIS FUNGOIDES

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2018

Willemze, R. et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology,;29:30 – 40, 2018



MF - stage IA, IB - with skin directed therapies

- Topical steroids
- PUVA (Psoralen + UVA)
- Narow band UVB
- Topical chemotherapy
- Local radiotherapy,
- Total skin electron beam irradiation (TSEB)

Willemze, R. et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology,;29:30 – 40, 2018

MF - extensive infiltrated plaques and tumours or refractory to skin directed therapies

- PUVA and retinoids (incl. Bexarotene)
- PUVA and Interferon alpha
- Total skin electron beam irradiation

Doses of 30-36 Gy or lower doses of 10-12Gy

Willemze, R. et al. Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Annals of Oncology,;29:30 – 40, 2018

TREATMENT OF MYCOSIS FUNGOIDES WITH RADIOTHERAPY

Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group, 2015

RADIOTHERAPY IN MF

- Radiation therapy is a highly effective treatment approach for mycosis fungoides,
- is indicated at all stages
- can roughly be divided into:
  - local skin irradiation and
  - total skin electron beam (TSEB) irradiation.

RADIOTHERAPY IN MF

Radical local skin RT

- Is curative in early localized disease, esp. in unilesional MF
- Low energy x-ray or electron beam radiotherapy technique is the standard approach.
- The treatment margin is 2 cm with total dose of 24 to 30 Gy administered in 3 weeks.

RADIOTHERAPY IN MF

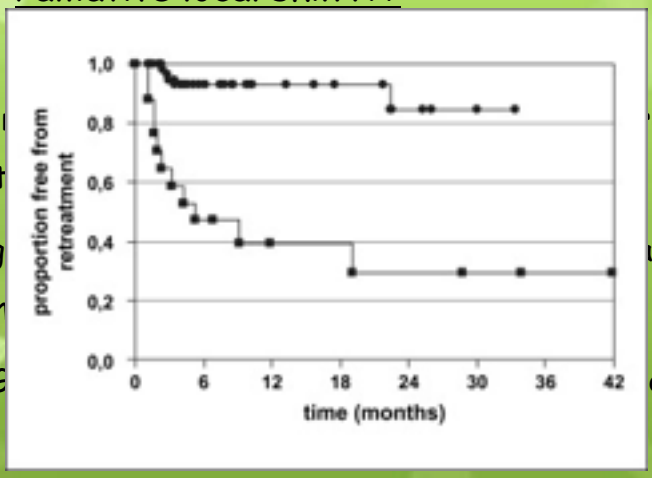
Palliative local skin RT

- ultralow doses (2 Gy X 2) achieve a complete response rate <30%,
- higher doses (8 Gy) are recommended, which achieve complete response rates >90%.
- 8 Gy may be given in a single fraction with good results

RADIOTHERAPY IN MF

Palliative local skin RT

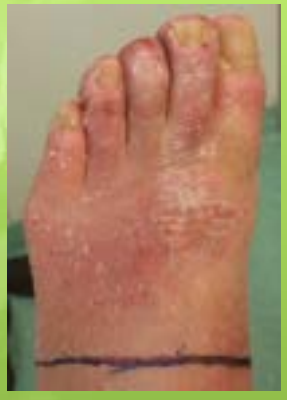
- ult… …esponse rat…
- hig… …chieve cor…
- 8 G… …d results



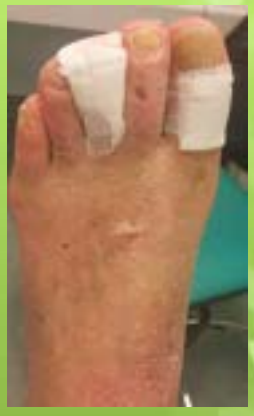
Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. Int J Radiat Oncol Biol Phys 2009;74:154-158.

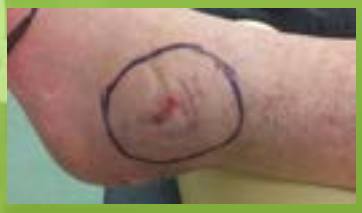
Patients treated for FM at the Institute of Oncology Ljubljana with palliative RT - cases

Palliative RT with the dose 9 Gy in 3 Gy fractions with 100 KV X-rays



After 1 month



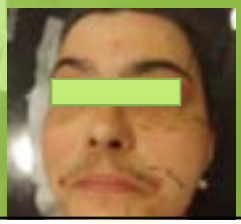
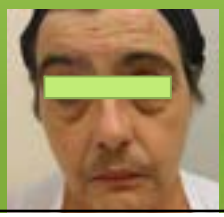


After 1 month

Orthovoltage (x-ray) machine of 100 – 280 kV

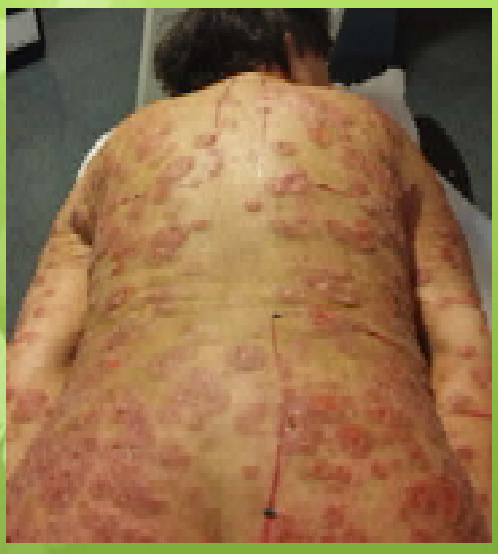
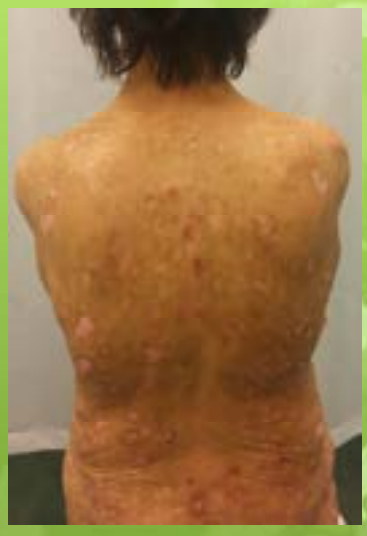

Palliative RT with the dose 9 Gy in 3 Gy fractions with 6 MeV electrons



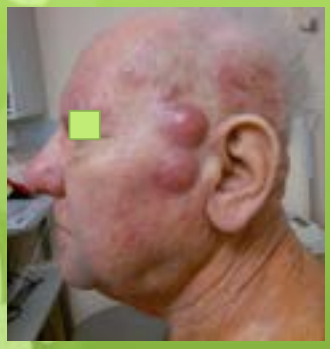



Remission in one month

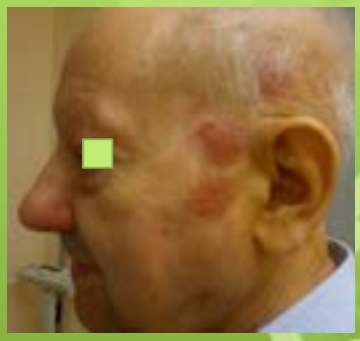
Palliative RT with the dose 9 Gy in 3 Gy fractions with electrons

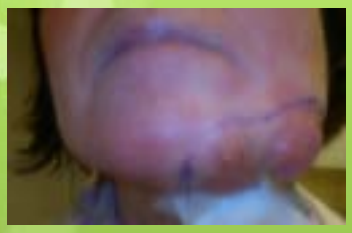
Palliative RT with the dose 9 Gy in 3 Gy fractions with 6 MeV electrons



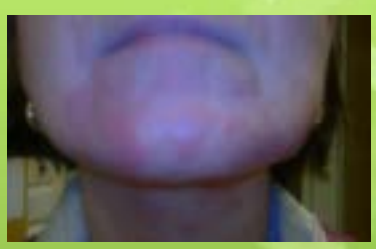
After 1 month

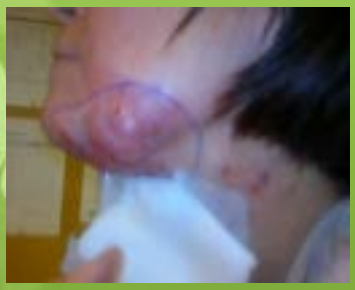


Palliative RT with the dose 9 Gy in 3 Gy fractions with 6 MeV electrons

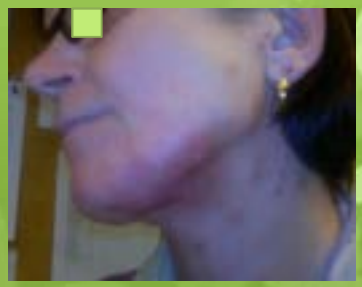


After 1 month





After 1 month

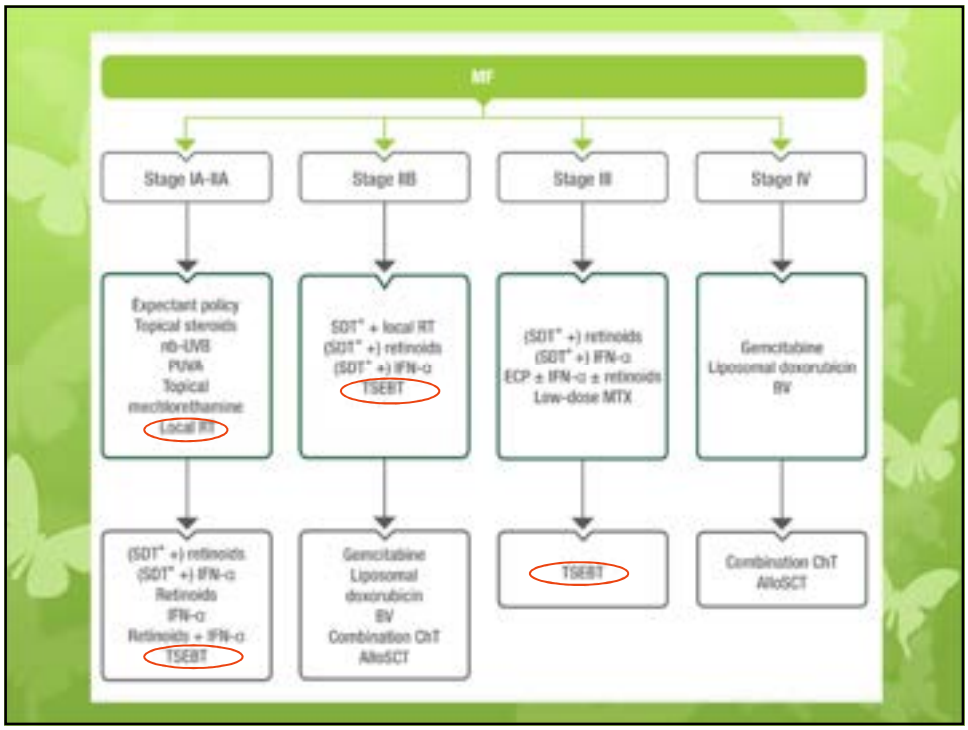


Linear accelerator – for RT with electrons

Total skin electron beam (TSEB) RT

- may be used for effective palliation, patients may often have long-term disease-free intervals
- Normally it is used in patients with history of rapid disease progression or treatment failure after initial topical approach.
- It can be employed as initial therapy in the presence of thick lesions - greater therapeutic effect than topical chemotherapy and phototherapy.
- has complete response rate of 80 – 97% after dose of 30 Gy.

Lena Specht et al. Modern Radiation Therapy for Primary Cutaneous Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group. Int J Radiation Oncol Biol Phys, Vol. 92, No. 1, pp. 32e39, 2015



TSEB RT

- Is technically challenging and requires careful attention to dosimetric technique.
- A variety of techniques may be used to ensure total skin coverage: - large electron field techniques

  - rotational techniques and

  - techniques involving patient or beam movement during irradiation

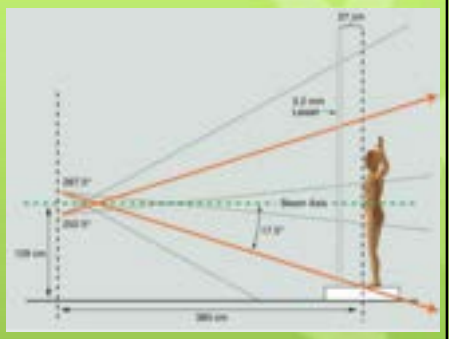
Generally, these require treating patients in the standing position on a rotating platform or else assuming multiple different positions to expose as much as possible all body surfaces.

The 6-field large electron field technique developed at Stanford is the most commonly used

Hoppe RT. Mycosis fungoides: Radiation therapy. Dermatol Ther.2003;16:347-354.

The suggested treatment regimen is that of 30 – 36 Gy in currative intent, but CR often not durable.

- potential value of lower-dose (10-12 Gy), which has the benefits of being briefer in duration, with fewer side effects, and the opportunity for retreatment if required.

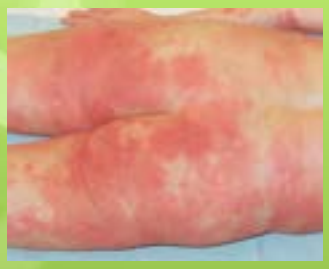


Hoppe RT. Mycosis fungoides: Radiation therapy. Dermatol Ther.2003;16:347-354.

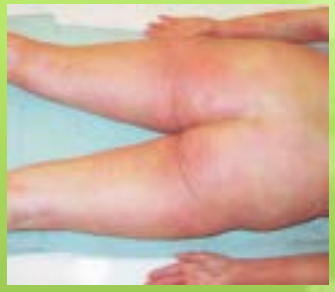
"Shadowed" areas, especially if they are involved by MF, require supplemental treatment.
This may include the top of the scalp, soles, and perineum, as well as areas under the breasts, ….

Hoppe RT. Mycosis fungoides: Radiation therapy. Dermatol Ther.2003;16:347-354.

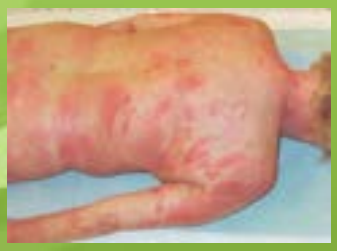
TSEB



Before TSEB



After TSEB



Before TSEB

After TSEB

TSEB in combination with other treatment modalities

TSEB can be combined with:

- any topical treatment (PUVA, steroids,..)
- ECP in Sezary disease
- Systemic chemotherapy in advanced FM

TSEB – side effects

Short term:

- Loss of skin appendages that regenerate within 4-6 months after RT
- Transient swelling of the hands and oedema of ankles
- Gynecomastia

Long term:

- Superficial atrophy with wrinkling, teleangiectasies, xerosis, uneven pigmentation
- Increased incidence of radiation induced cutaneous neoplasia, higher in patients with additional therapy

CONCLUSIONS

- RT is an effective treatment in CTCL, the prescribed dose needed for radical treatment depends on the type of CTCL
- In FM it can be supplied locally or by TSEB and repeated at relapse.
- RT can be combined with other treatments.
- Side effects are usually mild and transient.

Novosti v zdravljenju limfoma plaščnih celic

Milica Miljković specialistka internistične onkologije

Oddelek za zdravljenje malignih limfomov

Limfomska šola 2024

OI Ljubljana

Vsebina predavanja

- Epidemiologija
- Patogeneza, molekularna biologija, prognostični faktorji
- Prva linija sistemskega zdravljenja
- Autologna transplanatcija pri limfomu plaščnih celic
- Zdravljenje ponovitve bolezni
- Novosti v zdravljenju in prihodnost zdravljenja

Epidemiologija

- 3-7% vseh Non-Hodgkinovih limfomov
- Incidenca 4-8/million/leto
- Incidenca raste z leti in v Ameriki
- ¾ so moški bolniki
- Bolj pogost pri belcih
- Srednje preživetje je 3-5let
- 10 letno preživetje cc 30%
- 15-20% relapsirajo v dveh letih

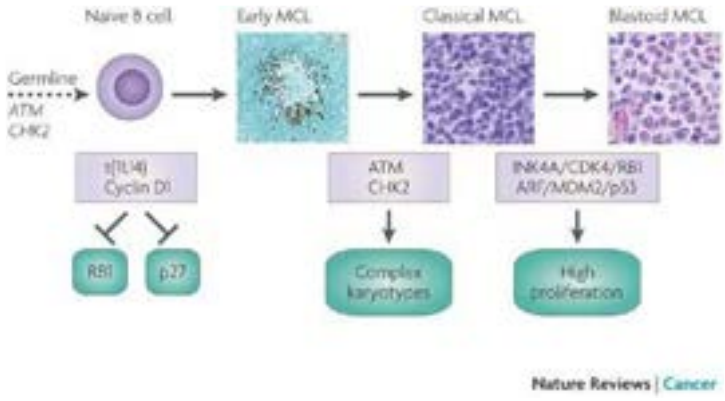
Slajd avtorja

Patogeneza in molekularna biologija

1. Translokacija (11;14) in ekspresija ciklin D1
2. Mutacija ATM (ataxia-telangiectasia mutant) gena
3. Ekspresija SOX-11: cc 90%
4. Aktivacija B celičnega receptorja (BCR)
5. Mutacije: TP53 (26.8%), RB1(24.3%), CDKN2A(23.9%), CCND1 (20.2%)

Slajd avtorja

Patogeneza in molekularna biologija



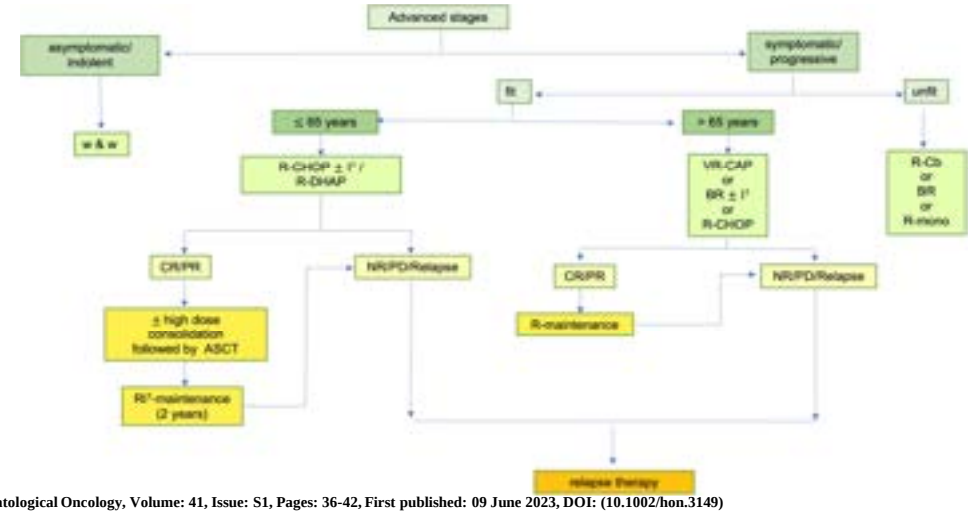
Vir: https://www.nature.com/articles/nrc2230

Prognostični faktorji

Age	MCL35 RNA expression analysis
Performance status	SOX11 expression
Central nervous system involvement at diagnosis	*TP53* mutations/deletions by sequencing analysis or immunohistochemistry
Stage of disease (I and II vs. III and IV)	*NOTCH1* mutations
Serum level of β_2-microglobulin and LDH	*CDKN2A* mutations
Morphology (classic vs. blastoid)	*WNSCT* mutations
MIPI	*MYC* alterations
Ki-67 (<30% vs. >30%)	*CCND1* mutations
Disease pattern (nodal/non-nodal)	*BIRC3* mutations (concerning ibrutinib treatment)
	CARD11 mutations (concerning ibrutinib treatment)
	SMARCA4 mutations (concerning venetoclax treatment)
	MRD testing

Vir: https://doi.org/10.1111/bjh.17419

Prva linija sistemskega zdravljenja



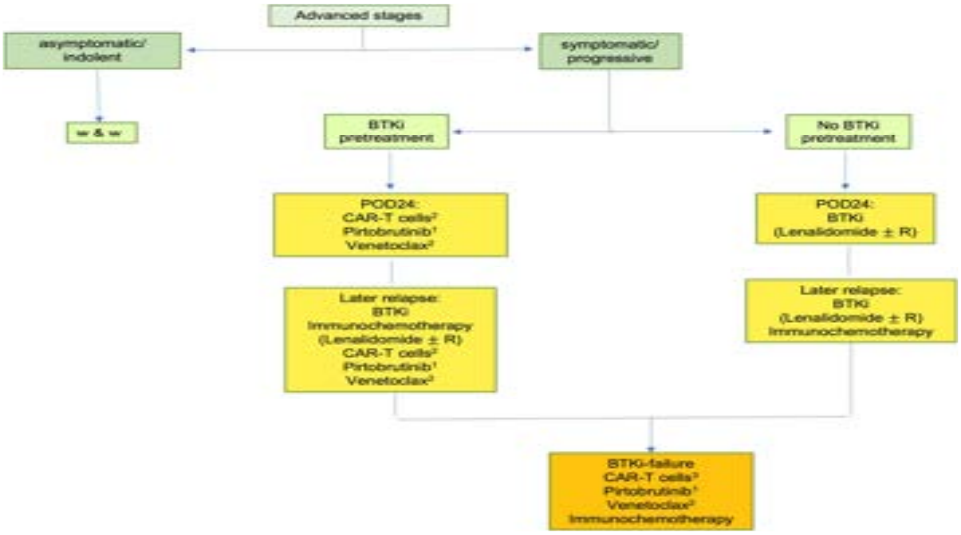
Hematological Oncology, Volume: 41, Issue: S1, Pages: 36-42, First published: 09 June 2023, DOI: (10.1002/hon.3149)
W-w: opazovanje, CR/PR: kompletna/delna remisija, NR/PD – brez odgovora/progress, R-CHOP (rituximab, ciklofosfamid, doksorubicin,vinkristin,prednizolon, R-DHAP (rituksimab, deksametazon, visokodozni citarabin,cisplatina), I- ibrutinib, ASCT(avtologna transplantacija), VR-CAP (rituksimab,ciklofosfamid,doksorubicin,bortezomib,prednizolon), BR (rituksimab, bendamustin), R-Cb (rituksimab, klorambucil)

Avtologna transplantacija

1. Pri mlajših (pod 65) in fit bolnikih
2. Komorbidnost?
3. Benefit pri bolnikih kateri so zdravljeni z HD ARA-C: daljši TTF 9.1 let vs 3.9 let

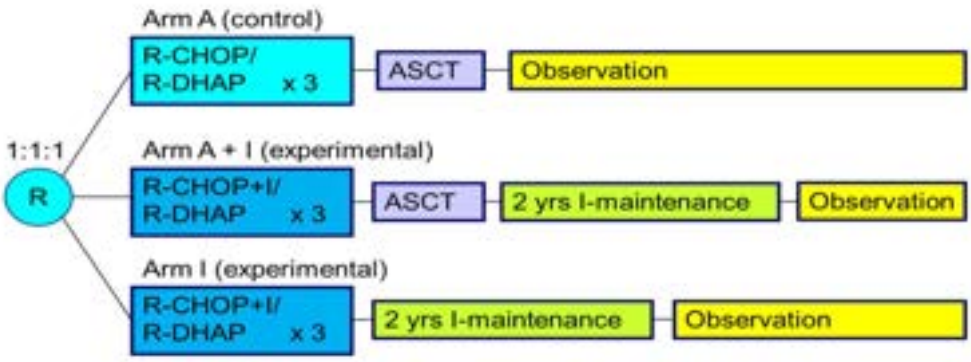
What is the role of up-front autologous stem cell transplantation in mantle cell lymphoma?
Anita Kumar [1] https://pubmed.ncbi.nlm.nih.gov/36485104/
Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network
Olivier Hermine [1] https://pubmed.ncbi.nlm.nih.gov/27313086/

Zdravljenje ponovitve bolezni



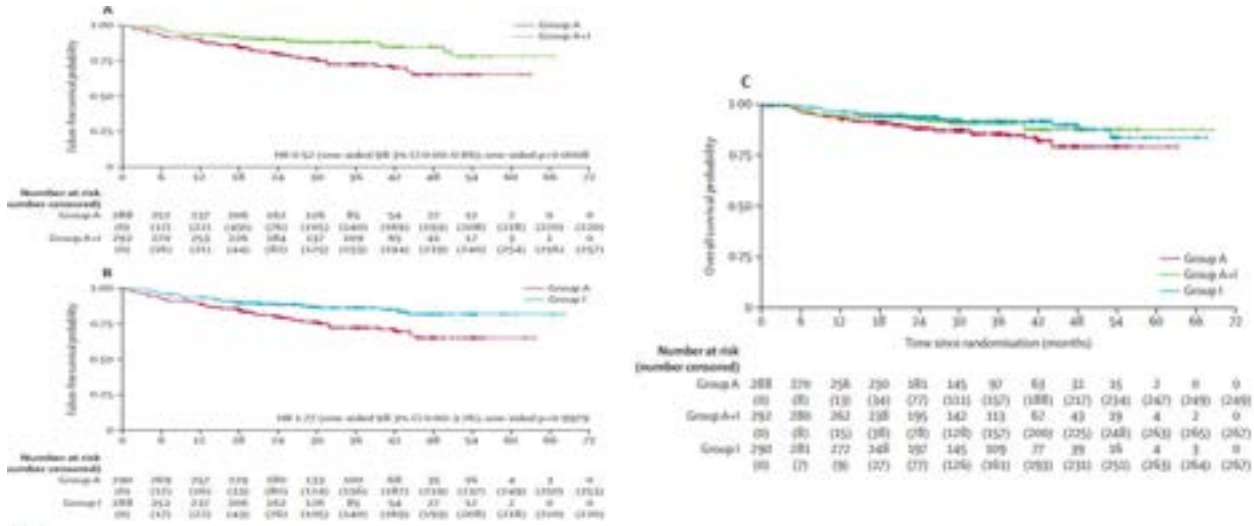
Hematological Oncology, Volume: 41, Issue: S1, Pages: 36-42, First published: 09 June 2023, DOI: (10.1002/hon.3149)

TRIANGLE študija



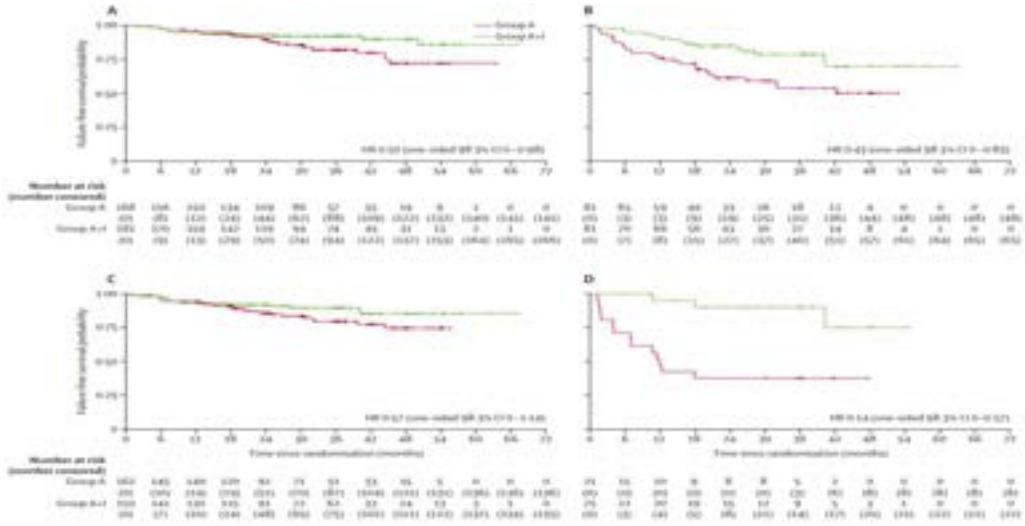
https://www.onkopedia.com/de/wissensdatenbank/wissensdatenbank/non-hodgkin_lymphome-indolent/v460_dreyling_mantelzell-lymphom.pdf

TRIANGLE studija



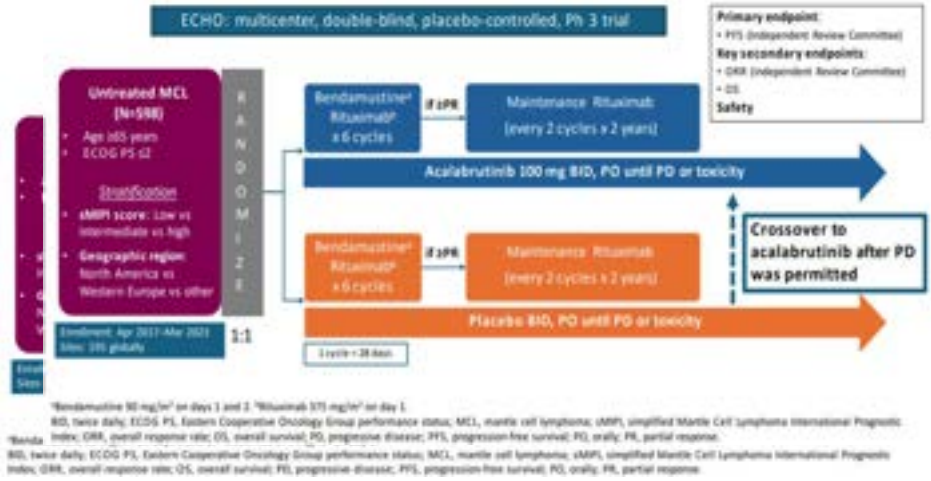
Failure-free survival for group A+I vs group A **(A)**, group A vs group I **(B)**, and overall survival for all treatment groups **(C)**

TRIANGLE studija



Failure-free survival for group A+I vs group A in selected subgroups of patients with low (50%) p53 (D)

ECHO studija



M. Wang et all EHA2024, Abstract LB 3439

ECHO studija

	Calquence plus bendamustine and rituximab (n = 299)	Placebo plus bendamustine and rituximab (n = 299)
Median PFS (months)	66.4	49.6
PFS HR (95% CI)	0.73 (0.57-0.94)	
PFS p-value	0.0160	
OS HR (95% CI)	0.86 (0.65-1.13)	
OS p-value	0.2743	

M. Wang et all EHA2024, Abstract LB 3439

SYMPATICO študija

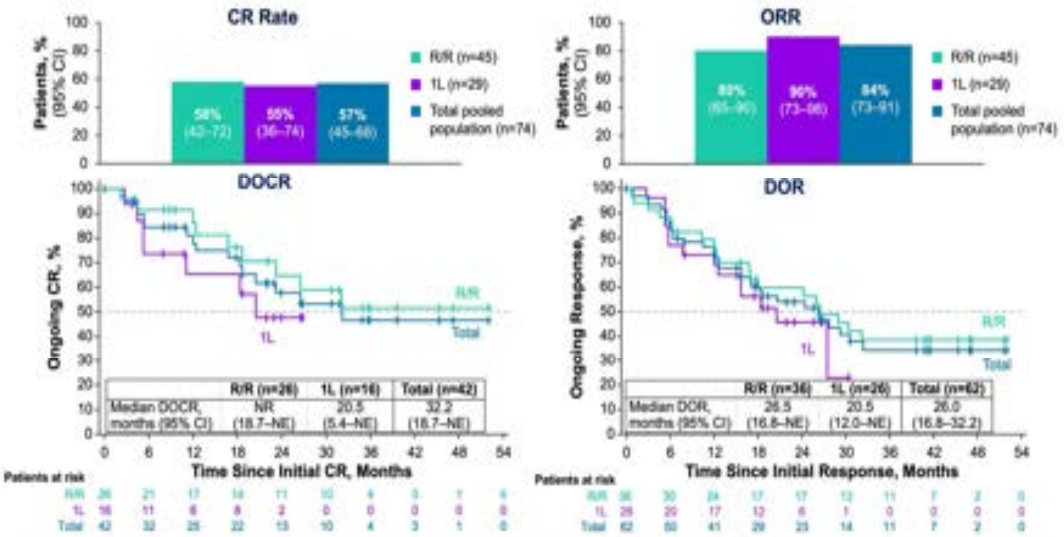
Blood 142 (2023) LBA-2-LBA-4

The 65th ASH Annual Meeting Abstracts

LATE BREAKING ABSTRACTS

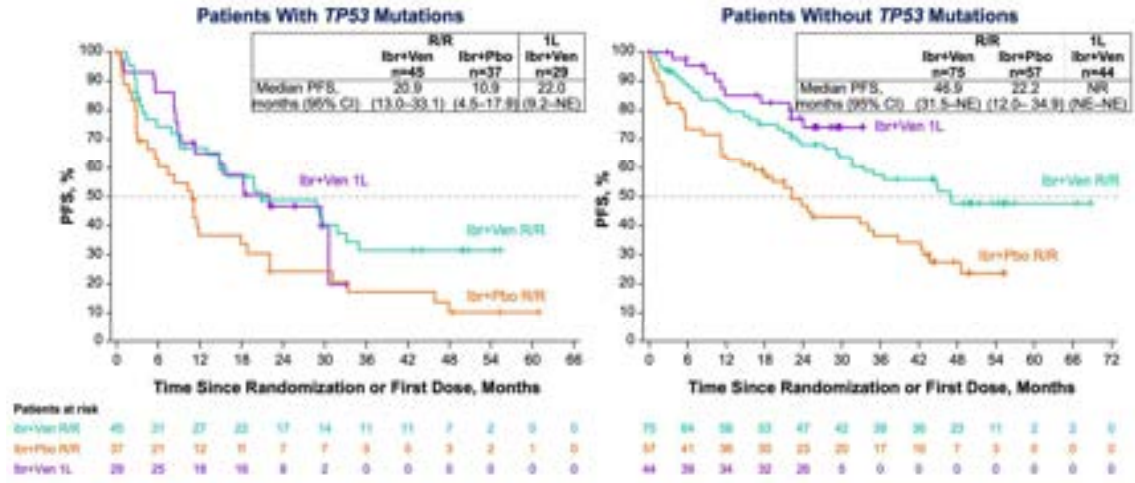
Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study

Michael Wang, MD[1], Wojciech Jurczak, MD PhD[2], Marek Trněný, MD[3], David Belada, MD[4], Tomasz Wrobel, MD PhD[5], Nilanjan Ghosh, MD PhD[6], Mary-Margaret Keating, MD[7], Tom van Meerten, MD PhD[8], Ruben Fernandez Alvarez, MD[9], Gottfried von Keudell, MD PhD[10], Catherine Thieblemont, MD[11], Frederic Peyrade, MD[12], Marc André, MD[13], Marc Hoffmann, MD[14], Edith Szafer Glusman, PhD[15], Jennifer Lin, MS, MA[15], James P. Dean, MD PhD[15], Jutta K. Neuenburg, MDPhD[15], Constantine S. Tam, MD MBBS[16]

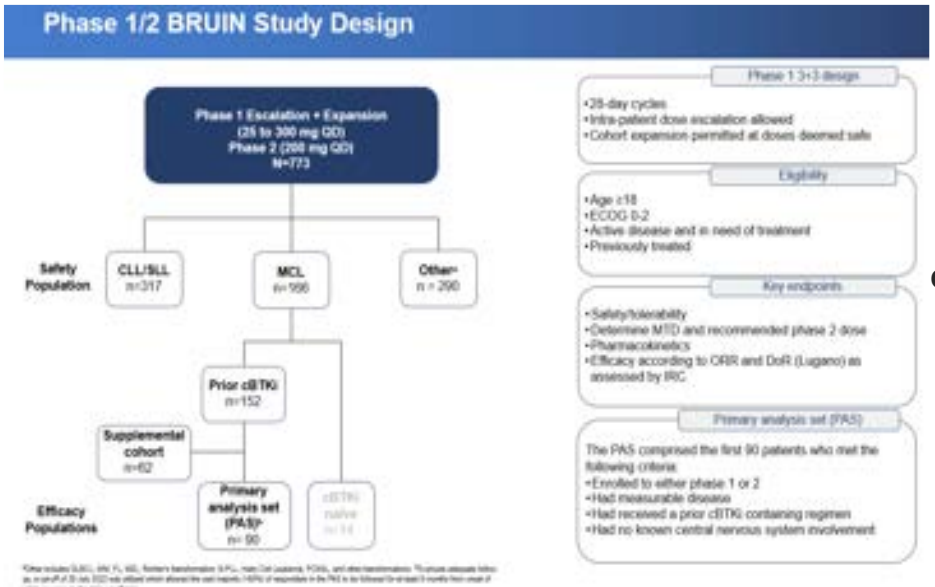


1L, first line; CR, complete response; DOCR, duration of complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; R/R, relapsed/refractory

Wang M, Jurczak W, Trněný M, et al. 2024 ASCO Annual Meeting, abstract 7007



Wang M, Jurczak W, Trněný M, et al. 2024 ASCO Annual Meeting, abstract 7007



ORR 58% (CR 20%)

DOI: 10.1056/NEJMoa2300696

BRUIN faze 3 študija

1. pirtobrutinib vs kovalentni BTKi in R/R MCL (BRUIN MCL-321)
2. BTKi naivni,CAR-T ali avtologni transplantaciji
3. Primarni cilj = PFS

https://doi.org/10.2217/fon-2022-0976

CAR-T

1. **ZUMA-2 (Brexucaptagene autoleucel):**

Median follow up: 35.6 months

ORR 91% (68% CR)

mDOR 28.2%, mPFS 25.8%, mOS 46.6%

2. TRANSCEND NHL 001, faza -1 (Lisocabtagene)

Median follow up: 16.1 months

ORR 83.1% (72.3%)

mDOR 15.7 mPFS 15.3

1. DOI: 10.1016/S1470-2045(21)00591-X
2. https://doi.org/10.1200/JCO.23.02214

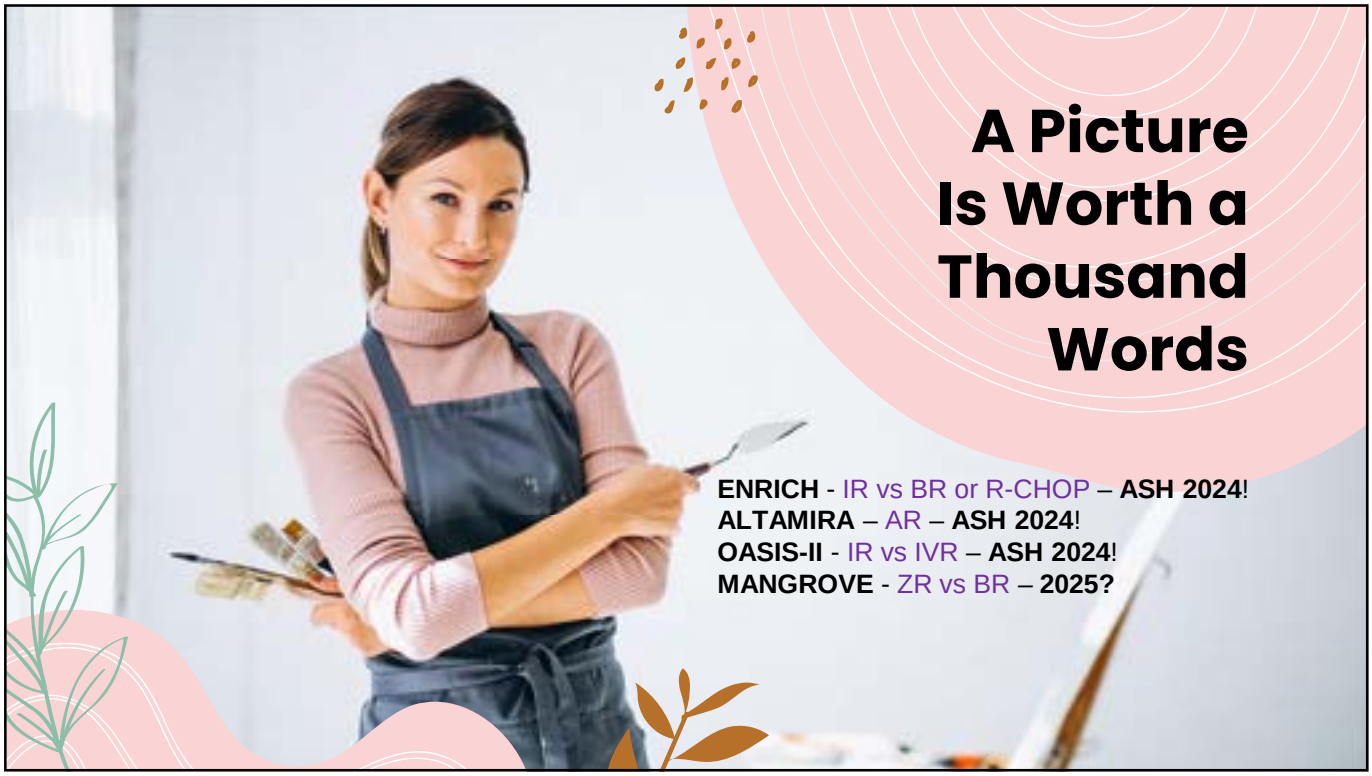
BISPECIFIČNA PROTITELESA

Glofitamab (R/R MCL): 60 uključenih

ORR 85% CR 78.3%

mPFS 16.8 m

https://doi.org/10.1200/JCO.23.02470



Novosti v zdravljenju marginalno celičnega limfoma

Aleš Christian Mihelač, dr. med.

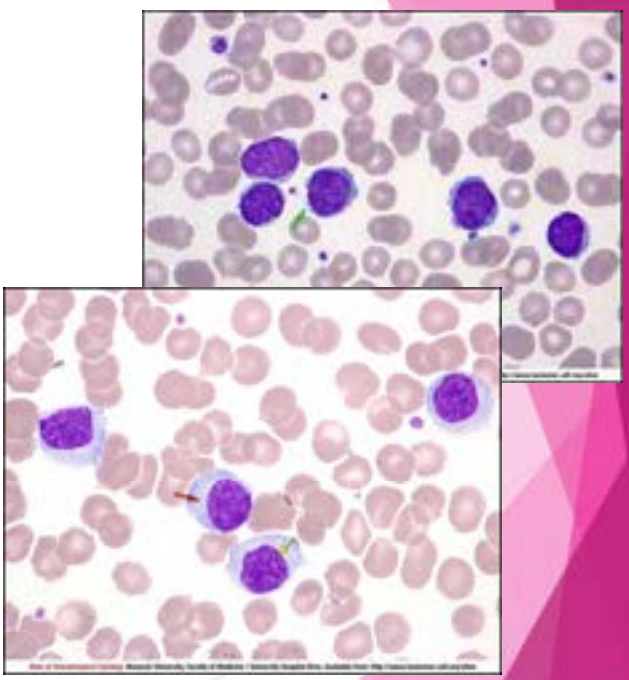
Ana Čebokli, dr. med.

Onkološki inštitut Ljubljana, Oddelek za zdravljenje limfomov

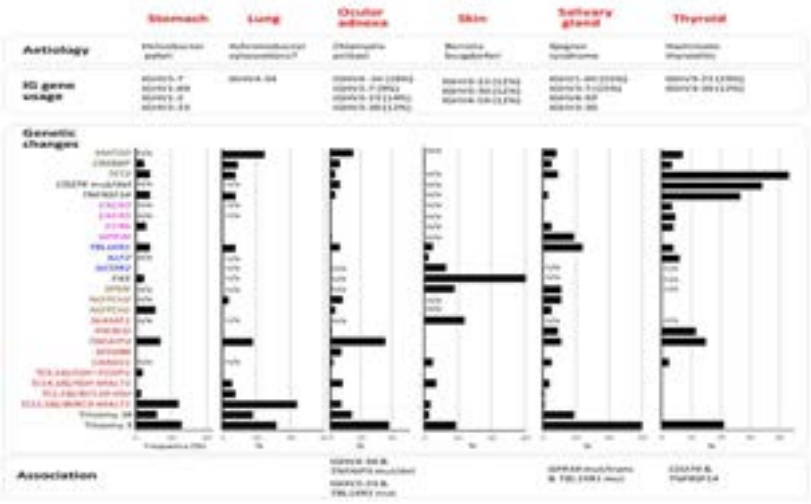
4. Limfomska šola, 15.11.2024

Uvod

- Indolentni B-celični limfom
- Kronični potek
- Večinoma dobra prognoza
- Najpogostejša mesta so želodec, vranica, očesni adneksi, pljuča, koža in žleze slinavke
- Ločevanje od LP limfoma s pomočjo MYD88 mutacije

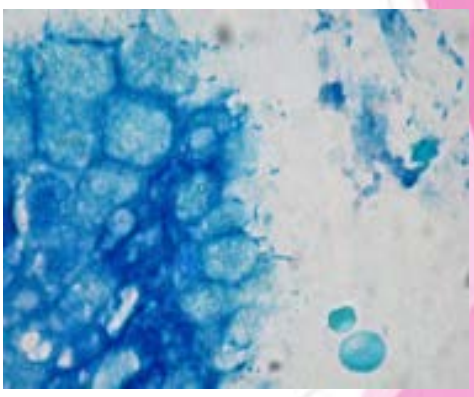


Enaki, vendar različni



MALT limfom želodca

- Eradikacija *H. pylori* (tudi če HP negativna)
- Prisotnost t(11;18) napoveduje rezistenco na eradikacijo
- Spremljamo do 18 mesecev, nato RT ali rituksimab v monoterapiji ob perzistentni bolezni
- Možni pozni relapsi po eradikaciji



Nodalni in splenični MZL

- Dolgo časa asimptomatski
- Nodalni MZL ponavadi napredovali stadij (tudi KM 30-40 % ter periferna kri v 10 %), vendar povečini ni masivne bolezni, B simptomi samo v 15 %
- Zdravljenje z RT 24-30 Gy stadij I in II, višji stadiji enako s kombinacijo anti-CD20 + kemoterapija
- Pri spleničnem MZL obvezno preveriti status hepatitisa C; splenektomija samo v izbranih primerih (zato diagnoza otežena)
- Retrospektivna študija 43 bolnikov kaže, da je rituksimab kot monoterapija isto učinkovita kot kombinacijska KT[1]

1) Else M, Marin-Niebla A, de la Cruz F, et al. Rituximab, used alone or in combination, is superior to other treatment modalities in splenic marginal zone lymphoma. Br J Haematol 2012;159:322-328.

Drugi marginalno cel. limfomi

- Pristop odvisen od razširjenosti bolezni, enako kot predhodno
- Zgodnejši stadiji: obsevanje prizadetega predela (24-30 Gy, lahko reducirano 4 Gy za orbite ali očesne adnekse)
- Možen poskus antibiotičnega zdravljenja z doksiciklinom
- Napredovali stadiji: asimptomatski opazovanje, simptomatski: anti CD20 protitelo +/- KT (klorambucil, bendamustin, COP ali CHOP)
- Študija GALLIUM – rituksimab in obinutuzumab imata podobno učinkovitost, vendar je toksičnost slednjega bistveno večja

Rituksimab + lenalidomid

- Raziskave kažejo učinkovitost tako pri predhodno nezdravljenih bolnikih kot tudi pri ponovljenih MZL
- Raziskava faze II z 48 bolniki kaže ORR 80 % (54 % CR in 26 % PR)1
- Raziskava MAGNIFY pri 76 bolnikih s ponovljenim/refraktarnim MZL kaže ORR 74 % (39 % CR)[2]

1) Kiesewetter B, Willenbacher E, Willenbacher W, et al. A phase 2 study of rituximab plus lenalidomide for mucosa-associated lymphoid tissue lymphoma. Blood 2017;129:383-385.
2) Lansigan F, Andorsky DJ, Coleman M, et al. P1156: Magnify Phase 3b Study of Lenalidomide + Rituximab (R2) Followed by Maintenance in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma: Complete Induction Phase Analysis. Hemasphere 2022;6:1043-4

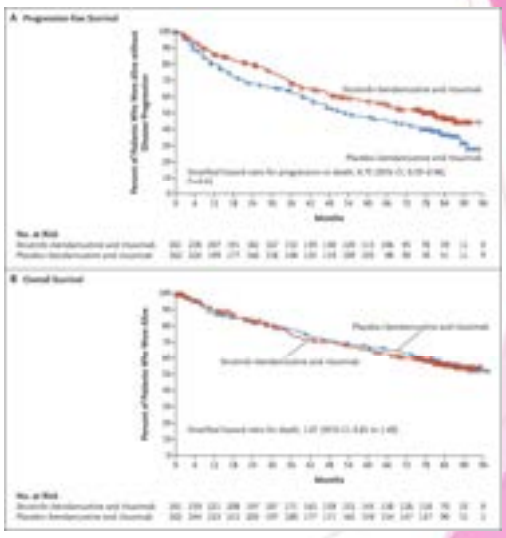
Zaviralci Brutonove tirozin kinaze (BTKi)

- Raziskava faze I/II 43 bolnikih z MZL kaže ORR 53 % (13 % CR) pri terapiji z akalabrutinibom, 12 mesečni PFS je je 67 %[1]
- Raziskava MAGNOLIA na 68 bolnikih s ponovljenim/refraktarnim MZL kaže ORR 68 % (26 % CR) pri terapiji z zanubrutinibom; 24 mesečni PFS 71 % in OS 86 %

1) Strati P, Coleman M, Champion R, et al. A phase 2, multicentre, open-label trial (ACE-LY-003) of acalabrutinib in patients with relapsed or refractory marginal zone lymphoma. Br J Haematol 2022;199:76-85.

Zaviralci Brutonove tirozin kinaze (BTKi)

- Pirtobrutinib (nekovalentni BTKi) kot možnost za ponovljen/refraktaren MZL
- Raziskava BRUIN – 36 bolnikov s ponovljenim/refraktarnim MZL (vključno s predhodnim kovalentnim BTKi), ORR 50 %, mediana PFS 17 mesecev
- Ibrutinib:
  - Raziskava SELENE ne kaže pomembne dobrobiti ibrutiniba k standardni KT v smislu PFS
  - Težava so tudi stranski učinki – pomembne krvavitve in motnje srčnega ritma



Wang ML, Jurczak W, Jerkeman M, et al. Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma. N Engl J Med 2022;386:2482-2494

Zaviralci fosfatidilinozitol 3-kinaze (PI3K) in CAR-T

- Zaradi pomembnih stranskih učinkov in vpliva na OS se zaviralcev PI3K (idelalizib, umbralizib, duvelizib, kopanlizib) ne priporoča za zdravljenje ponovljenega/refraktarnega MZL (diareja, jetrna okvara, pljučnice ipd.)
- Axicabtagen ciloleucel – študija ZUMA-5 s 158 bolniki s ponovljenim/refraktarnim indolentnim limfomom, od tega 31 MZL – ORR 92 % /74 % CR); 36 mesečni OS 75 %, PFS 65 %

Klaritromicin

- Raziskava IELSG40/CLEO – 43 bolnikov s ponovljenim/refraktarnim ekstranodalnim MZL, vsaj 1 predhodno zdravljenje, okvirno polovica bolnikov z napredovalim stadijem ter ≥2 zdravljenji – ORR 44 % (CR 14 %), v grobem podobno kot ORR pri študijah ibrutiniba in zanubrutiniba pri MZL

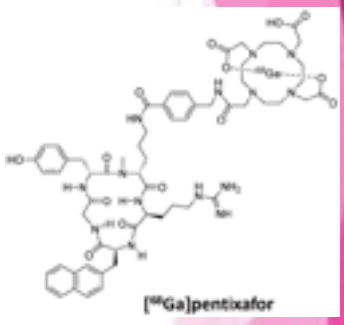
Systematic Review

The Clinical Role of CXCR4-Targeted PET on Lymphoproliferative Disorders: A Systematic Review

Maryam Zamanian [1], Domenico Albano [2,3], Giorgio Treglia [4,5,6,*], Alessio Rizzo [7] and Iraj Abedi [1]

3.3.2. MZL/MALT

Diagnostic accuracy: When Haug et al. used [^{68}Ga]Ga-Pentixafor PET/MRI to investigate MZL and B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) lymphoma, they observed high radiopharmaceutical uptake in all of the regions affected, including the stomach, orbit, lungs, and other involved areas in most patients (33/36). Three patients with no increase in uptake had previous orbital MALT lymphoma surgery [47]. Other results of examining patients with LPD in the study by Buck et al. used PET/CT, as the SUVmax value was in descending order for MZL (12), B (10), and T-cell lymphoma (8). The TBR values were the same as those for MZL (6.9), B (6.2), and T-cell lymphoma (5.7) [36]. Kosmala et al. examined the tumor burden in 73 MZL patients by [^{68}Ga]Ga-Pentixafor PET/CT and showed a decrease in uptake in the lymphoma-sink effect regions, which occurred as decreased uptake in the normal organs of patients with a high-burden tumor status [34].



[^{68}Ga]pentixafor

Zaključki

- Kroničen potek, povezan z okužbami/avtoimunimi boleznimi
- Malo neposrednih / prospektivnih raziskav, zdravljenje osnovano na podatkih zdravljenja drugih indolentnih B limfomov (FL)
- Izziv predstavlja R/R bolezen ali transformacija

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

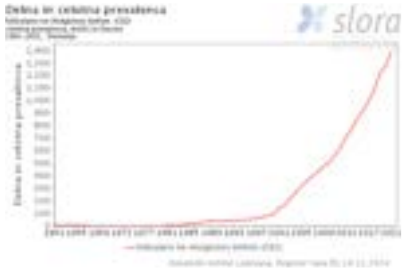
Novosti v zdravjenju folikularnega limfoma

Urška Rugelj

4. Limfomska šola
Ljubljana, 15. 11. 2024

Epidemiologija

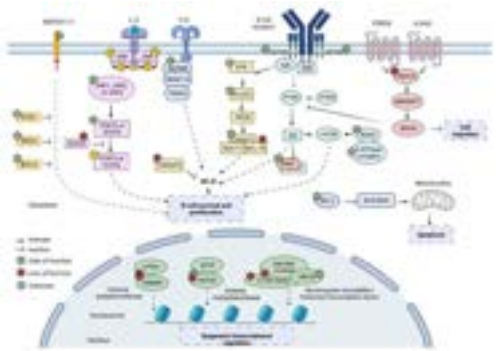
- Najpogostejši indolentni limfom
- L. 2021 164 novih primerov, prevalenca 1382[1]
- 5 letno preživetje >90%, mediano preživetje po 20 letih opazovanja ni doseženo[2]
- Glavni vzrok smrti povezan z boleznijo je transformacija limfoma



1:www.slora.si, 2:Batlevi, C.L. *et al. Blood Cancer J.* 2020., 3: Jacobsen E. *Am J Hematol.* 2022

Značilnosti FL

- Prisotnost t(14, 18) pri 90% bolnikih– višja ekspresija BCL2
- Pogoste epigenetske spremembe KMT2D, CREBBP in EZH2[1]
- Pomemben del patogeneze je tumorsko mikrookolje
- Dva obraza
  - Indolenten potek
  - Transformacija



López, C. et al. *Hemato* 2022. https://doi.org/10.3390/hemato3040041

1:Amin, R., Braza, M.S. *J Exp Clin Cancer Res.* 2022.

Naš kažipot

Rituksimab v monoterapiji

Chemo-free režimi

CAR-T

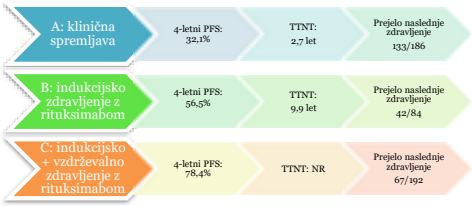
Bispecifiki

Nova prijemališča

Študije v teku

Monoterapija z rituksimabom

- Randomizirana študija faze 3,
  - Vključeni bolniki z nizkim tumorskim bremenom in asimptomatski, st. II-IV, FL gr. 1-3a, mFU 12,3 let



- Študija ni pokazala razlik v celokupnem preživetju in zdravljenje z rituksimabom ni vplivalo na odgovore na naslednje linije zdravljenja
- Učinkovitost monoterapije so poročali tudi v drugih študijah in pri simptomatskih bolnikih

Ardeshna KM, et al. *Blood,* 2010.
Northend M., et al. *Blood* 2022.
Martinelli G., et al. *J Clin Oncol.* 2010

Imunomodulatorna terapija- Lenalidomid

„Chemo-free“ pristop

RELEVANCE študija faze 3, prva linija FL, uvedba terapije glede na GELF kriterije

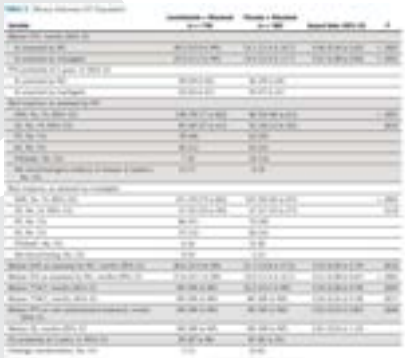
- 1010 bolnikov, randomizacija 1:1
  - R-lenalidomid (18 ciklusov)
  - R-kemoterapija (72% R-CHOP, 23% R-benda, 5% R-CVP)
  - Dokazana neinferiornost režima brez kemoterapije

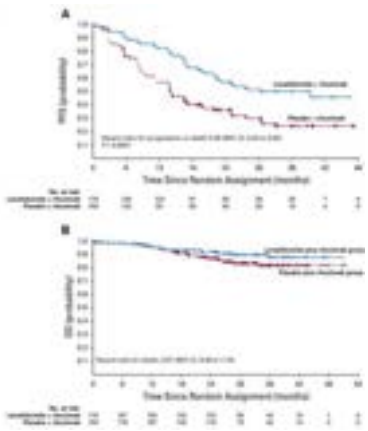
Morschhauser M, NEJM 2018

Imunomodulatorna terapija- Lenalidomid

AUGMENT študija

- R/R FL ali MZL, študija faze 3, 12 ciklusov terapije, 358 bolnikov
  - R-lenalidomid
  - R-placebo



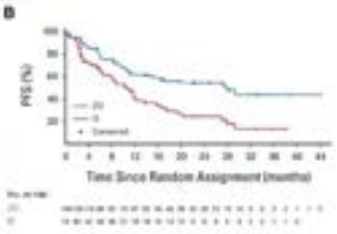


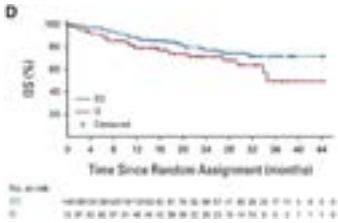
Leonard JP, et al. JCO 2019

Zanubrutinib - Obinutuzumab

ROSEWOOD: randomizirana študija faze 2, 217 bolnikov

- Zanubrutinib+Obinu vs Obinu monoterapija – 2:1
- R/R FL po vsaj 2 linijah zdravljenja
- ORR 69% vs 46%, CR 39% vs 19%
  - mPFS 28 vs 10,4mes
  - mFU 20,2 mes



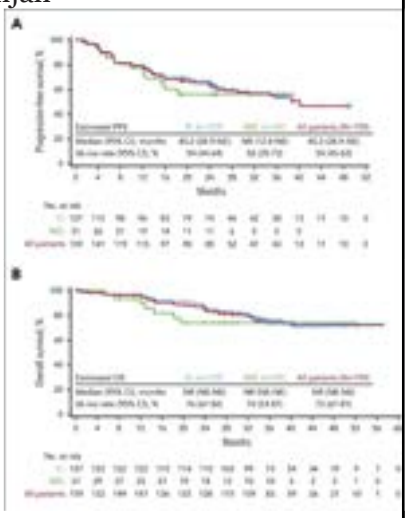


Zinzani PL, et al. JCO 2023

CAR-T celična terapija

Axi-cel: ZUMA-5 – študija faze 2, 109 bolnikov

- R/R FL ali MZL po dveh predhodnih linijah zdravljenja
- Bolniki so lahko prejeli premostitveno terapijo
- ORR 92%, 74% CR
  - Po 18 mes. PFS 69%, OS 88%
- CRS 82%, Gr ≥3 7%
- ICANS 59%, Gr ≥ 3 19%

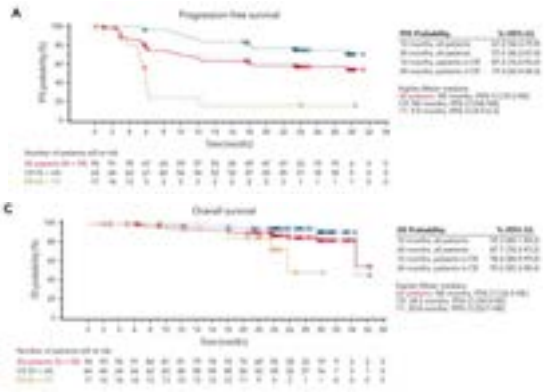


Jacobson CA, et al. The Lancet Oncology, 2022, Neelapu SS, et al. Blood, 2024

CAR-T celična terapija

Tisa-cel: ELARA– študija faze 2, 98 bolnikov

- R/R FL po dveh predhodnih linijah zdravljenja
- ORR 86%, 69% CR
  - 12-mes. PFS 67%
- CRS 49%, Gr ≥3 0%
- ICANS 37,1%, Gr ≥ 3 4%

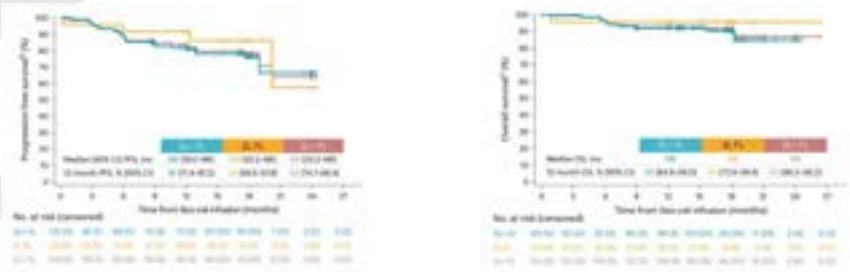


Dreyling M, et al. *Blood*. 2024

CAR-T celična terapija

Liso-cel: TRANSCEND FL – študija faze 2, 130/101 bolnik

- R/R FL po eni/vsaj dveh predhodnih linijah zdravljenja
- ORR 97%, 94% CR (tretja linija)
  - 12-mes. PFS 81%, OS 92%
- CRS 58%, Gr ≥3 1%
- ICANS 15%, Gr ≥3 2%

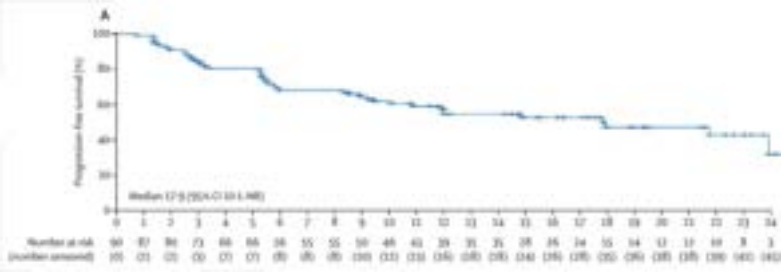


Morschhauser, F., *et al. Nat Med,2024*

Bispecifična protitelesa

Mosunetuzumab – GO29781 študija faze 2, 90 bolnikov

- R/R FL po vsaj 2 redih zdravljenja, CD20+ ni bil pogoj
- ORR 80%, CR 60%
  - mPFS 24,0mes (mFU 37,4 mes)
- CRS 44%, Gr ≥3 2%
- ICANS 4%, Gr ≥3 0%

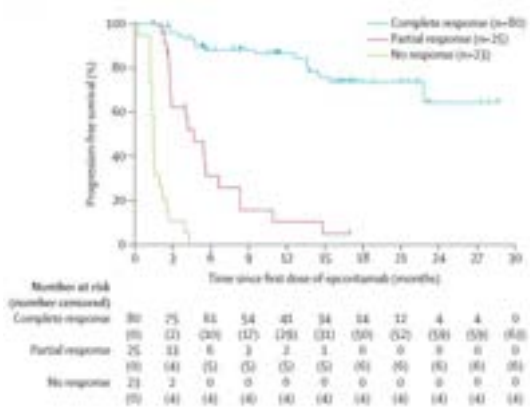


Budde LE, et al, The Lancet Oncology, 2022., Schuster S, et al. ASH 2023

Bispecifična protitelesa

Epcoritamab – EPCORE NHL-1 študija faze 1/2, 128 bolnikov

- R/R FL po vsaj 2 redih zdravljenja
- ORR 82%, CR 62,5%
  - mPFS 15,4 mes (mFU 17,4mes)
- CRS 67%, Gr ≥3 2%
- ICANS 6%

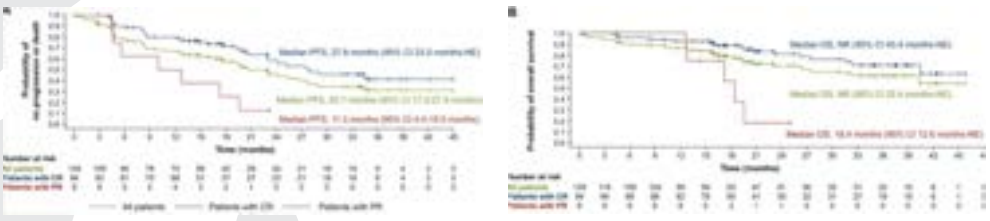


Linton KM, et al. Lancet Haematol. 2024

Bispecifična protitelesa

Odronextamab – ELM-2 študija faze 2, 128 bolnikov

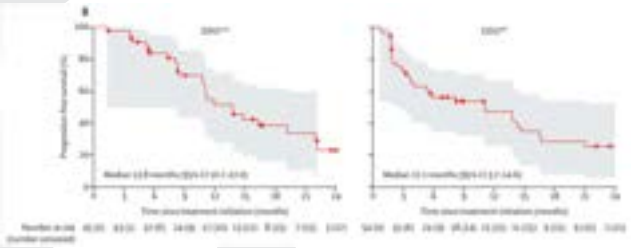
- R/R FL po vsaj 2 redih zdravljenja
- ORR 80%, CR 72%
  - mPFS 20,7 mes (mFU 26,6 mes)
- CRS 55,9%, Gr ≥3 5,9%
- ICANS 54,4% Gr ≥3 7,4%

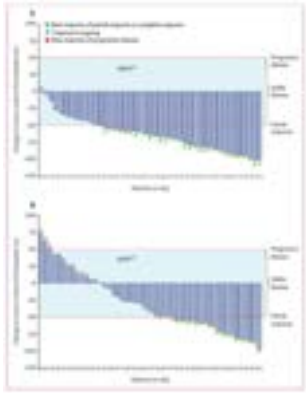


Vilasboas JC, et al. Blood, 2023

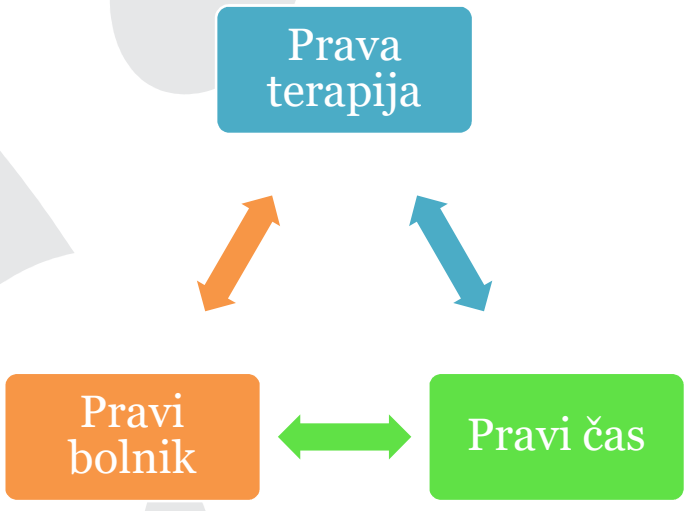
Tazemetostat – EZH2 inh

- Mutacija EZH2 prisotna pri 20-25% bolnikov
- Študija faze 2, R/R FL po vsaj 2 linijah sistemske terapije, vključenih 99 bolnikov
- mFU 22 mesecev v kohorti $EZH2^{mut}$ in 35,9 mes pri $EZH2^{wt}$
- ORR 69% in mPFS 13,8 mes pri $EZH2^{mut}$
- ORR 35% in mPFS 11,1 mes pri $EZH2^{wt}$





Kako ob taki množici terapij izbrati pravo?



Prihodnost

Aktivne študije, ki trenutno vključujejo bolnike:

- Symphony 1: R² +/- tazemetostat
- EPCORE FL-1: R² +/- epcoritamab
- Mohagany: R² vs. R-Zanubrutinib
- Celestimo: R² vs. Mosunetuzumab - lenalidomid
- OLYMPIA-5: R² vs. Odronextamab - lenalidomid
- InMIND: R² +/- Tafasitamab
- LEDA: Tisa-cel vc. SoC
- ZUMA – 22: Axi-cel vs. SoC

Zaključek

- Folikularni limfom je postaja neozdravljiva kronična bolezen, saj se mediano celokupno preživetje približuje 20 let
- Ob tem bo vedno bolj pomembna izbira terapije, ki bi ob zadovoljivi učinkovitosti ponudila najboljšo kakovost življenja z najmanj stranskimi učinki
- Pomembno bo izbrati pravo zaporedje različnih vrst sistemske terapije, da omogočamo čim daljše PFS
- Terapija individualno prilagojena bolniku

Novostiv zdravljenju KLL in Waldenstroemove makroglobulinemije

Univerza v Ljubljani
Medicinska fakulteta

Matevž ŠKERGET
15.11.2024

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

ZHS
Združenje hematologov Slovenije

Laboratorijske preiskave pred zdravljenjem

FISH: del(17p), del(11q)

Kariotip (CpG-ODN + IL2 proliferacija): > 3 spremembe- kompleksni kariotip

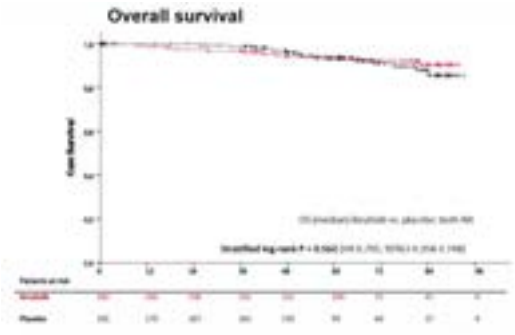
Molekularne: Mutacijski status IgHV in p53

Beta 2 mikroglobulin

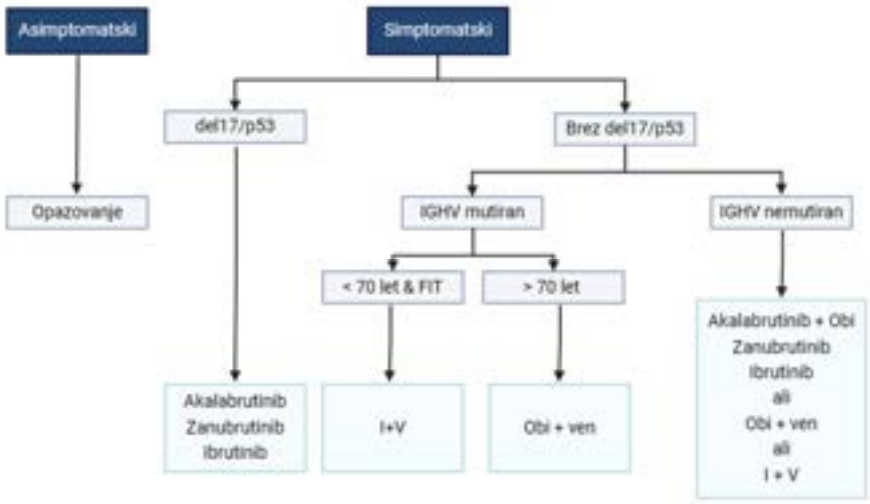
oGF (predvsem pri fludarabinu)

Coombs (tudi haptoglobin)

Serologija za viruse



Langerbeins CLL12 study



Mnenje avtorja

Sosledje zdravljenja

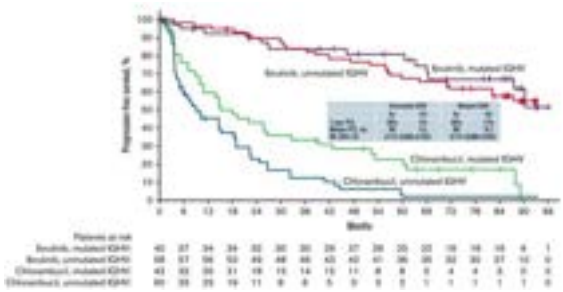
BTK → BTK → R-ven

O-ven → R-ven → BTK

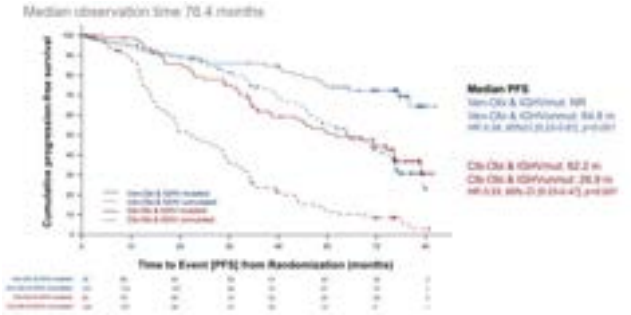
O-ven → BTK → BTK

IVen → IVen → IVen?

Mnenje avtorja

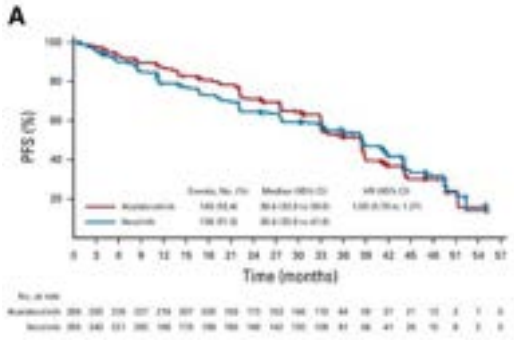


Barr. Blood Adv 2022.

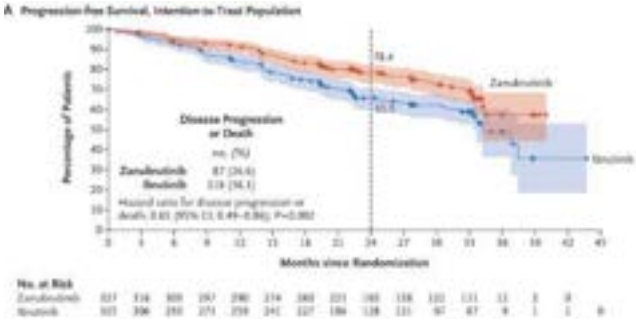


Al-Sawaf. ICML 2023

Ibrutinib vs acalabrutinib



doi: 10.1200/JCO.21.01210.



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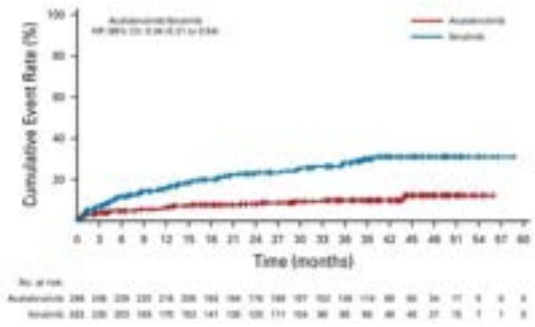
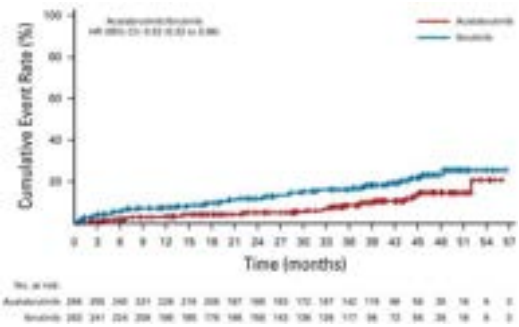




Byrd. JCO 2021

Novi sopojavi

BTK zaviralci

Arterijska hipertenzija (20-25 %)

Atrijska fibrilacija (do 16 %)

Ventrikularne motnje/smrt

Krvavitve (kl. pomembne 3-5 %)

BCL2 zaviralec

Sindrom tumorskega razpada

Hematološka toksičnost

BTKi- spremljanje

- EKG pred uvedbo in na 3 mesece
- Merjenje krvnega pritiska v domačem okolju 1x tedensko
- Bolniki z velikim tveganjem – UZ srca/kardiolog

Ibrutinib - venetoclax

Captivate MRD kohorta

18 - 70 let
ECOG 0 – 1
Normalno ledv. in jetrno delovanje

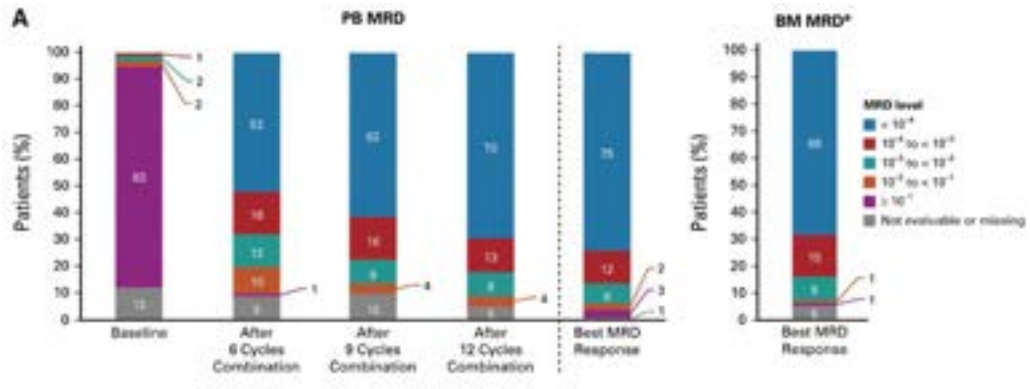
Wierda JCO 2021

Glow raziskava

>65 or < 65 let
CIRS > 6; CrCl < 70
ECOG 0-2

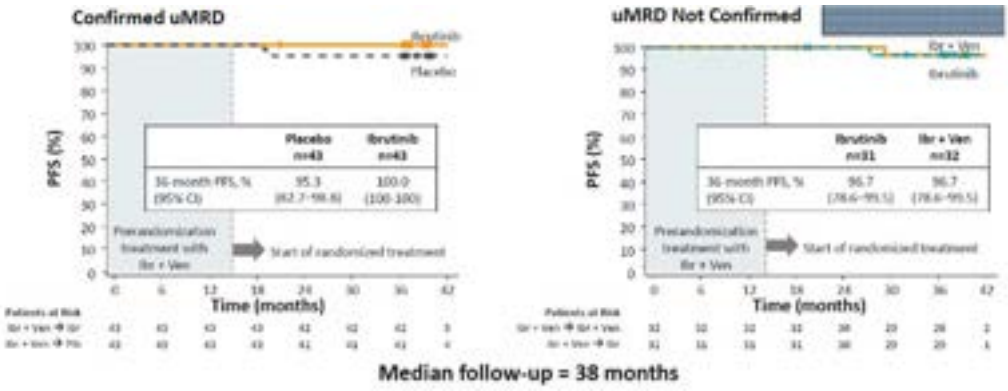
Nieman Lancet Onc. 2023

Captivate – MRD kohorta



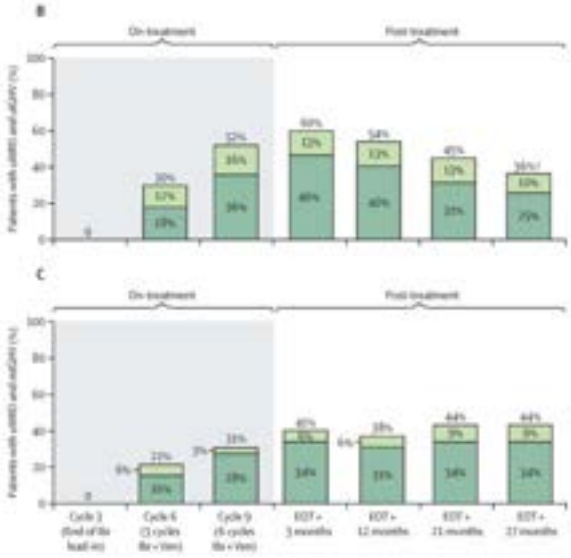
Wierda JCO 2021

Captivate – MRD cohort



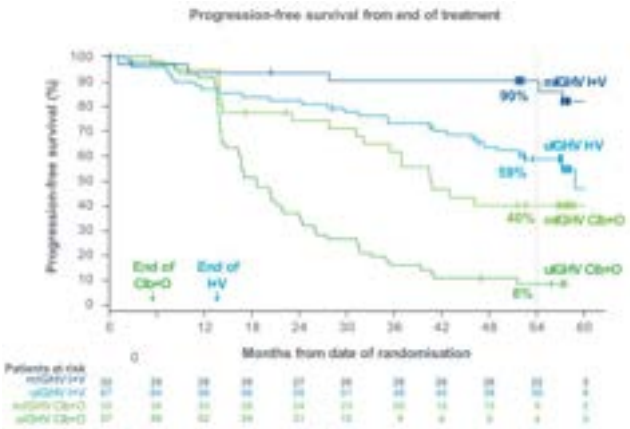
Tam. Blood 2022

Glow faza III



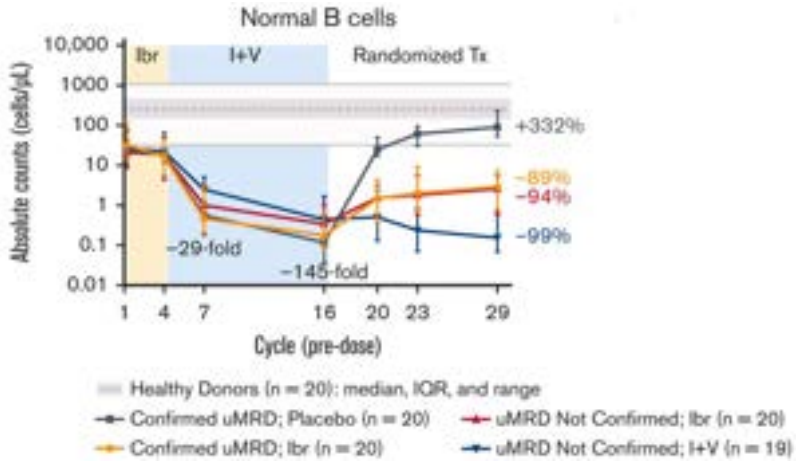
Nieman Lancet Onc. 2023

Glow faza III



Moreno ASH 2023

KLL- časovno omejeno zdravljenje



Moreno Blood Adv. 2023

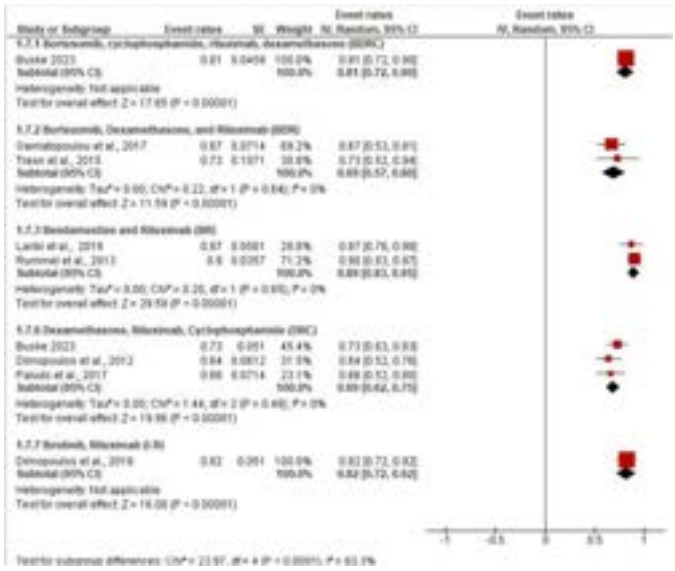
Waldenstromova bolezen

Nevropatija (anti MAG)
Hiperviskoznost
Krioglobulinemija
Amiloidoza

Waldenstromova bolezen

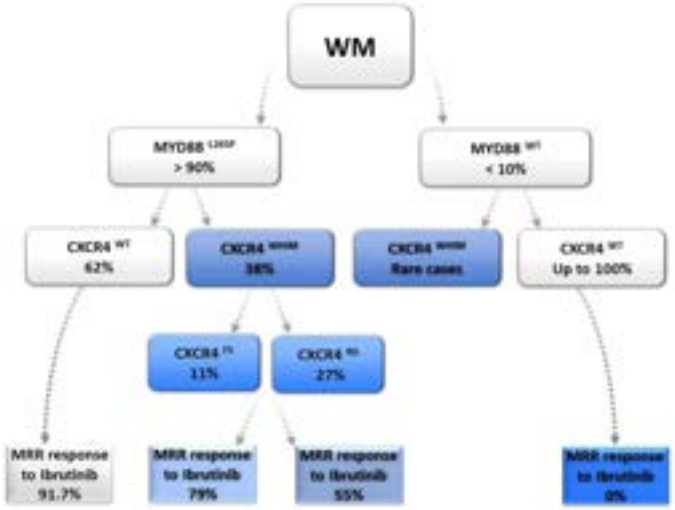
Rituksimab/bendamustin
Bortezomib/rituksimab/deksametazon
Rituksimab/ciklofosfamid/deksametazon
BTK zaviralci

Waldenstromova bolezen



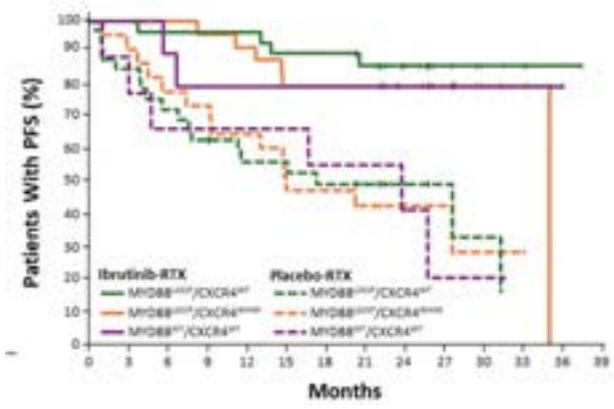
Chan WL. Blood Cancer J. 2023

Waldenstromova bolezen



Kaiser. Leukemia 2020

Waldenstromova bolezen



Buske. JCO 2021

Novosti pri zdravljenju Richterjeve transformacije KLL v DVCLB

Barbara Jezeršek Novaković
4. limfomska šola
15.11.2024

Definicija Richterjeve transformacije

Richterjeva transformacija (RT) je opredeljena z razvojem/pojavom visoko malignega limfoma pri bolnikih s predhodno ali sočasno diagnozo kronične limfocitne levkemije (KLL)/drobnoceličnega limfoma B (SLL).

Prvič opisana leta 1928 - Maurice N. Richter - 'reticular cell sarcoma' with presence of 'leukemic and tumor cells'.

Definicija Richterjeve transformacije 1964 - Lortholary s kolegi.

Incidenca/histopatološke oblike Richterjeve transformacije

Ocenjena incidenca Richterjeve transformacije pri bolnikih s predhodno KLL/SLL, zdravljeno s kemoterapijo/kemoimunoterapijo, je 0,5–1% na leto.

Različne histopatološke oblike RT:

-bolj pogosta oblika difuznega velikoceličnega limfoma B RT-DVCLB (do 90–95% RT) in

-redkeje zastopana oblika Hodgkinovega limfoma RT-HL (do 5–10% RT)

-posamični primeri (<1%) plazmablastne transformacije.

Klonalna sorodnost med RT-DVCLB in predhodno KLL in prognoza

Definicija klonalne sorodnosti med RT-DVCLB in KLL temelji na analizi preureditve IGHV-D-J genov (s PCR ali NGS).

Ker pa ekspresija PD-1 na transformiranih celicah B v 90% korelira z molekularno definirano klonalno sorodnostjo med RT-DVCLB in KLL, lahko ekspresija PD-1 služi kot nadomestek za določanje klonalne sorodnosti RT-DVCLB s KLL.

Klonalna sorodnost med RT-DVCLB in predhodno KLL in prognoza

Večina RT-DVCLB (približno 80%) je klonalno sorodnih s predhodno KLL, kar predstavlja pravo transformacijo. Klonalno nesorodni DVCLB so ´de novo´ DVCLB, ki nastanejo pri bolnikih s predhodno KLL (običajno IGHV mutirano obliko).

Bolniki s klonalno sorodnimi RT-DVCLB imajo mediano celokupno preživetje krajše od 1 leta, bolniki s klonalno nesorodno RT pa 65 mesecev – podobno kot velja za ´de novo´ DVCLB.

Klonalna sorodnost med RT-HL in predhodno KLL je opisana samo pri 30% bolnikov.

Diagnoza Richterjeve transformacije

Klinična slika:

-naglo klinično poslabšanje s pojavom B simptomov, hitro lokalizirano povečanje posamičnih bezgavk, ekstranodalne lokalizacije, povišanje LDH, hiperkalcemija zbujajo sum na RT;

-tovrstna simptomatika pa ni specifična za RT (50–60% primerov), lahko je povezana z akcelerirano KLL ali solidnim rakom.

Diagnoza Richterjeve transformacije

Diagnoza RT mora biti histološka iz odstranjene bezgavke v celoti, izberemo bezgavko z visokimi SUV vrednostmi (>5, !!!višja pozitivna napovedna vrednost ob SUV vrednostih >10).

SUV vrednosti <5 praktično izključujejo RT.

Diagnoza Richterjeve transformacije

Dejavniki tveganja za razvoj RT:

-*TP53* aberacije (mutacije in delecije), *NOTCH1* mutacije, *CDKN2A* alteracije, kompleksen kariotip, nemutiran status *IGHV*, stereotipiziran vzorec IGHV tipa 8 (definiran z ekspresijo stereotipiziranega IGHV4-39/IGHD6-13/IGHJ5 B celičnega receptorja) in *c-MYC* aktivacija;

-ostali dejavniki tveganja za RT vključujejo povišano LDH, povišan beta-2 mikroglobulin, napredovalo bolezen (napredoval Binet/ Rai stadij), slabo ECOG stanje zmogljivosti in bezgavke večje od 3 cm v premeru;

-dejavnika tveganja sta tudi neodzivnost na prvo zdravljenje KLL/SLL in večje število predhodnih zdravljenj.

Molekularne razlike med RT-DVCLB in de novo DVCLB

Histološki izgled RT-DVCLB in ´de novo´ DVCLB sta podobna, obstajajo pa molekularne razlike (ki omogočajo tarčne pristope k zdravljenju RT-DVCLB):

- Ekspresija receptorja programirane celične smrti PD-1 je na površini klonalno sorodnih RT-DVCLB prisotna v približno 80% primerov, pri ´de novo´ DVCLB le v 4%.
- Mutacije v *TP53*, *NOTCH1*, *MYC* in delecije v *CDKN2A*, pa tudi uporaba stereotipiziranega vzorca IGHV tipa 8, so vse bolj pogoste pri klonalno sorodnih RT-DVCLB.

Molekularne razlike med RT-DVCLB in de novo DVCLB

-mutacije *TP53* najdemo pri 60 do 80% klonalno sorodnih RT-DVCLB - razlaga za kemorezistenco RT-DVCLB; uporaba BCL-2 zaviralcev lahko sproži od TP53 neodvisno celično smrt in vsaj delno zmanjša rezistenco;

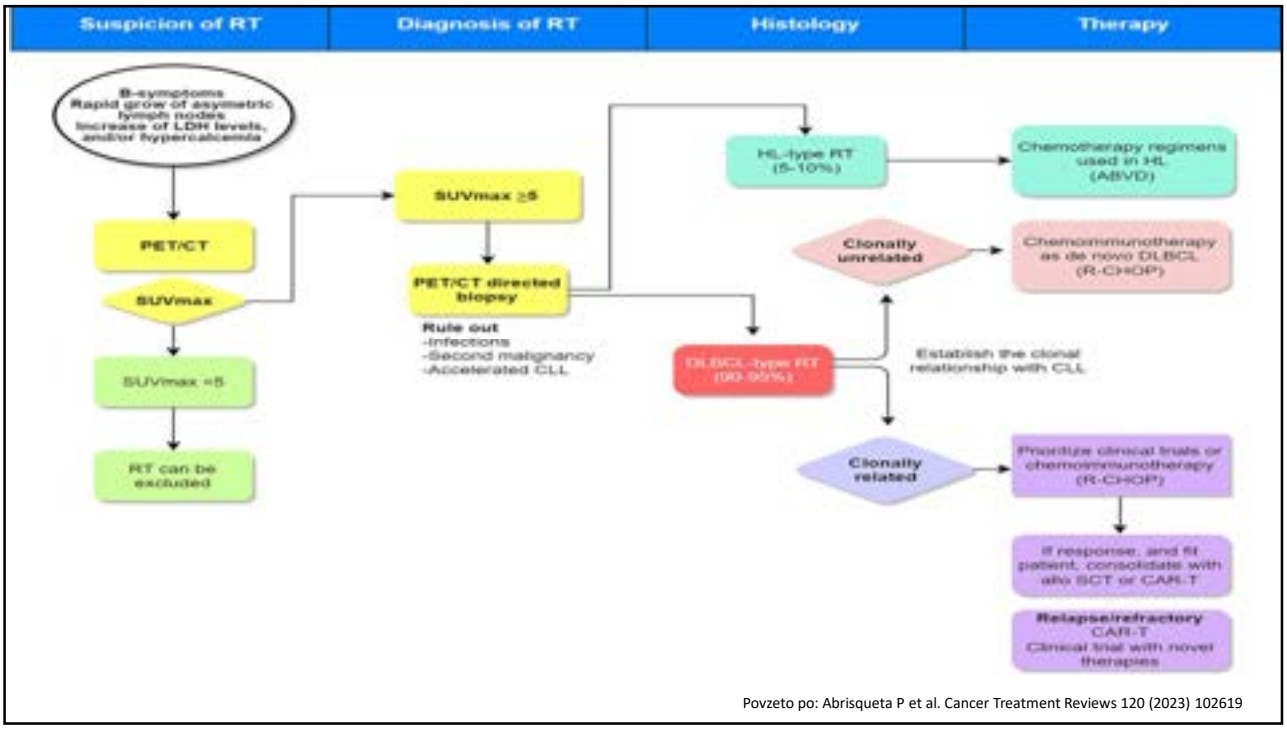
-delecije v *CDKN2A* najdemo pri 20% RT-DVCLB - razlaga za visoko proliferacijsko aktivnost RT-DVCLB, saj omogočijo napredovanje celic skozi celični ciklus in nenadzorovano replikacijo neoplastičnih celic; nakazuje na možnost uporabe zaviralcev od ciklina odvisne kinaze;

Molekularne razlike med RT-DVCLB in de novo DVCLB

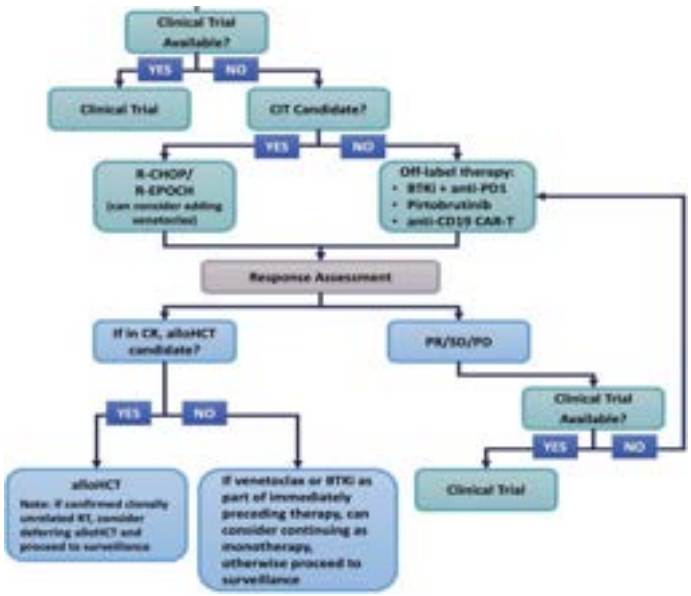
-mutacije *MYC* najdemo pri 30% klonalno sorodnih RT-DVCLB in mutacije *NOTCH1* pri 30% klonalno sorodnih RT-DVCLB - tudi razlaga za visoko proliferacijsko aktivnost RT-DVCLB preko sprememb v MYC aktivaciji;

-pogostejša uporaba stereotipiziranega vzorca IGHV tipa 8 pri klonalno sorodnih RT-DVCLB pomeni, da ta konformacija B celičnega receptorja spodbuja nastanek RT-DVCLB in preživetje teh celic.

Ni še znano, kako tarčno delovati na zadnje 3 opisane spremembe.



Povzeto po: Abrisqueta P et al. Cancer Treatment Reviews 120 (2023) 102619



Povzeto po: Ryan CE et al. Ascopubs.org: DOI https://doi.org/10.1200/EDBK_390804

Zdravljenje s kemoterapijo ali imunokemoterapijo

Regimen	Years of Recruitment	n	Median Age in Years	ORR (%)	CR (%)	Median OS (Months)
Anthracycline-containing regimens						
R-CHOP [39]	2003–2008	19	69 (N/A)	47%	7%	23 months
O-CHOP [40]	2011–2014	37	66 (43–90)	47%	27%	11.4 months
HyperCVXD [41]	NR (published in 2000)	29	61 (36–75)	41%	38%	10 months
Rituximab and GM-CSF with alternating hyperCVAD and MTX/cytarabine [42]	1999–2001	30	59 (27–79)	43%	18%	8.5 months
R-EPOCH [43]	2006–2014	46	67 (36–83)	39%	N/A	5.9 months
Platinum-containing regimens						
OFAR1 [44]	2004–2006	20	59 (34–77)	50%	20%	8 months
OFAR2 [45]	2007–2010	39	63 (40–81)	43%	8.6%	6.6 months
Fludarabine-containing regimens						
PFA or CFA [46]	1992–1996	12	59 (49–74)	45%	N/A	17 months
FACPGM [47]	1997–2001	15	62 (42–74)	5%	5%	2.2 months

Povzeto po: Briski R et al. Cancers 2023, 15, 1857

Vloga transplantacije v zdravljenju RT

Pri bolnikih, ki na začetno zdravljenje dosežejo remisijo, predstavlja PKMC možnost dolgotrajne remisije – prospektivnih podatkov praktično ni.

Podatki retrospektivne raziskave pri 20 bolnikih, ki so bil zdravljeni s PKMC kot konsolidacijo ali kot reševalno terapijo: bolniki (7), ki so bili zdravljeni z alogenično PKMC v remisiji, so imeli 75% 3 letno OS; samo 27% 3 letno OS pri tistih, ki so dosegli remisijo na prvo zdravljenje, vendar niso nadaljevali z alogenično PKMC.

Vloga transplantacije v zdravljenju RT

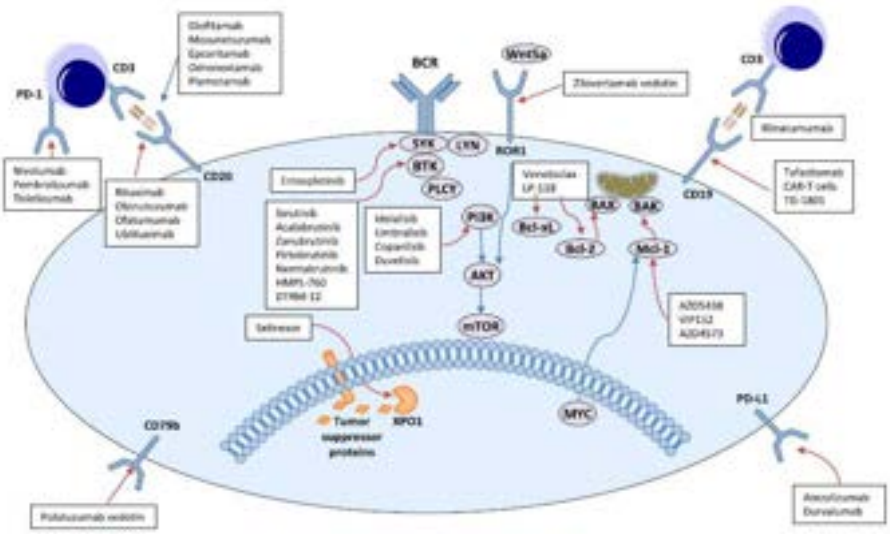
Podatki druge retrospektivne raziskave so pokazali 45% 3 letno PFS po avtologni PKMC (82% bolnikov v remisiji ob PKMC) in 27% 3 letno PFS po alogenični PKMC (60% bolnikov v remisiji ob PKMC).

Novejše retrospektivne raziskave po alogenični PKMC so pokazale od 39% 4 letnega PFS do 65% 2 letnega PFS s kondicioniranjem nižje intenzitete.

Vloga transplantacije v zdravljenju RT

Ena največjih retrospektivnih raziskav (118) je po alogenični PKMC pokazala 66% 3 letno PFS pri bolnikih v popolni remisiji ob PKMC, 43% pri bolnikih v delni remisiji in 5% pri neodzivni bolezni. V tej raziskavi je bilo 3 letno PFS po avtologni PKMC 48%.

Najprimernejša: alogenična PKMC s kondicioniranjem nižje intenzitete.



Povzeto po: Abrisqueta P et al. Cancer Treatment Reviews 120 (2023) 102619

Rezultati zdravljenj z novimi učinkovinami - monoterapija

Zavora BCL2

-venetoklaks (7) – ORR 43%, zelo kratko trajanje odgovora;

Zavora BTK

-kovalentni:

ibrutinib (4) – ORR 75%, trajanje odgovora 6,1 meseca; (2) – ORR 50%;

akalabrutinib (25) – ORR 40%, trajanje odgovora 6,2 meseca, mPFS 3,2 meseca;

zanubrutinib (13) – ORR 62%, mPFS 17,3 mesecev in mOS 29,3 mesecev;

Rezultati zdravljenj z novimi učinkovinami - monoterapija

Zavora BTK

-nekovalentni:

pirtobrutinib (75) – ORR 52%, mPFS 3,7 meseca, mOS 13,1 meseca;

nemtabrutinib (6) – ORR 50%;

Rezultati zdravljenj z novimi učinkovinami – imunoterapevtski pristopi v monoterapiji

Zavora PD-1

-pembrolizumab (9) – ORR 44%, mOS 10,7 meseca; (23) - ORR 13%, mPFS 1,6 meseca in mOS 3,8 meseca;

CAR T terapija

-institucijski antiCD19 CAR T (6) – ORR (vsi CR) 67%, mPFS >5,5 mesecev;

-aksikabtagen ciloleucel (9) – ORR 89%, mPFS > 6 mesecev;

-prospektivna raziskava z breksokabtagen autoleucelom vključuje bolnike;

Rezultati zdravljenj z novimi učinkovinami – imunoterapevtski pristopi v monoterapiji

Bispecifična protitelesa

-blinatumomab po 2 ciklih R-CHOP (če niso dosegli CR) (25) - ORR 36%;

-blinatumomab (9) – ORR 22%, mOS 10,3 mesecev;

-glofitamab (10; 6 evaluabilnih) – ORR 83%;

-epkoritamab (10) – ORR 60%;

Proti ROR1 (receptor tyrosine kinase-like orphan receptor 1) usmerjen konjugat protitelo-zdravilo

-zilovertamab vedotin (7) – ORR 57%, trajanje odgovora 2,8 meseca.

BTK zaviralci kombinacije

R-CHOP +/- Akalabrutinib	NCT03899337
Obinutuzumab + Venetoklaks + Ibrutinib	NCT04939363
Zanubrutinib + Tislelizumab	NCT04271956
Akalabrutinib + Venetoklaks + Durvalumab	NCT05388006
R-EPOCH + Ibrutinib	NCT04992377
Ipilimumab + Ibrutinib + Nivolumab	NCT04781855
Pirtobrutinib + Venetoklaks + Obinutuzumab	NCT05536349

PD-1 zaviralci

Pembrolizumab + Ublituksimab + Umbralisib	NCT02535286
Zanubrutinib + Tislelizumab	NCT04271956
Akalabrutinib + Venetoklaks + Durvalumab	NCT05388006
Ipilimumab + Ibrutinib + Nivolumab	NCT04781855
Duvelizib + Nivolumab	NCT03892044
Kopanlizib + Nivolumab	NCT03884998

PD-L1 zaviralci

Atezolizumab + Obinutuzumab + Venetoklaks	NCT02846623
Atezolizumab + Obinutuzumab + Venetoklaks	NCT04082897
Atezolizumab + Rituksmab + Gemcitabin + Oksaliplatin	NCT03321643

Povzeto po: Briski R et al. Cancers 2023, 15, 1857

BCL-2 zaviralci kombinacije

Venetoklaks + DA-R-EPOCH ali R-CHOP	NCT03054896
Obinutuzumab + Venetoklaks + Ibrutinib	NCT04939363
Akalabrutinib + Venetoklaks + Durvalumab	NCT05388006
Pirtobrutinib + Venetoklaks + Obinutuzumab	NCT05536349
Akalabrutinib + Venetoklaks + Durvalumab	NCT05388006
Atezolizumab + Obinutuzumab + Venetoklaks	NCT02846623
Atezolizumab + Obinutuzumab + Venetoklaks	NCT04082897
Duvelizib + Venetoklaks	NCT03534323
LP-118 (BCL2/BCLX zaviralec)	NCT04771572

Bispecifična protitelesa

TG-1801 (anti-CD47/CD19) +/- Ublituksimab	NCT04806035
XmAb13676 (anti-CD20/CD3)	NCT02924402
Blinatumumab po R-CHOP	NCT03931642
Epkoritamab	NCT04623541

Konjugati protitelo-zdravilo

Zilovertamab Vedotin (MK-2140) +/-Nemtabrutinib	NCT05458297
AutoPKMC, ki ji sledi Polatuzumab Vedotin	NCT04491370

Zaviralec od ciklina odvisne kinaze 9

VIP152	NCT04978779

Povzeto po: Briski R et al. Cancers 2023, 15, 1857

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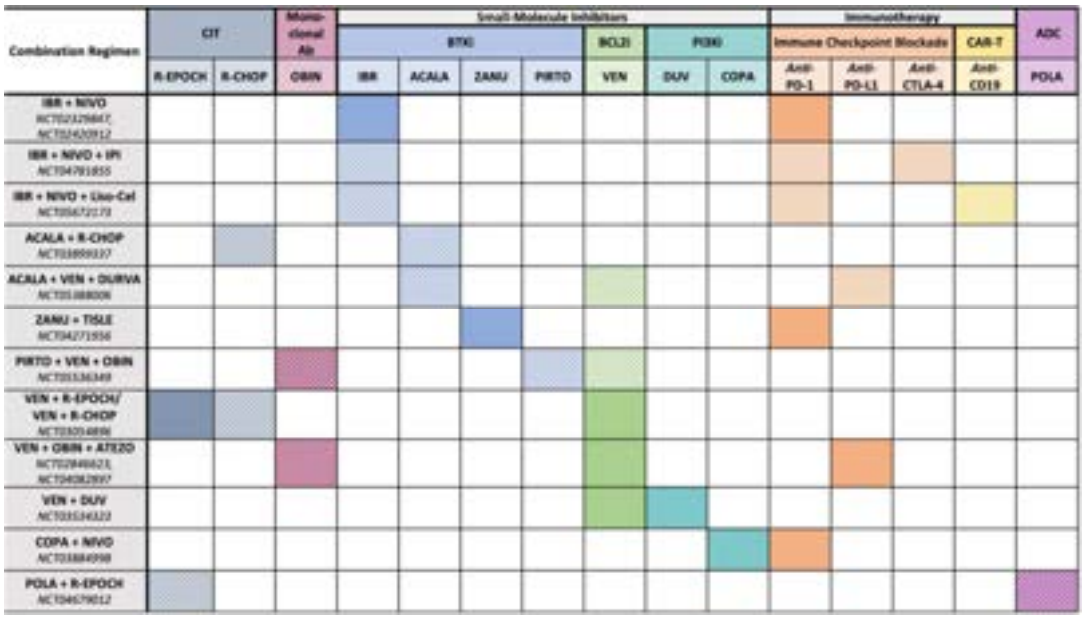

Povzeto po: Ryan CE. ascopubs.org: DOI https://doi.org/10.1200/EDBK_390804

Rezultati zdravljenj z novimi učinkovinami - kombinacije

Kombinacije s kemoimunoterapijo

-venetoklaks in DA-R-EPOCH (26) – ORR 61,5%, CR 50% (pri 20 na venetoklaksu CR 65%), mOS 19,6 mesecev (8 konsolidacija z alogenično PKMC in 11 vzdrževalno venetoklaks);

-venetoklaks in R-CHOP – raziskava poteka;

-akalabrutinib in R-CHOP – raziskava poteka.

Rezultati zdravljenj z novimi učinkovinami - kombinacije

Kombinacije zaviralca BCL2 in zaviralca fosfatidil-inozitol 3 kinaze (PI3K)

-venetoklaks in duvelizib (8) – raziskava poteka – ORR 50%.

Kombinacija zaviralca BTK in zaviralcev imunskih kontrolnih točk

-ibrutinib in nivolumab (20; predhodno zdravljeni za RT) - ORR 65%, trajanje odgovora 6,9 mesecev in mPFS 5 mesecev;

-ibrutinib in nivolumab (24; 58% nezdravljeni za RT) – ORR 42%, mOS 13 mesecev (nezdravljeni mOS 24,1 meseca, neodzivni 9,1 meseca);

-zanubrutinib in tislelizumab (48 evaluabilnih) – raziskava poteka – ORR 58,3%, mPFS 10 mesecev in mOS 15,4 mesecev.

Rezultati zdravljenj z novimi učinkovinami - kombinacije

Kombinacije zaviralca PI3K in zaviralcev imunskih kontrolnih točk

-kopanlizib in nivolumab (14) – ORR 29%.

Kombinacija zaviralca BCL2, zaviralca imunskih kontrolnih točk in protitelesa proti CD20

-venetoklaks, atezolizumab, obinutuzumab (8) – ORR 88%, mPFS 13 mesecev; druga raziskava s to kombinacijo poteka.

Zaključek

Richterjeva transformacija KLL v klonalno soroden RT-DVCLB je redka bolezen z izjemno neugodno prognozo.

Pri bolnikih, ki so v dobri kondiciji, edino možnost dolgotrajne remisije omogoča alogenična PKMC, pri kateri pa je izhod bolezni odvisen od stanja remisije v času PKMC. Pri teh bolnikih je glavni cilj zdravljenja pred PKMC doseči popolno remisijo.

Na splošno pa lahko zaključimo, da napredek v razumevanju biologije te redke bolezni in razvoj novih tarčnih zdravljenj omogočata boljšo obravnavo vseh bolnikov s to boleznijo.

Jaypirca je prvi in edini odobreni reverzibilni BTK inhibitor, ki lahko ponovno vzpostavi odgovor pri odraslih bolnikih z MCL potem ko kovalentni BTK inhibitor ni več opcija[1,2]

Indikacija

Zdravilo Jaypirca je kot monoterapija indicirano za zdravljenje odraslih bolnikov s ponovitvijo limfoma plaščnih celic (MCL – mantle cell lymphoma), ali za na zdravljenje neodzivne oblike te bolezni, po predhodnem zdravljenju z zaviralcem Brutonove tirozin kinaze (BTK).

Skrajšan povzetek glavnih značilnosti zdravila

▽ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

Ime zdravila: Jaypirca 50 mg filmsko obložene tablete, Jaypirca 100 mg filmsko obložene tablete. **Kakovostna in količinska sestava:** Ena filmsko obložena tableta vsebuje 50 mg/100 mg pirtobrutiniba. **Terapevtske indikacije:** Zdravilo Jaypirca je kot monoterapija indicirano za zdravljenje odraslih bolnikov s ponovitvijo limfoma plaščnih celic (MCL – mantle cell lymphoma), ali za na zdravljenje neodzivne oblike te bolezni, po predhodnem zdravljenju z zaviralcem Brutonove tirozin kinaze (BTK). **Odmerjanje in način uporabe:** Zdravljenje z zdravilom Jaypirca mora uvesti in spremljati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Odmerjanje Priporočeni odmerek je 200 mg pirtobrutiniba enkrat dnevno. Zdravljenje se mora nadaljevati do napredovanja bolezni ali nesprejemljive toksičnosti. Prilagajanje odmerka glede na starost, pri bolnikih z blago, zmerno ali hudo okvaro ledvic ali pri bolnikih z blago, zmerno ali hudo okvaro jeter ni potrebno. Način uporabe Zdravilo Jaypirca je namenjeno za peroralno uporabo. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pri bolnikih, zdravljenih z zdravilom Jaypirca, je prišlo do resnih okužb, vključno s smrtnimi primeri. Okužbe stopnje 3 ali višje, o katerih so najpogosteje poročali, so bile pljučnica, covidna pljučnica, covid-19 in sepsa. Pri bolnikih s povečanim tveganjem za oportunistične okužbe je treba razmisliti o profilaktičnem protimikrobnem zdravljenju. Na podlagi stopnje okužbe in morebitne pridružene nevtropenije bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, je prišlo do krvavitev, vključno s smrtnimi primeri, s trombocitopenijo ali brez nje. Opazili so večje krvavitve stopnje 3 in višje, vključno z gastrointestinalno in intrakranialno krvavitvijo. Bolnike je treba spremljati glede znakov in simptomov krvavitve. Pri krvavitvah stopnje 3 ali 4 bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, je prišlo do citopenij stopnje 3 ali 4, vključno z nevtropenijo, anemijo in trombocitopenijo. Med zdravljenjem je treba spremljati celotno krvno sliko, kot je medicinsko indicirano. Na podlagi stopnje citopenije bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, so opazili atrijsko fibrilacijo in atrijsko undulacijo, zlasti pri bolnikih z atrijsko fibrilacijo v anamnezi in/ali več pridruženimi srčno-žilnimi boleznimi. Bolnike je treba spremljati glede znakov in simptomov atrijske fibrilacije in atrijske undulacije, potrebno je posneti elektrokardiogram, kot je medicinsko indicirano. Na podlagi stopnje atrijske fibrilacije/atrijske undulacije bo morda potrebna prekinitev zdravljenja. Pri bolnikih, zdravljenih z zdravilom Jaypirca, je pogosto prišlo do drugih primarnih malignih bolezni, najpogosteje nemelanomskih kožnih rakov. Med zdravljenjem z zdravilom Jaypirca so redko poročali o sindromu tumorske lize (TLS – *tumour lysis syndrome*). Bolniki z velikim tveganjem za TLS so tisti, ki imajo pred zdravljenjem veliko tumorsko breme. Bolnike je treba oceniti glede morebitnega tveganja za TLS in jih skrbno spremljati, kot je klinično indicirano. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Pirtobrutinib se presnavlja predvsem prek CYP3A4, UGT1A8 in UGT1A9. V klinični študiji je itrakonazol, močan zaviralec CYP3A4, povečal vrednost AUC pirtobrutiniba za 48 %, vrednosti C_{max} pirtobrutiniba pa ni spremenil. V klinični študiji je rifampin, močan induktor CYP3A, zmanjšal vrednost AUC in C_{max} pirtobrutiniba za 71 % oziroma 42 %. Pirtobrutinib je zmeren zaviralec CYP2C8 in BCRP. Pirtobrutinib je šibek zaviralec P-gp, CYP2C19 in CYP3A. **Neželeni učinki :** Najpogostejši neželeni učinki katere koli stopnje so: utrujenost (26,3 %), nevtropenija (22,8 %), driska (22,1 %) in kontuzije (19,0 %). Najpogostejši hudi neželeni učinki (stopnje ≥ 3) so: nevtropenija (19,7 %), anemija (7,9 %) in trombocitopenija (6,6 %). *Zelo pogosti:* nevtropenija, trombocitopenija, anemija, krvavitev, podplutbe, kontuzije, driska, bolečine v trebuhu, navzea, izpuščaj, artralgija, utrujenost. *Pogosti:* pljučnica, okužba sečil, okužba zgornjih dihal, limfocitoza, glavobol, atrijska fibrilacija/atrijska undulacija, hematurija, epistaksa, hematom, petehije. **Imetnik dovoljenja za promet z zdravilom:** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, Nizozemska. **Datum zadnje revizije besedila:** 16.8.2024. **Režim izdaje:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Samo za strokovno javnost.**

BTK=Bruton's tyrosine kinase; MCL=mantle cell lymphoma.

Referenci: 1. Povzetek glavnih značilnosti zdravila Jaypirca, zadnja odobrena verzija. **2.** Mato AR, Shah NN, Jurczak W, *et al*. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 021;397(10277):892-901.

Pomembno: Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. Pred predpisovanjem zdravila Jaypirca si preberite zadnji veljavni Povzetek glavnih značilnosti zdravil. Podrobne informacije o zdravilu so objavljene na spletni strani Evropske agencije za zdravila http://www.ema.europa.eu

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Zdravilo POTELIGEO® je indicirano za zdravljenje odraslih bolnikov s fungoidno mikozo (FM) ali Sézaryjevim sindrom (SS), ki so predhodno prejeli vsaj eno sistemsko zdravljenje.[1]

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

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Pred predpisovanjem zdravila, prosimo, preberite celoten povzetek glavnih značilnosti zdravila (SmPC).
Učinkovina: mogamulizumab (4 mg/ml). **Pakiranje:** koncentrat za raztopino za infundiranje. Ena viala vsebuje 20 mg mogamulizumaba v 5 ml raztopine (4 mg/ml) v 10-ml stekleni viali. **Indikacije:** zdravljenje odraslih bolnikov s fungoidno mikozo (FM) ali Sézaryjevim sindromom (SS), ki so predhodno prejeli vsaj eno sistemsko zdravljenje. **Odmerjanje in način uporabe:** priporočeni odmerek zdravila POTELIGEO je 1 mg/kg. Daje se samo v obliki intravenske infuzije, ki traja najmanj 60 minut. Zdravljenje smejo uvesti in nadzorovati zdravniki z izkušnjami pri zdravljenju raka. Zdravilo smejo bolnikom dajati samo zdravstveni delavci v okolju, kjer je na voljo oprema za oživljanje. V prvem 28-dnevnem krogu zdravljenja se zdravilo daje v tedenskih presledkih 1., 8., 15. in 22. dan, temu pa sledijo infuzije v dvotedenskih presledkih 1. in 15. dan vsakega nadaljnjega 28-dnevnega kroga zdravljenja, dokler bolezen ne napreduje ali se pojavijo nesprejemljivi toksični učinki. Pri prvi infuziji se priporoča predhodno zdravljenje z antipiretikom in antihistaminikom. Če se pojavi reakcija na infuzijo, je treba tudi pred nadaljnjimi infuzijami uporabiti predhodno zdravljenje. Pri bolnikih, ki so prejemali zdravilo POTELIGEO, se je pojavil medikamentozni izpuščaj (kožna reakcija na zdravilo); nekateri primeri so bili hudi in/ali resni. Če se pojavi izpuščaj (ki je povezan z zdravilom) s stopnjo resnosti 2 ali 3 (zmerna ali huda), je treba zdravljenje z zdravilom POTELIGEO prekiniti in izpuščaj ustrezno zdraviti, dokler se ne izboljša do stopnje 1 ali nižje (blaga resnost). Nato se lahko zdravljenje nadaljuje. Ob pojavu življenjsko nevarnega izpuščaja (stopnja 4) je treba zdravljenje z zdravilom POTELIGEO trajno opustiti. Pri bolnikih, zdravljenih z zdravilom POTELIGEO, so opazili akutne reakcije, povezane z infundiranjem. Te reakcije so bile večinoma blage ali zmerne (stopnje 1–2), vendar so poročali tudi o nekaj hudih reakcijah (3. stopnja). Večina reakcij, povezanih z infundiranjem, se pojavi med prvo infuzijo ali kmalu po njej (v 24 urah po dajanju zdravila), nato pa se pojavnost pri nadaljnjih krogih zdravljenja zmanjšuje. Če se pojavijo blage do hude reakcije (stopnje 1–3), povezane z infundiranjem, je treba infundiranje zdravila POTELIGEO začasno prekiniti in zdraviti simptome. Pri ponovni uvedbi infundiranja po odpravi simptomov je treba zmanjšati hitrost infuzije za najmanj 50 %. Če se reakcija ponovi, je treba razmisliti o opustitvi infundiranja. Ob pojavu življenjsko nevarne reakcije (stopnje 4), povezane z infundiranjem, je treba zdravljenje z zdravilom POTELIGEO trajno opustiti. **Kontraindikacije:** preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pri uporabi zdravila POTELIGEO pri bolnikih s T-celičnimi limfomi razen FM ali SS v kliničnih preskušanjih so pri manj kot 1 % bolnikov poročali o pojavu resnih kožnih reakcij, vključno s Stevens-Johnsonovim sindromom (SJS) in toksično epidermalno nekrolizo (TEN). O tem so poročali tudi v obdobju po prihodu zdravila na trg. Nekateri primeri so imeli smrtni izid. Bolnike je treba pozorno spremljati zaradi simptomov ali znakov, ki kažejo na SJS ali TEN. Če se pojavijo, je treba zdravljenje z zdravilom POTELIGEO prekiniti, zdravljenje pa se ne sme ponovno začeti, dokler SJS ali TEN nista izključena in se kožna reakcija izboljša do stopnje 1 ali nižje. Pri bolnikih s FM ali SS, zdravljenih z zdravilom POTELIGEO, obstaja večje tveganje za resno okužbo in/ali ponovno aktivacijo virusa. Kombinacij zdravila POTELIGEO s sistemskimi imunomodulirajočimi zdravili ali drugimi odobrenimi zdravili za zdravljenje FM ali SS niso preučili in zato niso priporočljive. Med zdravljenjem z zdravilom POTELIGEO se lahko uporabljajo topikalni steroidi ali majhni odmerki sistemskih kortikosteroidov; vendar je tveganje za resno okužbo in/ali ponovno aktivacijo virusa pri sočasni uporabi lahko večje. Bolnike je treba spremljati glede znakov in simptomov okužbe ter jih takoj zdraviti. Bolnike je treba pred začetkom zdravljenja z zdravilom POTELIGEO testirati za okužbo z virusom hepatitisa B. Bolnikom s pozitivnim testom za sedanjo/preteklo okužbo s hepatitisom B se priporoča, da se posvetujejo z zdravnikom, ki ima strokovno znanje o zdravljenju hepatitisa B. Pri bolnikih, pri katerih so po zdravljenju z zdravilom POTELIGEO opravili presaditev hematopoetskih matičnih celic (HSCT), so poročali o zapletih, vključno s hudo boleznijo presadka proti gostitelju (GVHD). Poročali so o večjem tveganju za zaplete pri presaditvi, če je zdravilo POTELIGEO dano nedolgo (približno 50 dni) pred HSCT. Bolnike natančno spremljajte in bodite pozorni na zgodnje znake zapletov, povezanih s presadkom. Pri bolnikih, ki so prejemali zdravilo POTELIGEO, so opazili sindrom tumorske lize (TLS). Bolnike je treba pozorno spremljati z ustreznimi laboratorijskimi in kliničnimi preiskavami za stanje elektrolitov, hidracije in delovanja ledvic, zlasti v prvem mesecu zdravljenja, in jih obravnavati skladno z najboljšo medicinsko prakso. Bolnike, ki imajo dejavnike tveganja, povezane z boleznimi srca, je treba spremljati in uvesti ustrezne previdnostne ukrepe. **Neželeni učinki:** resni neželeni učinki, o katerih so najpogosteje poročali, so bili pljučnica, pireksija, z infuzijo povezana reakcija in celulitis. Hudi neželeni učinki so vključevali respiratorno odpoved 4. stopnje (1,1 %) ter polimiozitis in sepso 5. stopnje (0,5 % pri obeh učinkih). Zelo pogosti (≥ 1/10) neželeni učinki so zaprtost, driska, navzea, stomatitis, utrujenost, periferni edem, pireksija, okužbe, reakcija, povezana z infundiranjem, glavobol, kožna reakcija na zdravilo (vključno z izpuščajem). Pogosti (≥ 1/100 do < 1/10) neželeni učinki so anemija, nevtropenija, levkopenija, trombocitopenija, hipotiroidizem, bruhanje, okužba zgornjih dihal, zvišanje ravni jetrnih encimov, zmanjšanje števila limfocitov. Za celoten seznam neželenih učinkov, prosimo, glejte SmPC. **Poročanje o domnevnih neželenih učinkih:** Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na: Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. **Imetnik dovoljenja za promet:** Kyowa Kirin Holdings B.V., Bloemlaan 2, 2132 NP Hoofddorp, Nizozemska. **Številka dovoljenja za promet:** EU/1/18/1335/001**. Način in režim izdaje:** H. **Datum prve odobritve:** 22. november 2018. **POTELIGEO® je registrirana blagovna znamka. Datum priprave informacije:** 01/2024.

† Vorinostat je odobrila FDA (ameriška zvezna uprava za hrano in zdravila) za zdravljenje MF in SS v Združenih državah in trenutno ni registriran v EU. Vsa sklicevanja na vorinostat v tem dokumentu so izključno za namen natančne komunikacije rezultatov študije MAVORIC in niso namenjena podpori uporabe vorinosata.

Literatura: 1. Povzetek glavnih značilnosti zdravila POTELIGEO® (mogamulizumab), september 2023. **2.** Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. Lancet Oncol. 2018;19(9):1192–1204.

KYOWA KIRIN

SAMO ZA STROKOVNO JAVNOST

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