Systemic Treatment for Cutaneous T cell Lymphomas

Singapore Lymphoma Scientific Symposium

Education Program 2025

Dr Esther Chang, NCCS

Classification of cutaneous T-cell lymphomas [2,4].

Cutaneous T-cell lymphoma	ICD-O-3 (morphology)
Mycosis fungoides (MF)	9700/3
MF variants and subtypes:	
Folliculotropic MF	
Pagetoid reticulosis	
Granulomatous slack skin	
Sézary syndrome (SS)	9701/3
Primary cutaneous CD30-positive lymphoproliferative disorders:	
Primary cutaneous anaplastic large cell lymphoma	9718/3
Lymphomatoid papulosis	9718/1
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Primary cutaneous peripheral T-cell lymphoma, unspecified	9709/3
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	9709/3
Primary cutaneous γ/δ T-cell lymphoma	9726/3
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	9709/1
Primary cutaneous acral CD8+ T-cell lymphoproliferative disorder*	9709/3

~75%

EORTC consensus recommendations for MF and SS, EJC 2023

Mycosis Fungoides vs Sezary Syndrome

MF	SS
Most common form of CTCL	Rarer form of CTCL
Flat, red scaly patches, thicker plaques or larger nodules/tumours with occasional nodal/visceral involvement	Triad of erythroderma accompanied with lymphadenopathy and peripheral blood involvement of CD4+ T cells
Slow chronic/ indolent course	Aggressive leukemic variant
Can mimic other skin conditions and may be years before it is diagnosed or progress, hence if diagnosed early, prognosis is generally favourable	Aggressive, advanced form of CTCL associated with poor prognosis
Early/limited stage MF treated with skin directed therapies first	Requires systemic therapy

Staging of MF and SS

ISCL (International Society of Cutaneous Lymphoma) Clinical staging of MF and SS follows the TNMB system

T – Tumour (% skin involvement or presence of tumour nodules)
N – Node
M.- Metastasis (visceral involvement)
B – Blood tumour burden and cloamnity

TNMB staging for mycosis fungoides and Sézary syndrome [1].

Skin	
T1	Limited patches, papules, and/or plaques covering <10% of the skin surface. May further stratify into T1a (patch only) versus T1b (plaque +/- patch).
T2	Patches, papules, or plaques covering ≥10% of the skin surface. May further stratify into T2a (patch only) versus T2b (plaque +/- patch).
T3	One or more tumours (≥ 1-cm diameter)
T4	Confluence of erythema covering ≥80% body surface area
Node	
N0	No clinically abnormal peripheral lymph nodes; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or National Cancer Institute (NCI) $LN_{0–2}$ N1a Clone negative N1b Clone positive
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3 N2a Clone negative N2b Clone positive
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN_4; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
*Blood**	
B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B0a	Clone negative
B0b	Clone positive
B1	Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumour burden: ≥1000/μl Sézary cells with positive clone

SS is staged as T4 N2/3/x M0 B2.

* Blood staging for MF/SS is further defined as B0 = <250/ml of $CD4^+/CD26^-$ or $CD4^+/CD7^-$ cells, B1 = does not meet criteria for B0 or B2, and B2 = ≥1000/ml of $CD4^+/CD26^-$ or $CD4^+/CD7^-$ cells or other aberrant population of lymphocytes identified by flow cytometry [3,240].

EORTC consensus recommendations for MF and SS, EJC 2023

Staging and Prognosis

Table 3

Clinical stages (5-year disease free survival [DSS] according to Olsen et al. [1]).

Stage	T	N	M	B	5-year DSS (%)
IA	1	0	0	0,1	98
IB	2	0	0	0,1	89
IIA	1,2	1,2	0	0,1	89
IIB	3	0–2	0	0,1	56
IIIA	4	0–2	0	0	54
IIIB	4	0–2	0	1	48
IVA1	1–4	0–2	0	2	41
IVA2	1–4	3	0	0–2	23
IVB	1–4	0–3	1	0–2	18

Early/Limited

Advanced

SS is by default advanced as is is staged T4 N2/3/X B2

EORTC consensus recommendations for MF and SS, EJC 2023

Principals of systemic treatment of MF and SS

1. Fundamental to choosing the best therapeutic approach for each patient is the correct diagnosis and the correct staging

Principals of systemic treatment of MF and SS

2. Treatment of MF is generally palliative and should follow a step-wise approach, giving priority to QOL

Principals of systemic treatment of MF and SS

3. Systemic therapies can be given in pts with early stage disease refractory to Skin-directed therapies or in pts with advanced disease

Retinoids

- Family of polyisoprenoid lipids with multiple actions
- Examples: all-trans retinoic acid acitretin, isotretinoin, bexarotene (only retinoid developed and approved for treatment of CTCL)
- Can be given in combination with phototherapy for better ORR
- Adverse effects include teratogenicity, dry skin/mucous membranes, dose dependent hypothyroidism, hypertriglyceridemia, hypercholesterolemia and neutropenia

ORIGINAL REPORTS | May 01, 2001

Bexarotene Is Effective and Safe for Treatment of Refractory Advanced-Stage Cutaneous T-Cell Lymphoma: Multinational Phase II-III Trial Results

Authors: Madeleine Duvic, Kenneth Hymes, Peter Heald, Debra Breneman, Ann G. Martin, Patricia Myskowski, Connie Crowley, and Richard C. Yocum, for Members of the Bexarotene Worldwide Study Group | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 19, Number 9 • https://doi.org/10.1200/JCO.2001.19.9.2456

Home | JAMA Dermatology | Vol. 137, No. 5

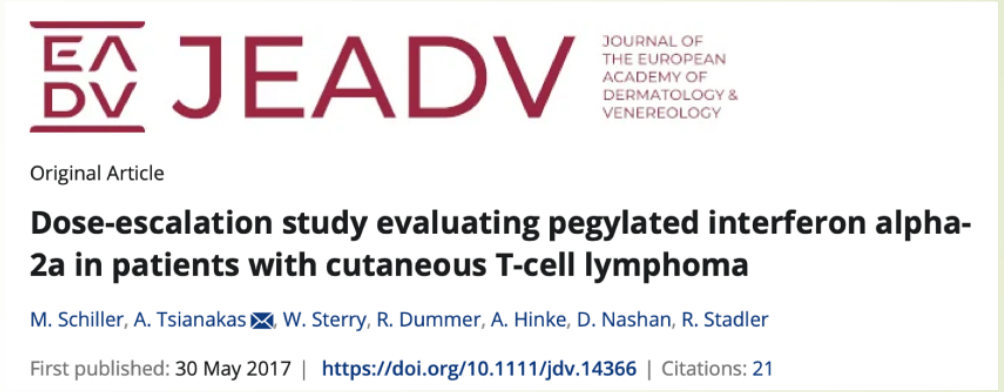
Study FREE

Phase 2 and 3 Clinical Trial of Oral Bexarotene (Targretin Capsules) for the Treatment of Refractory or Persistent Early-Stage Cutaneous T-Cell Lymphoma

Madeleine Duvic, MD; Ann G. Martin, MD; Youn Kim, MD ; et al

Interferon-alpha

- Long history in treatment of CTCL
- Pegylated interferon alpha 2a currently available
- Subcutaneous preparation
- Given once weekly
- ORR 50-60%
- AE: neutropenia, anemia, flu-like symptoms, fatigue, hepatotoxicity



Methotrexate (oral)

- Low dose methotrexate
- Given weekly in doses ranging from 5 to 25mg once weekly
- Can be given in combination with retinoids or skin directed therapies
- Majority of patients will respond (60-70%) but rarely will MTX induce CR
- Responses also typically short-lived
- But toxicity profile very manageable

CD30 targeting ADC, Brentuximab

- Antibody drug conjugate consisting of anti CD30 IgG1 antibody linked to MMAE.
- Landmark phase 3 randomized ALCANZA trial found Brentuximab to have ORR of 55%, mPFS 16.7months, response lasting 4months,
  - N= 97, Stage IA to IVB, 2nd line +
  - CD30 positive malignant cells ≥10%
  - Comparator: physician's choice of MTX vs Bexarotene
  - AE: Peripheral neuropathy 67%, majority resolves with treatment d/c
- Other studies include BV in SS and LyP patients, or BV in patients with CD30 positivity as low as 0% --> all demonstrated BV activity

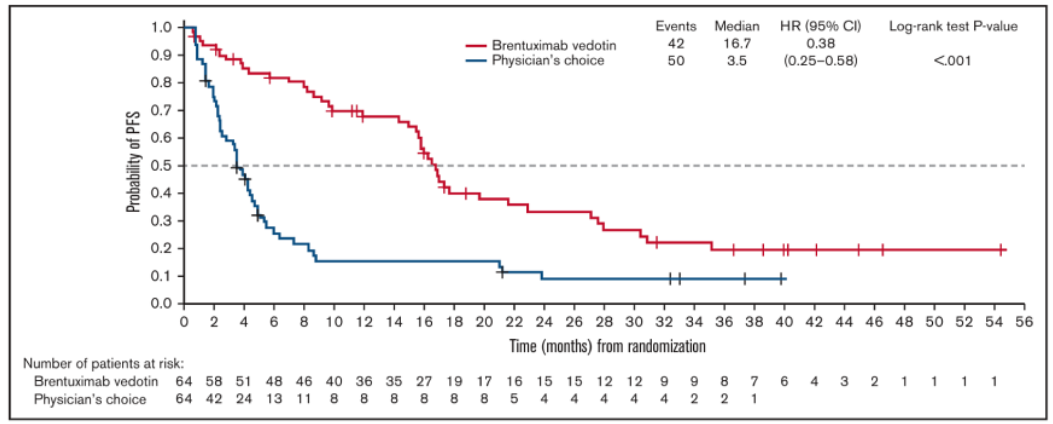


Figure 1. PFS per IRF in the ITT population. PFS was defined as the time from randomization until disease progression per IRF or death of any cause, whichever occurred first. Patients who were lost to follow-up, withdrew consent, or discontinued treatment because of undocumented disease progression after the last adequate disease assessment were censored at the last disease assessment.

- Note: CD30 positivity varies within individuals and when taken at different time points, expression levels may differ.

Blood advances 2021 Vol 5 (23) pp 5098-5106

CCR4 antibody, Mogamulizumab

- Defucosylated humabnised IgG1 monoclonal antibody against CCR4
- Has enhanced ADCC activity
- Ph3 randomized MAVORIC trial of Moga vs Vorinostate found improved PFS 7.7mo vs 3.1mo
- Blood response highest (68%). Skin response (42%) better than nodal response (17%)
- Moga is **superior in SS compared to MF**, and also superior in stage III/IV vs I/II
- Induces rapid reductions of CD4+ cell counts
- AE : infusion related reactions, drug rash (which will need to be differentiated from PD of MF/SS), diarrhea and fatigue

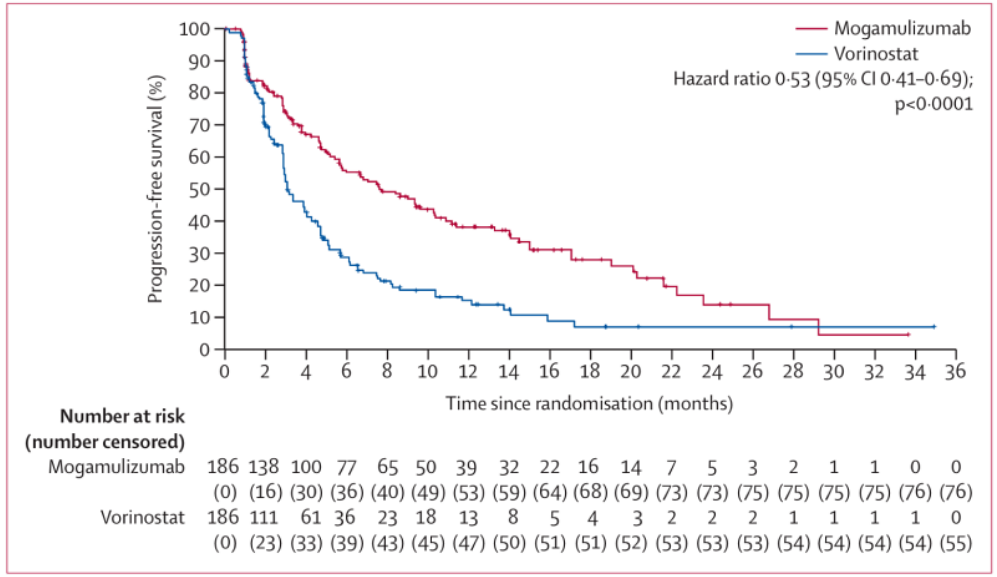
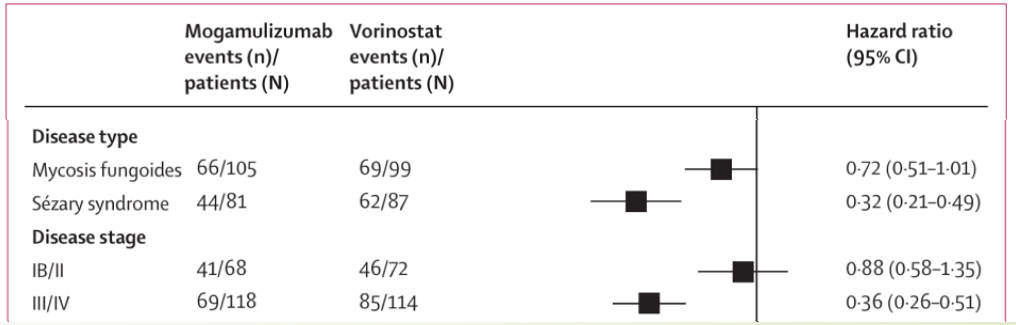


Figure 2: **Progression-free survival by investigator assessment**



Lancet Oncology 2018, Vol 19 pp 1192-1204

Chemotherapy

- Single agent therapy recommended in favour of QOL
- Options include
  - Liposomal Doxorubicin
    - 20mg/m2 given Q2weekly for total 12 doses; EORTC 21012, n = 49, 3rd line, ORR 40%, mDOR 6months
    - consideration for maintenance Q4weekly after induction; Single centre experience, n =18; ORR 78%, mDOR 31 weeks
  - Gemcitabine
    - Low dose gemcitabine: cumulative dose of 1800-2000mg/m2 monthly; German multicenter study, n =37, ORR 62%
    - Low dose Gem; monthly cumulative 2000-3000mg/m2 either in 1000mg Q1w vs 100mg/m2 Q2w in a month; Italian retrospective study, n = 22, ORR 55%, mPFS 17months

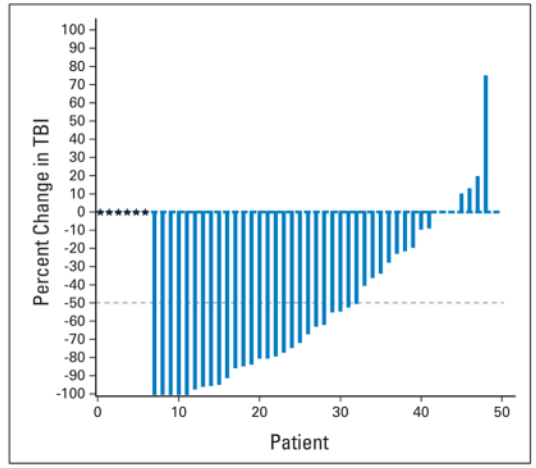


Fig 2. Waterfall plot of the percentage change in tumor burden index (TBI). Star symbols represent patients with nonevaluable TBI.

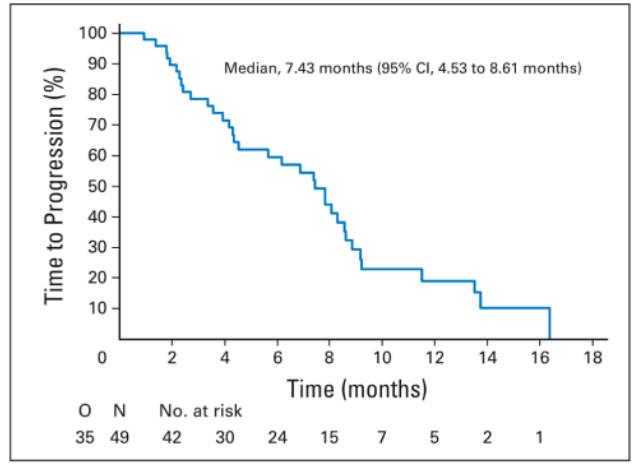


Fig 3. Time to progression. O, observed.

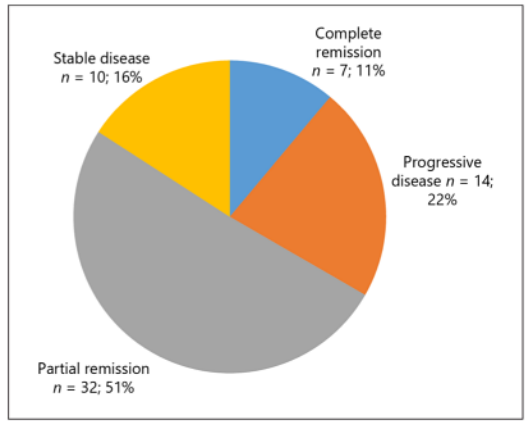


Fig. 1. Response rates of patients with low-dose gemcitabine (N = 63).

J Clin Oncol 2012; 30(33) pp 4091-4097

Dermatology 2022; 238 pp 498-506

Histone deacetylase inhibitors

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PARTIAL ACCESS | ORIGINAL REPORTS | October 13, 2009

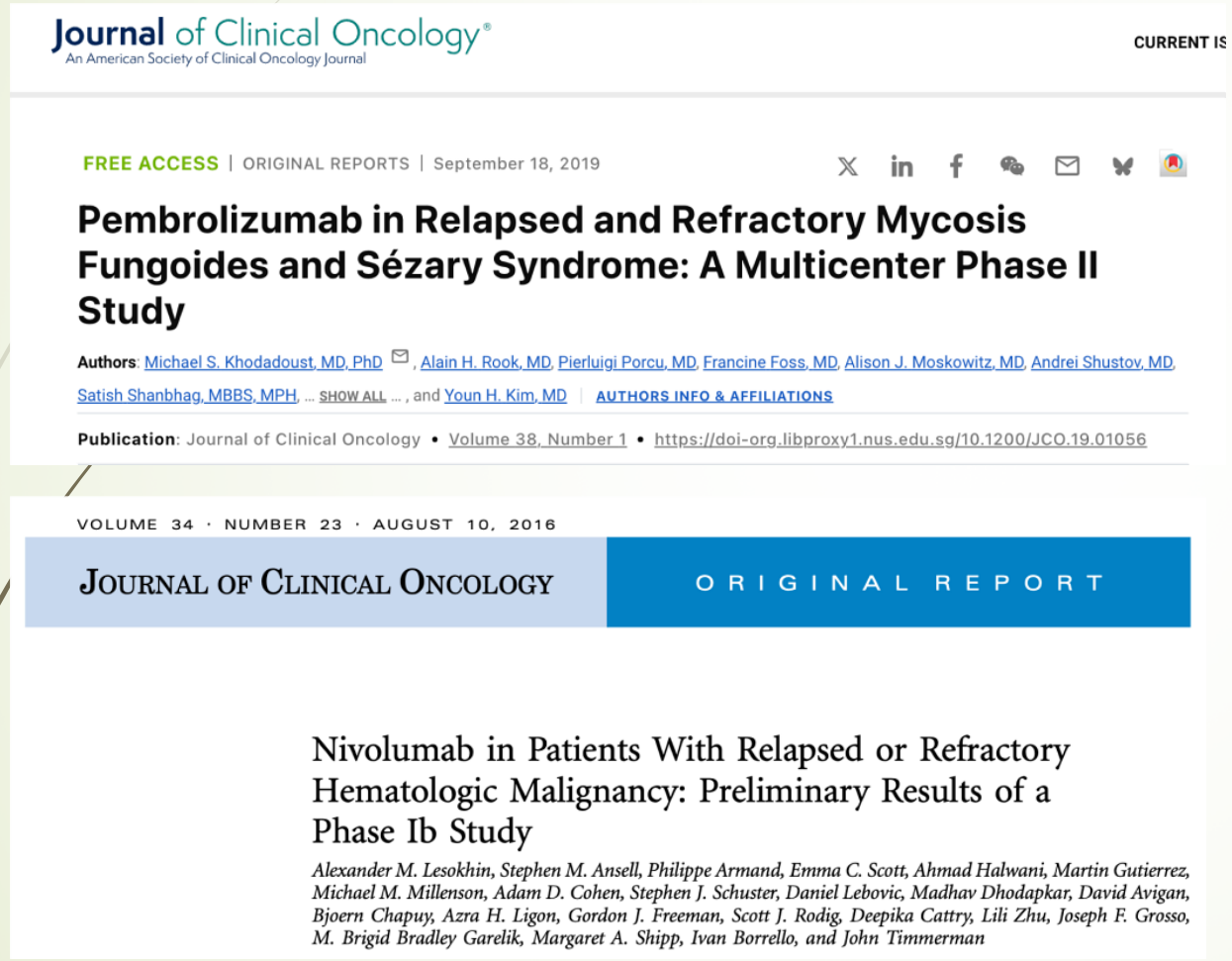
Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma

Authors: Richard L. Piekarz, Robin Frye, Maria Turner, John J. Wright, Steven L. Allen, Mark H. Kirschbaum, Jasmine Zain, ... SHOW ALL ... , and Susan E. Bates | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 27, Number 32 • https://doi.org/10.1200/JCO.2008.21.6150

- Cause growth arrest, cellular differentiation and apoptosis.
- Antitumour effects hypothesized to occur via modulation of gene expression
- Romi 14mg/m2 given D1/8/15 Q21 day , median no. of cycles: 4
- ORR 34% (CR 7%, PR 26%)
- AE : fatigue, CINV, cytopenias, raised tranasminases, hypophosphatemia

Immunotherapies



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CURRENT IS

FREE ACCESS | ORIGINAL REPORTS | September 18, 2019

Pembrolizumab in Relapsed and Refractory Mycosis Fungoides and Sézary Syndrome: A Multicenter Phase II Study

Authors: Michael S. Khodadoust, MD, PhD, Alain H. Rook, MD, Pierluigi Porcu, MD, Francine Foss, MD, Alison J. Moskowitz, MD, Andrei Shustov, MD, Satish Shanbhag, MBBS, MPH, ... SHOW ALL ... , and Youn H. Kim, MD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 38, Number 1 • https://doi-org.libproxy1.nus.edu.sg/10.1200/JCO.19.01056

VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

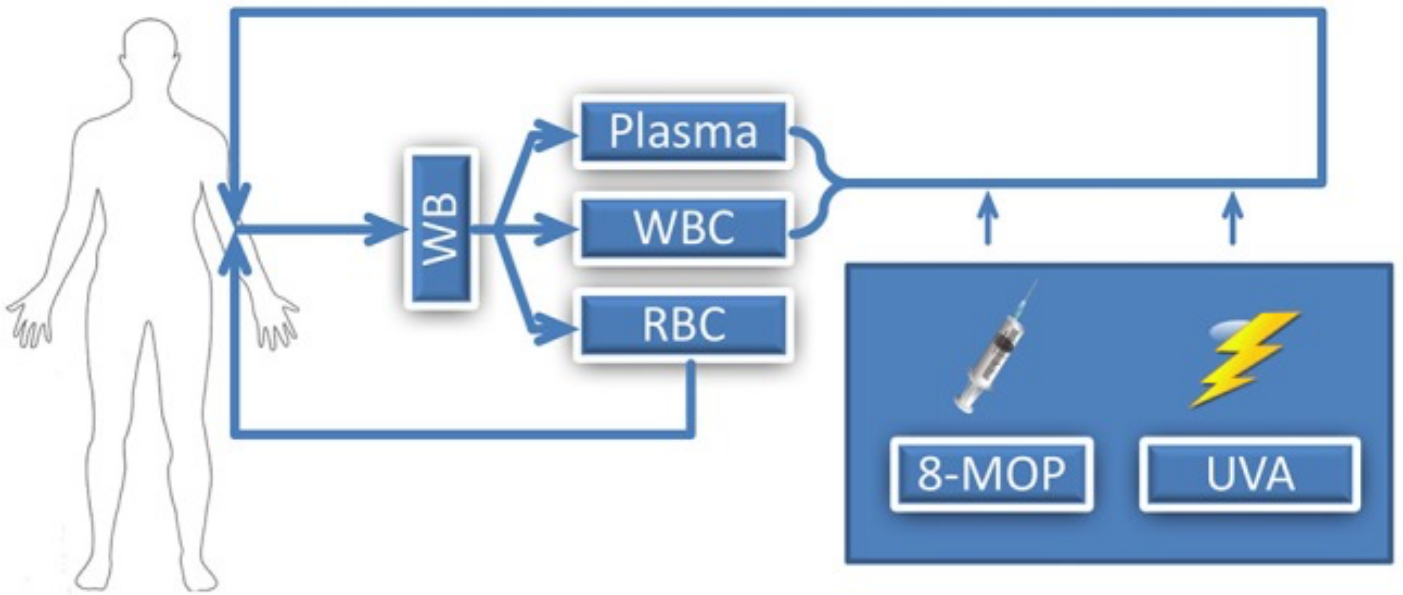
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study

Alexander M. Lesokhin, Stephen M. Ansell, Philippe Armand, Emma C. Scott, Ahmad Halwani, Martin Gutierrez, Michael M. Millenson, Adam D. Cohen, Stephen J. Schuster, Daniel Lebovic, Madhav Dhodapkar, David Avigan, Bjoern Chapuy, Azra H. Ligon, Gordon J. Freeman, Scott J. Rodig, Deepika Cattry, Lili Zhu, Joseph F. Grosso, M. Brigid Bradley Garelik, Margaret A. Shipp, Ivan Borrello, and John Timmerman

- Promising activity of checkpoint inhibitors
- ORR 38% in small ph2 trial, n=24 showed pembro had clinical activity in heavily pretreated MF/SS
- In Phase 1b study of nivo, ORR lower at 15%
- Concerns of hyper-progression as this is a T cell lymphoma and the malignant tumour cells may act as an immunological effector cell with unexpected effects upon checkpoint inhibitrion

Extracorporeal photochemotherapy



- Leucopheresis based therapy
- FDA approved since 1988 for treatment of SS
- Buffy coat exposed to UVA irradiation in the presence of photosensitizing agent prior to reinfusion back to patient
- ORR ~55%

Frontiers in medicine (2018) 5:236

Hematopoietic stem cell transplant

- Autologous HSCT has no role in MF/SS treatment
- Allogeneic HSCT is the only curative option for MF/SS with advanced disease but published evidence are retrospective studies
- Reported 2-7 year OS between 79% and 32%
- Near or CR should be achieved prior to transplantation
- Best not to be used as a ‘last resort’ but rather in patients with high risk of disease progression and not yet refractory
- High risk for post transplant relpse and morbidity and mortality from alloSCT
- Consider in patients who are fit, young, minimal premorbid conditions

Table 2. Allogeneic HSCT in MF/SS-CTCL

Reference	N	Intervention	Efficacy	Transplant-related toxicities
Hosing et al[55]	47	6% ablative 94% RIC/NMA	ORR = n/a, 2-year PFS 40%, 2-year OS 67% 4-year PFS 26%, 4-year OS 51%	1-year NRM 10% 2-year NRM 17% Gr 2–4 aGVHD 40%; cGVHD 28%
Duarte et al[56]	60	33% ablative 67% RIC/NMA	ORR = n/a, 2-year PFS 34%, 2-year OS 54% 5-year PFS 32%, 5-year OS 46% 7-year PFS 30%, 7-year OS 44%	1-year NRM 20% 7-year NRM 22%
Paralkar et al[57]	12	17% ablative 83% RIC	ORR = 67%, 2-year PFS 23%, 2-year OS 56%	1-year NRM 25%
De Masson et al[58]	37	32% ablative 68% RIC/NMA	ORR = n/a, 2-year PFS 31%, 2-year OS 57%	1-year NRM 18% 2-year NRM 18% Gr 2–4 aGVHD 76%; cGVHD 44%
Lechowicz et al[59]	129	36% ablative 64% RIC/NMA	ORR = n/a, 1-year PFS 31%, 1-year OS 54% 5-year PFS 17%, 5-year OS 32%	1-year NRM 19% 5-year NRM 22% Gr 2–4 aGVHD 41%; cGVHD 43%
Isufi et al[60]	16 (n = 23; 16 MF/SS; 7 G/D TCL)	RIC except 2 haploidentical	CR rate = 56% OS 75% (12 of 16 patients) w/median follow-up 5.5 years	100-day NRM 12% Gr 2–4 aGVHD 50%; cGVHD 56%
Weng et al[61]	35	100% NMA	ORR (CR) = 80% (57%), 2-year PFS 60%, 2-year OS 68% 5-year PFS 41%, 3-year OS 62%, 5-year OS 56%	1-year NRM 3% 2-year NRM 14% Gr 2–4 aGVHD 16%; cGVHD 32%

aGVHD, acute GVHD; cGVHD, chronic GVHD; Gr, grade; NMA, non-myeloablative; RIC, reduced-intensity conditioning.

Hematology 2021; ASH education program pp 303-312

Maintenance therapy

- Continuous exposure to either SDT or systemic therapy once remission has been achieved
- Main purpose is to maintain response and prevent relapse
- Supported by little evidence but in practice, modalities with excellent safety profile are used
- Options include
  - Low dose, low frequency PUVA
  - Topical chlormethine
  - Retinoids
  - Tapering doses of IFN-alpha
  - Long term liposomal doxo?

Table 6a
Recommendations for first-line treatment of MF stage IIB.

Systemic therapies*	
Retinoids**	level 2
IFN-α***	level 2
TSEB	level 2
Brentuximab vedotin****	level 2
Mogamulizumab****	level 2
Monochemotherapy (pegylated liposomal doxorubicin, gemcitabine, pegylated liposomal doxorubicin)	level 4
Low dose MTX	level 4
Localised RT*****	level 4

Table 7a
Recommendations for first-line treatment of MF stage IIIA and B.

Systemic therapies*	
Retinoids**	level 2
IFN-α***	level 2
ECP****	level 3
Brentuximab vedotin*****	level 2
Mogamulizumab*****	level 2
low dose Methotrexate (MTX)	level 4
TSEB	level 2

Table 8
Recommendations for treatment of MF stages IVA and IVB*.

Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)**	level 3
Radiotherapy (TSEB and localised)***	level 4
Brentuximab vedotin****	level 2
Mogamulizumab*****	level 2
Alemtuzumab (mainly in B2)	level 3
Allogeneic stem cell transplantation	level 2

Table 9a
Recommendations for first-line treatment of SS.

ECP*	level 3
Systemic therapies in combination with ECP or PUVA	
Retinoids**	level 3
IFN-α***	level 3
Chlorambucil + prednisone	level 3
Low dose MTX	level 4

EORTC consensus recommendations for MF and SS, EJC 2023

Some thoughts/conclusions …

- MF and SS have a heterogenous clinical presentation and behavior
- Treatment of most patients are palliative in intent
- Important to sequence therapies to maximise QOL
- Combination or sequencing systemic treatment with skin directed therapies can help with better response and/or maintaining remission
- Multidisciplinary care is paramount in management of CTCL patients
- Accessibility of treatments options has to be factored
- AlloHSCT should be considered in selected high risk advanced MF/SS and should not be used as a 'last resort' treatment