Histone deacetylase inhibitors for CTCL

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Overview of Lecture

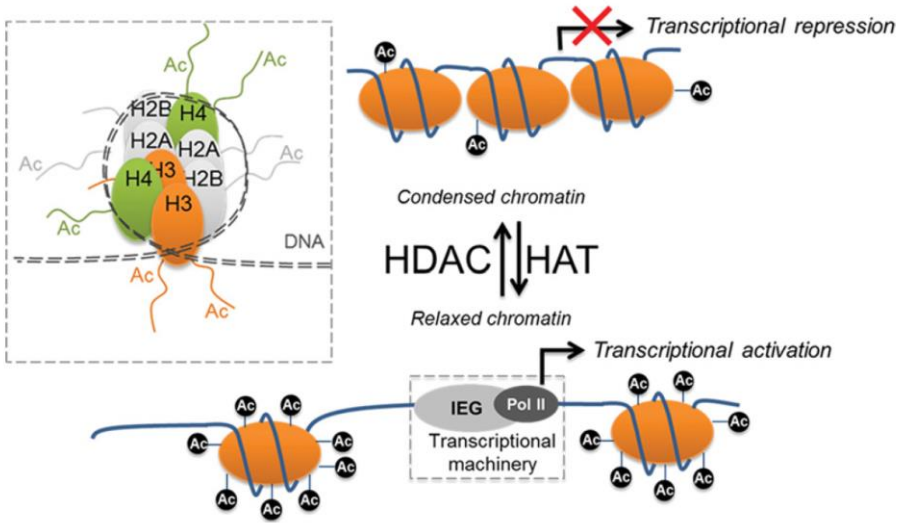
- Histone deacetylases (HDACs) and Histone acetyl transferases (HATs)
- HDAC classification I-IV
- HDAC–Inhibitor (HDAC-I) classification, mode of action
- HDAC-I as anti-cancer drug

  Licenced HDAC-I

  - Vorinostat
  - Romidepsin
  - Belinostat
  - (Panobinostat)
- Clinical Trials in Europe
  - RESMAIN Trial - Resminostat maintenance therapy in advanced CTCL
  - Global patterns of treatment in advanced MF; HDAC-I experience

Histone Deacetylase Enzymes (HDACs)

- Histone deacetylases (HDACs) are a group of enzymes which, along with histone acetyltransferases (HATs), regulate the acetylation of histone & non-histone proteins
- HDACs target both histone and non-histone proteins that are involved in cell cycle, cell death, cell invasion, and angiogenesis
- HDAC enzymes in humans are sub-divided into 4 main classes I-IV, based on homology of accessory domains to 'yeast' histone deacetylases



Class of HDACs: Classes I, II, and IV are zinc-dependent enzymes and Class III are NAD^+-dependent

Class I (related to yeast RPD3 gene)

- Includes HDAC – 1,3,8
- Ubiquitously expressed in the nucleus in all tissues. HDAC1 and HDAC2 are primarily nuclear while HDAC3 and HDAC8 can shuttle in and out of the nucleus and many substrates including tumour suppressors, steroid receptors, and transcription factors have been identified as substrates which are deaceylated by Class I HDACs

Class II (related to yeast Hda1 gene)

- Includes **IIA** ; HDAC 3,5,7,9, **IIB** HDAC 6,10
- Associated with tissue specific functions, and deacetylate many nonhistone proteins.

Class III (related to the Sir2 gene)

- Known as the ‘sirtuins’ include SIRT 1-7
- Widely expressed in human tissues and regulate a variety of biological functions such as oxidative stress, DNA repair, metabolism, and aging.

Class IV

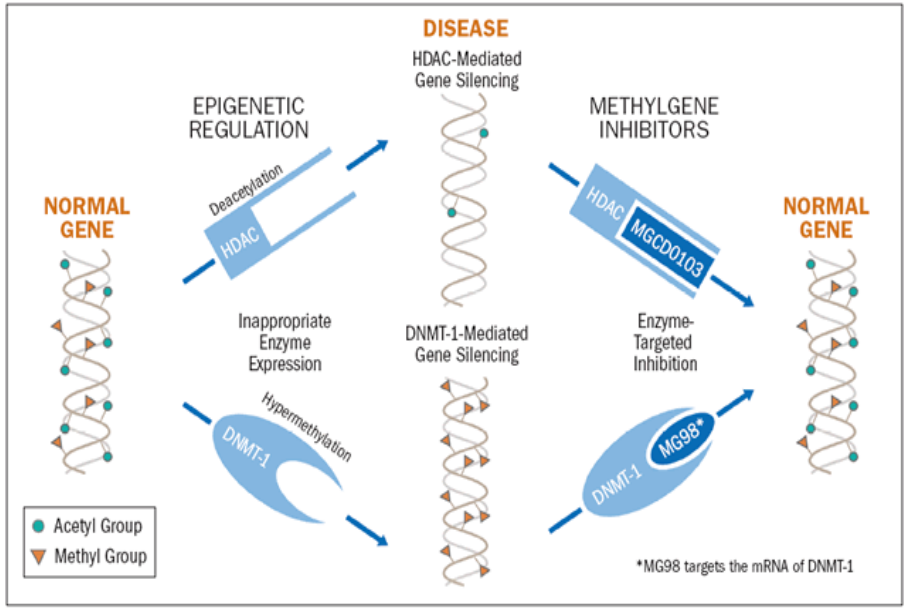
- Includes HDAC 11 has features of both Class I and II

Histone deacetylase inhibitors (HDAC-I); Classification

- The "classical" HDAC-I act exclusively on Class I, II and Class IV HDACs
- These classical HDAC-I are divided into several group & named according to the chemical moiety that binds to the zinc ion; listed in decreasing order of the typical zinc binding affinity.
  1. Hydroxamic acids or hydroxamates eg. vorinostat, belinostat, and panobinostat
  2. Cyclic peptides eg. romidepsin
  3. Benzamides eg.chidamide
  4. Short-chain fatty acids (electrophilic ketones, aliphatic acid compounds eg. phenylbutyrate and valproate
- The sirtuin Class III HDACs are dependent on NAD+ and are, therefore, inhibited by nicotinoamide as well as derivatives of NAD, dihydrocoumarin, naphthopyranone, and 2-hydroxynaphthaldehydes.

Histone deacetylase inhibitors (HDAC-I)

- Histone deacetylase (HDAC) inhibitors are epigenetic regulators that have enormous therapeutic potential
- Beyond their effects on the histone–DNA complex, HDAC inhibitors affect the acetylation status of many non-histone proteins such as chaperones, oncogenic transcription factors and other mediators of signal transduction
- Cause a myriad downstream affects that are beyond the scope of this lecture
- Long history of use in psychiatry and neurology as mood stabilizers and anti-epileptics – valproate
- Number developed for cancer therapy, In the late 1990s, studies in various leukaemias found HDACs involved in silencing of tumour suppressor genes
- More recently being investigated as possible treatments for malaria, HIV, inflammatory diseases, polycythaemia, myocardial infarct



HDAC ATTACK: By exploiting epigenetics, HDAC inhibitors offer a novel route to treating cancer and other conditions including neurodegeneration, inflammation, and diabetes.

HDAC-I as anti-cancer drugs

For over two decades, HDACs have been considered as attractive targets in drug discovery. A large number of HDAC inhibitors have been developed and patented, and a substantial amount has entered clinical trials. Moreover, the FDA has approved four HDAC inhibitors for the treatment of cancer patients in the US

Approved

- CTCL – vorinostat (FDA 2006) and romidepsin (FDA 2009)
- PTCL NOS – belinostat (PXD101) and romidepsin
- Myeloma – panobinostat (FDA , EMA 2015)

All pan HDAC-I

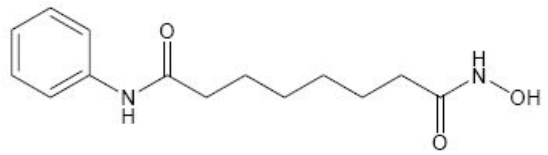
- Chidamide approved by China in 2015 for PTCL

Selective class I HDAC-I

Phase II Trials

- Mocetinostat (MGCD0103); including follicular lymphoma Hodgkin lymphoma and acute myeloid leukemia
- Abexinostat (PCI-24781); phase II trials for sarcoma & lymphoma
- Entinostat (MS-275); in phase II for Hodgkin lymphoma, lung cancer and breast cancer
- SB939; phase II trial for Recurrent or Metastatic Prostate Cancer
- Resminostat (4SC-201); RESMAIN phase II maintenance trial in advanced CTCL
- Givinostat (ITF2357); for refractory leukemias and myelomas
- Quisinostat (JNJ-26481585)

Vorinostat



- Orally bioavailable HDAC-I, single daily dose
- Vorinostat is a potent inhibitor of the activity of class I & II HDAC
- Induces expression of the p21 tumour suppressor gene
- Induce cell-cycle arrest and apoptosis in a broad range of cancer cell lines, including CTCL
- Surprisingly despite disruption of re-modelling of chromatin in cells may only alters expression of 2% of genes
- FDA approval for CTCL refractory to 2 systemics including bexarotene, Oct 2006 who have persistent/recurrent disease following the failure of 2 systemic therapies.
- Single-arm open-label trial US & Canada, enrolled 74 patients with stage IB+ CTCL failed two systemic therapies (RR 30%, duration 26 weeks); 33 patients RR 24.2%, duration 15.1 weeks

Duvic M, Talpur R, Ni X, Zhang C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood. 2007;109:31-39.
Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007;25:3109-3115.

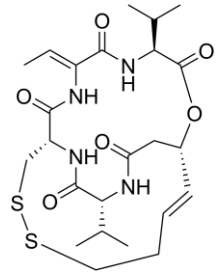
Adverse affects HDAC-I are similar, generally well-tolerated with different toxicity profile cf to classical chemotherapeutic agents. The primary toxicities nausea/vomiting/diarrhoea, fatigue, and a transient decrease in Hb, platelet and white cell counts. Due to asymptomatic ECG changes with prolongation of QT patients are closely monitored; however, no greater incidence of cardiac adverse events than other chemotherapeutic agents.

Table 2 Subramanian S et al; Clinical Toxicities of Histone Deacetylase Inhibitors. Pharmaceuticals 2010, 3, 2751-2767

Dose-limiting toxicities of HDAC inhibitors in phase I single-agent trials.

Agent	Dose-limiting Toxicities	Schedule
Pivanex	None	6 h IV qd ×5; 21 d
Sodium Phenylbutyrate	Somnolence, confusion, hypokalemia, hyponatremia, hyperurecemia	120 h IV; 21 d
Sodium Phenylbutyrate	Short-term memory loss, sedation, confusion, nausea/vomiting	0.5–2 h IV BID d 1–5 & 8–12; 28 d
Valproic acid	Neurocognitive impairment, neuroconstipation, somnolence	1 h IV qd ×5; 21 d
Belinostat	Fatigue, elevated creatinine, elevated uric acid, decreased potassium, status epilepticus, paresthesia, vasculitis, renal failure	30 min IV qd ×5; 21 d
Belinostat	Fatigue, atrial fibrillation, nausea/vomiting, diarrhea	30 min IV qd ×5; 21 d
Dacinostat	Transaminase, fatigue, atrial fibrillation, elevated creatinine, QTc prolongation, febrile neutropenia, hyperbilirubinemia, death	3h IV d 1–3; 21 d
Panobinostat	QTcF prolongation	30 min IV d1–7; 21 d
Panobinostat	Diarrhea	Oral TIW; 28 d
Vorinostat	Dehydration, thrombocytopenia, diarrhea, fatigue, ALT/AST, anorexia, nausea/vomiting	Oral qd or BID or BID d 1–3 qw
Vorinostat	Fatigue, nausea/vomiting, diarrhea	Oral TID or BID ×14 d; 21 d
Vorinostat	Fatigue	Oral BID ×5 d qw or BID ×14 d q21d
Vorinostat	Thrombocytopenia, anorexia, fatigue	Oral BID ×14 d; 21 d
Romidepsin	Thrombocytopenia, fatigue	4 h IV d 1, 8 & 15; 28 d
Romidepsin	Fatigue, nausea/vomiting, thrombocytopenia, atrial fibrillation	4 h IV d 1 & 5; 21 d
Romidepsin	Hypocalcemia, sick sinus syndrome, asymptomatic T-wave inversion	4 h IV d 1, 8 & 15; 28 d
Entinostat	Nausea, vomiting, anorexia, fatigue	Oral q14d
Entinostat	Fatigue, LDH, hypertriglyceridemia, hyperglycemia, hypoalbuminemia, hypocalcemia, infection, anorexia, nausea, somnolence, weakness/unsteady gait	Oral qw ×2; 28 d or qw ×4; 42 d
Entinostat	Hypophosphatemia, hypoalbuminemia, hyponatremia	Oral qw ×4; 42 d
Entinostat	Asthenia, hypophosphatemia	Oral q14d or qw ×3; 28 d
Mocetinostat	Fatigue, nausea/vomiting, diarrhea, mucositis, acid reflux, gastritis, hip/leg pain	Oral TIW
Mocetinostat	Fatigue, nausea/vomiting, anorexia, dehydration	Oral TIW ×2; 21 d

Romidepsin (depsipeptide)



- **Romidepsin** is a natural HDAC-I obtained from the bacteria Chromobacterium violaceum, intravenous, high inhibitory activity for class I histone deacetylases
- Romidepsin results in cell cycle arrest and apoptosis in lung carcinoma cells by increasing the level of $p21^{Waf1/Cip1}$ and hypophosphorylated Rb
- Another mechanism of romidepsin is the inhibition of the PI3K/AKT pathway seen in lung and colorectal cancer cells. Moreover, expression of the pro-survival nuclear factor-kappa B pathway genes are downregulated in cells isolated from CTCL/PTCL patients
- FDA Approval November 2009, indicated for the treatment of adult patients with CTCL or PTCL who have received at least one prior systemic therapy. EMA adopted a negative opinion 2012
- The clinical efficacy romidepsin was demonstrated in two non-comparative, multicentre, phase II trials in patients with relapsed (n=71, n=96), refractory or advanced CTCL; both trials, overall RR 34%, CR 6% with an acceptable tolerability profile. A sub-analysis in CTCL demonstrated an ORR of 45% in patients with tumoral mycosis fungoides and 60% in with the folliculotropic MF

Piekarz et al; Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with CTCL. J Clin Oncol. 2009 Nov 10;27(32):5410-7
Whittaker SJ et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol. 2010;28:4485-4491.
Foss et al. Clinical efficacy of romidepsin in tumor stage and folliculotropic mycosis fungoides. Clin Lymphoma Myeloma Leuk. 2016;16:637-643.

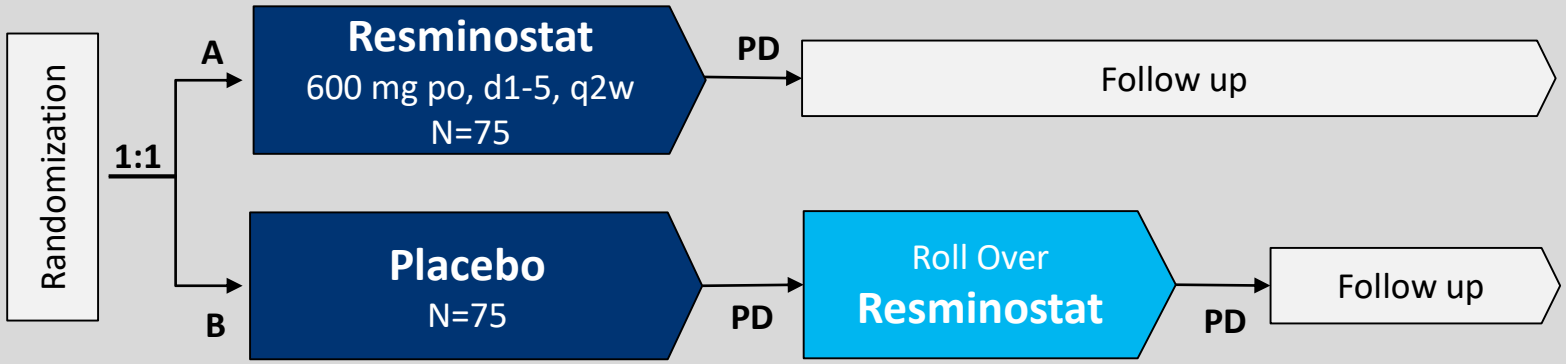
RESMAIN Study; A double blind, placebo controlled phase II trial to evaluate resminostat for maintenance treatment in advanced stage (IIB-IVB) mycosis fungoides (MF) or Sézary Syndrome (SS)

4SC EpiScience for Life

Patients

- Mycosis fungoides (stage IIB – IVB) or Sézary Syndrome
- CR, PR or SD 2-8 weeks after prior systemic therapy

Design Maintenance treatment



Primary endpoint: PFS
Key secondary endpoint: TTSW (Pruritus)

Secondary endpoints:
ORR, PFS2, Safety, HrQoL etc.

PD = progressive disease, po = per os, q2w = every 2 weeks
PFS = progression free survival, TTSW = time to symtom worsening, ORR = overall response rate
HrQoL = health related quality of life

University Hospitals Birmingham NHS
NHS Foundation Trust

Resminostat – Study Medication

- Orally available HDAC-inhibitor targeting HDAC class 1, 2b and 4
  - Film coated tablets
- Linear PK (t½ ~ 3,5 h)
- Dosing schedule: 600 mg po, d1-5, 2 week schedule
- Treatment duration until PD or unacceptable toxicity
- Most frequent AEs:
  - GI disorders (nausea, vomiting, diarrhoea),
  - Hematologic disorders (thrombocytopenia, anemia, neutropenia)
  - Fatigue, decreased appetite, dysgeusia
- Side effects were mainly mild to moderate, manageable and reversible
- No significant effects observed on the cardiovascular system

RESMAIN – Key Trial Objectives

Primary objective

- Does maintenance treatment with resminostat significantly increase **PFS** in advanced stage MF/SS patients?

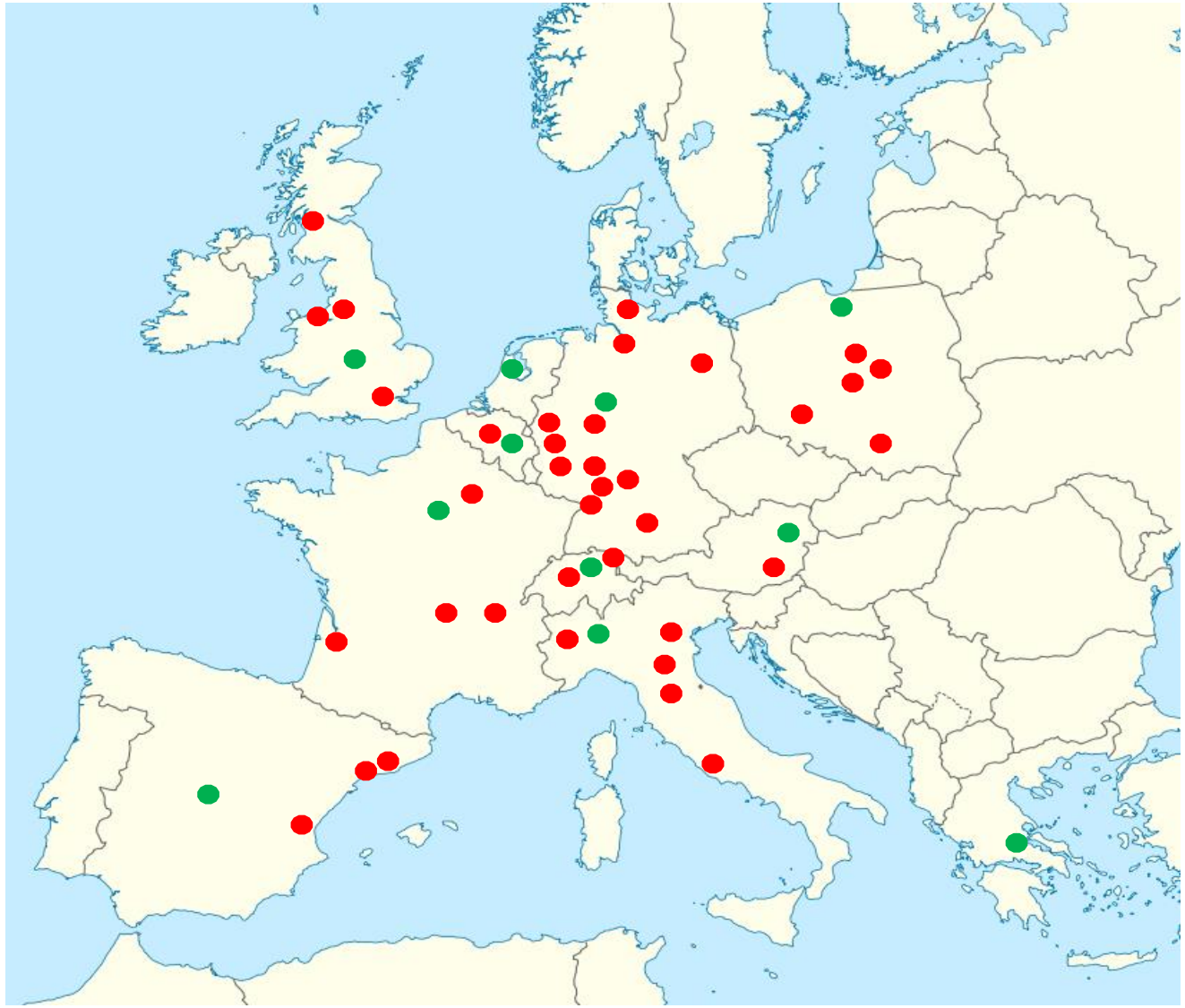
Key secondary objective

- Does maintenance treatment with resminostat significantly prolong **time to symptom (pruritus) worsening?**

Further objectives

- TTP, TTNT, ORR, OS, PK, Safety and HrQoL

RESMAIN – Sites



- Enrolment plan
  - 150 patients
  - 27 months
- Trial Centres
  - 54 Centres, in 11 European countries
- Planned Trial Period
  - FPI: Dec 2016
  - LPO: Dec 2019
- # Randomised May 2017
  - 66 patients
  - From 37 Centres in 11 countries

Site	Investigator	City	# pat randomized
UK01	J. Scarisbrick	Birmingham	8
BE01	S. Woei-A-Jin	Leuven	6
CH01	R. Dummer	Zurich	6
DE01	R. Stadler	Minden	3
FR01	M. Bagot	Paris	3
IT01	P. Quaglino	Turin	3
ES02	E. González Barca	Barcelona	3
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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ORIGINAL ARTICLE

Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium

P. Quaglino[1*†], M. Maule[2†], H. M. Prince[3,4], P. Porcu[5], S. Horwitz[6], M. Duvic[7], R. Talpur[7], M. Vermeer[8], M. Bagot[9], J. Guitart[10], E. Papadavid[11], J. A. Sanches[12], E. Hodak[13,14], M. Sugaya[15], E. Berti[16], P. Ortiz-Romero[17], N. Pimpinelli[18], O. Servitje[19], A. Pileri[20], P. L. Zinzani[21], T. Estrach[22], R. Knobler[23], R. Stadler[24], M. T. Fierro[1], S. Alberti Violetti[16], I. Amitay-Laish[13,14], C. Antoniou[11], C. Astrua[1], S. Chaganti[25], F. Child[26], A. Combalia[22], S. Fabbro[5], P. Fava[1], V. Grandi[18], C. Jonak[23], E. Martinez-Escala[10], M. Kheterpal[6], E. J. Kim[27], C. McCormack[3,4], T. Miyagaki[15], D. Miyashiro[12], S. Morris[26], C. Muniesa[19], V. Nikolaou[11], G. Ognibene[28], F. Onida[16], S. Osella-Abate[1], S. Porkert[23], C. Postigo-Llorente[17], C. Ram-Wolff[9], S. Ribero[1], K. Rogers[28], M. Sanlorenzo[1], R. Stranzenbach[24], N. Spaccarelli[27], A. Stevens[25], D. Zugna[2], A. H. Rook[27], L. J. Geskin[28], R. Willemze[8], S. Whittaker[26], R. Hoppe[29], J. Scarisbrick[25‡] & Y. Kim[29‡]

Global patterns of care in advanced stage mycosis fungoides/Sezary syndrome: a multicenter retrospective follow-up study from the Cutaneous Lymphoma International Consortium

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Annals of Oncology, Volume 28, Issue 10, 1 October 2017, Pages 2517–2525,

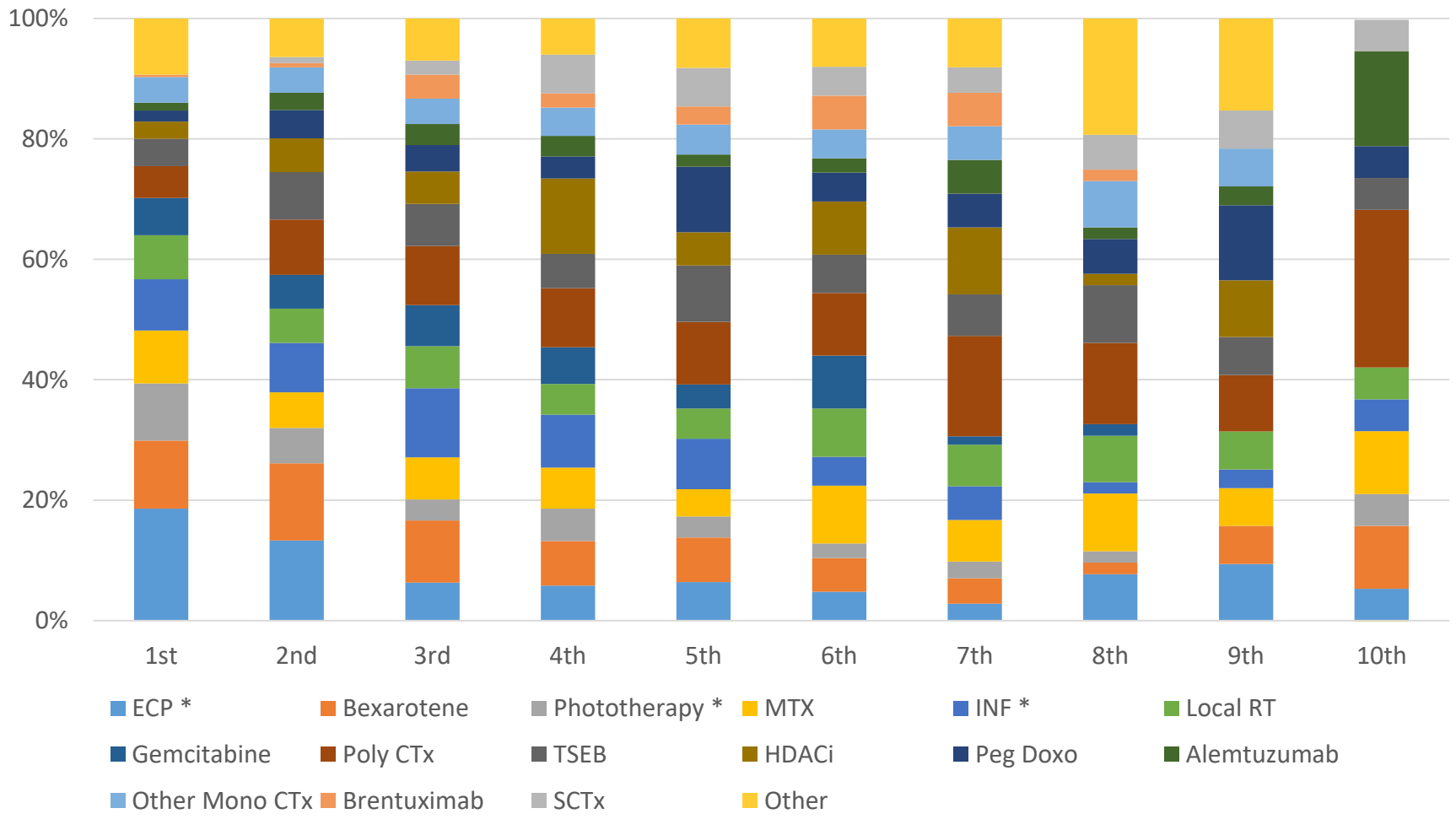
This study included 853 patients from 21 specialist centres (14 European, 4 USA, 1 each Australian, Brazilian and Japanese).

'large treatment heterogeneity with up to 24 different drugs, modalities or combinations used as first-line treatment'

'chemotherapy as first treatment is associated with a higher risk of death'

'significant differences were found between USA and non-USA centres, but these differences did not significantly impact on survival'

Real-world treatment; heterogeneity of treatment approaches were found, with up to 24 different modalities or combinations used as first-line and 31% of patients receiving 4 or more treatments



Modified from Quaglino et al, EJC, 2017

An increase with lines of therapy for poly-chemotherapy, TSEBT, HDACi, pegylated doxorubicin, new target therapies and transplantation . HDACi were used in all stages but, as expected, more frequently in USA (FDA approval),

Table 3. Distribution of treatments performed in time (percentage of patients treated with that therapy out of the total no. of patients treated in a given treatment line) in the first 10 treatment lines

Therapy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	*P* for trend
ECP (alone or in combination)	18.6	13.3	6.3	5.8	6.4	4.8	2.8	7.7	9.4	5.3	0.952
Bexarotene	11.3	12.8	10.3	7.4	7.4	5.6	4.2	1.9	6.3	10.5	0.001
Phototherapy (alone or in combination)	9.5	5.9	3.5	3.4	3.5	2.4	2.8	1.9		5.3	0.949
Methotrexate	8.8	5.9	7.0	6.8	4.5	9.6	6.9	9.6	6.3	10.5	0.232
Interferon	7.7	7.7	10.8	8.5	8.4	4.8	5.6	1.9	3.1	5.3	0.616
Local RT	7.3	5.7	7.0	5.1	5.0	8.0	6.9	7.7	6.3	5.3	0.442
Gemcitabine	6.2	5.6	6.8	6.1	4.0	8.8	1.4	1.9			0.378
Polychemotherapy	5.3	9.2	9.8	9.8	10.4	10.4	16.7	13.5	9.4	26.3	<0.0001
TSEBT	4.5	7.9	7.0	5.7	9.4	6.4	6.9	9.6	6.3	5.3	0.028
Chlorambucil	3.6	2.5	2.1	2.7	2.0	1.6		1.9			0.067
HDACi	2.9	5.6	5.4	12.5	5.5	8.8	11.1	1.9	9.4		<0.0001
Other Retinoids	2.7	2.7	1.9	1.0			1.4		3.1		0.029
Pegylated Doxorubicin	1.8	4.7	4.4	3.7	10.9	4.8	5.6	5.8	12.5	5.3	<0.0001
Alemtuzumab	1.3	2.9	3.5	3.4	2.0	2.4	5.6	1.9	3.1	15.8	0.006
Interferon plus Bexarotene or Other Retinoids	0.8	0.5	0.7	0.3							0.020
Other Monochemotherapy	0.7	1.7	2.1	2.0	3.0	3.2	5.6	5.8	6.3		<0.0001
Denileukin Diftitox	0.5	0.3	0.7	0.7	1.0		1.4	3.9	6.3		0.008
Brentuximab vedotin	0.4	0.7	4.0	2.4	3.0	5.6	5.6	1.9			<0.0001
Pralatrexate	0.2	0.8	1.4	2.0	1.0	1.6	1.4	5.8	3.1		<0.0001
Topical Nitrogen Mustard (Mechlorethamine)	0.1	0.2	0.5			1.6		1.9			0.001
Bevacizumab					0.5						–
Lenalidomide				0.7	1.5						–
Mogamulizumab		1.2	0.9	2.4	2.5	2.4	2.8	5.8	3.1		<0.0001
Transplantation		1.0	2.3	6.4	6.4	4.8	4.2	5.8	6.3	5.3	<0.0001
Zanolimumab		0.2	0.2	0.3				1.9			0.003

Where next HDAC-I?

- Combination therapy
  - Minimalise overlapping toxicities
  - Increase RR (synergistic effect)
    - PD-1/PDL-1
    - BCL2 – I
    - Proteasome inhibitor
    - Protein Kinase - I
    - CHOP
    - HDAC - I
- Maintenance therapy – stable disease as a measurable endpoint
- Precision medicine – biomarkers to select out the ~30% responders