BEXAROTENE - CONTAINING REGIMENS

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BEXAROTENE: PROPOSED MECHANISMS OF ACTION
(*rev. in Pileri A et al. Immunotherapy 2013*)

- **Th2 cytokine (IL4) downregulation**

- **induction of apoptosis**
  - bcl2-independent activation of caspase 3
  - decrease survivin levels
  - increased CD95 expression

- downregulation CCR4 expression by malignant T-cells

- increase of Treg levels

- increase chromosome 12 copies

EUROPEAN JOURNAL OF CANCER 42 (2006) 1014–1030

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Review

EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome ☆

Franz Trautinger[a], Robert Knobler[a,*], Rein Willemze[b], Ketty Peris[c], Rudolph Stadler[d], Liliane Laroche[e], Michel D'Incan[f], Annamari Ranki[g], Nicola Pimpinelli[h], Pablo Ortiz-Romero[i], Reinhard Dummer[j], Teresa Estrach[k], Sean Whittaker[l]

Table 5 – Recommendations for second-line treatment of MF (stages IA, IB, and IIA)[a]

Recommended treatments	Level of evidence	References
Systemic therapies		
Oral bexarotene	B 1b	[65]
IFN-α monotherapy	B 2b	[55,99,100,102,105]
IFN-α tretinoids	B 1b	[61,80,98,104]
Denileukin diftitox	B 1b	[30,72]
Low-dose MTX	C 4	[106]
Systemic therapies + SDT		
IFN-α + PUVA	B 1b	[80,109,110,113]
Retinoids + PUVA	C 4	[114]
Bexarotene + PUVA	C 4	[115]

Table 7 – Recommendations for second-line treatment of MF (stage IIB)[a]

Recommended treatments	Level of evidence	References
Bexarotene	B 2b	[120]
Chemotherapy	C 4	[49,50,103,121]
Denileukin diftitox	B 1b	[72]

Table 9 – Recommendations for second-line treatment of MF (stage III)[a]

Recommended treatments	Level of evidence	References
Bexarotene	B 2b	[120]
Chemotherapy	C 4	[15,16,121,103,51,130]

Table 12 – Recommendations for second-line treatment of SS[a]

Recommended treatments	Level of evidence	References
Bexarotene	B 2b	[120]
Chemotherapy	C 4	[52,130,137]
Alemtuzumab	C 2b	[67,135]
MTX	C 4	[138]

Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)

Part II. Prognosis, management, and future directions

Sarah I. Jawed, BA,[a] Patricia L. Myskowski, MD,[a] Steven Horwitz, MD,[b] Alison Moskowitz, MD,[b] and Christiane Querfeld, MD, PhD[a]
New York, New York

J Am Acad Dermatol
February 2014

Refractory early stage MF (stage IA-IIA)	
Combination therapy	PUVA or NBUVB and IFNα (low-dose) PUVA or NBUVB and bexarotene (low-dose)

Advanced MF/SS (stage IIB-IVB)	
Combined therapy	IFNα and phototherapy IFNα and retinoids/ rexinoids Retinoid and phototherapy ECP and IFNα ECP and retinoids/ rexinoids

SYSTEMIC THERAPIES

Key points

- **Single-agent systemic therapy (eg, bexarotene) is often used after skin-directed therapy is inadequate or in cases of advanced disease**
- **Immunomodulators, such as interferons and retinoids, are commonly used as first-line monotherapy in advanced mycosis fungoides and are also used in low-dose combination with topical agents**

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REVIEW

The utility of bexarotene in mycosis fungoides and Sézary syndrome

This article was published in the following Dove Press journal:
OncoTargets and Therapy
3 February 2015
Number of times this article has been viewed

Manisha R Panchal
Julia J Scarisbrick

Department Dermatology, University Hospital Birmingham, Birmingham, UK

Abstract: Cutaneous T-cell lymphoma (CTCL) is an umbrella term that encompasses a group of neoplasms that have atypical T-lymphocytes in the skin. Mycosis fungoides (MF) is the most common type of CTCL and Sézary syndrome (SS) is the leukemic form. Treatment for CTCL is dependant on the stage of disease and response to previous therapy. Therapy is divided into skin-directed treatment, which tends to be first line for early-stage disease, and systemic therapy, which is reserved for refractory CTCL. Bexarotene is a retinoid and was licensed in Europe in 2002 for use in patients with advanced disease that have been refractory to a previous systemic treatment. We review the use of bexarotene as monotherapy and in combination with other treatments.

Keywords: retinoid, CTCL, cutaneous T-cell lymphoma

Table 2 Single and multicenter studies of bexarotene as monotherapy and combination therapy

Study	Study type n	Stage of disease	Treatment	Inclusion criteria	Exclusion criteria	Results
Ten-year experience of bexarotene therapy for CTCL[35]	Retrospective cohort study N=37	Early stage (IA–II): 26 Advanced: 3 Sézary syndrome: 4 Peripheral T-cell lymphoma: 1 Subcutaneous panniculitis: 2	Majority had previous treatments 35 patients started bexarotene as monotherapy 15/37 patients underwent combination therapy	None stated	None stated	75% ORR was observed 83% ORR in patients with early-stage disease 33% ORR in patients with advanced disease
Phase II study of gemcitabine and bexarotene (GeMBEX) in the treatment of CTCL[37]	Single arm, multicenter, Phase II trial N=36	Stage IB–IVB Histologically confirmed CTCL Majority of patients had advanced-stage disease with 30.6% T3 patients	Gemcitabine (2′2′-difluorodeoxycytidine) and bexarotene combination treatment	Age >18 years Failure of skin-directed therapy Life expectancy >6/12 ECOG <1 Adequate organ function	Primary cutaneous CD30+ anaplastic large cell lymphoma Previous failure of bexarotene treatment History of pancreatitis, biliary tract disease, or uncontrolled diabetes	80% of patients demonstrated a reduction in mSWAT score Study stopped as patients did not achieve the desired response at interim analysis
Efficacy and safety of bexarotene combined with PUVA compared with PUVA treatment alone in stage IB and IIA MF: final results from EORTC Phase III RCT[38]	Randomized Phase III trial	Stage IB–IIA	PUVA + bexarotene vs PUVA alone	Stage IB–IIA disease	None stated	22% CR was observed in the control group receiving PUVA alone 31% CR was observed in the cohort receiving combination therapy No significant difference in the RR between the groups. Overall treatment duration was shorter in the combination therapy group
Vorinostat combined with bexarotene for treatment of cutaneous T-cell lymphoma: in vitro and Phase I clinical evidence supporting augmentation of retinoic acid receptor/retinoid X receptor activation by histone deacetylase inhibition[39]	Open-label, non-randomized, multicenter Phase I trial N=23	Stage IB or higher disease previously refractory to systemic therapy	Vorinostat and bexarotene Different dosing regime	18 years of age, CTCL (stage IB or higher) with progressive, persistent, or recurrent disease refractory to at least one systemic therapy (not including bexarotene), life expectancy of at least 3 months persistent disease was defined as a failure to achieve at least 50% disease improvement after at least 3 months of therapy	Uncontrolled hyperlipidemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, hypervitaminosis A, uncontrolled thyroid disease Risk factors for (or history of) pancreatitis Prior treatment with any HDAC inhibitor, received known CYP3A4 inhibitors within 2 weeks of the study starting, received an allogeneic transplant, currently using colony-stimulating factors or had a clinically significant medical illness	PR in four patients, unconfirmed response in two patients, and stable disease in 15 patients
Evaluation of the efficacy of the combination of oral bexarotene and methotrexate for the treatment of early-stage treatment–refractory CTCL[30]	Retrospective study N=12	All patients that were treated with combination therapy between 2000–2007 Stage IA–IIB	Bexarotene and methotrexate	None stated	None stated	CR in one patient (8%), seven had a PR (58%), and four had no response (33%)

Abbreviations: CR, complete response; CTCL, cutaneous T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; HDAC, histone deacetylase; MF, mycosis fungoides; mSWAT, multiple sequence web viewer and alignment tool; ORR, overall response rate; PR, partial response; PUVA, psoralens and ultraviolet A; RCT, randomized controlled trial; RR, relative risk.

Low-dose Bexarotene +PUVA

Among the patients treated at our phototherapy center, a CR was achieved with less cumulative Joules (133) than our previously institutional experience with PUVA monotherapy (157)

…The RR was 87% with a CR of 53%...

The results with Bexarotene 150 mg were similar to 300 mg

The lower dose was generally better tolerated

Serious photoreactions were not reported

These preliminary findings are encouraging to support the further exploration of this combination modality

USA, multicentric, dose-randomized ***Guitart J 2006***

Multicentric Study Group of Cutaneous Lymphoma

Florence Lymphoma Group

MF stage IB/IIA

Refractory/Relapsed after PUVA +/- IFN

Low dose Bexarotene plus PUVA

Induction

2 ° Intens — *MR, SD, Prog*

CR,VGPR, PR

Bexa 300 mg/die

Maintainance

1 ° Intens. — *VGPR, PR, MR, SD*

1 mese

CR

Bexa 225 mg/die

Maintainance

1 ° phase — *VGPR, PR, MR, SD*

CR

Bexa 150 mg/die

Maintainance

PUVA 3/sett	PUVA 2/sett	PUVA 1/sett	PUVA 1/2sett	PUVA 1/mese
1 month	2 mos	2 mos	2 mos	4 mos

	After induction		End Maintainance	
Response	N.	%	N.	%
OR	12	100	12	100
CR	5	42	6	50
VGPR	6	50	5	42
PR	1	8	1	8

Rupoli S et al, submitted

STUDY DESIGN

STANDARD DOSE: 300 mg/m^2/die

150 mg/die (300mg/die if BSA>2m^2) for 2 weeks,
then 300 mg/die (450 mg/die if BSA> 2 m^2) for 6 mos

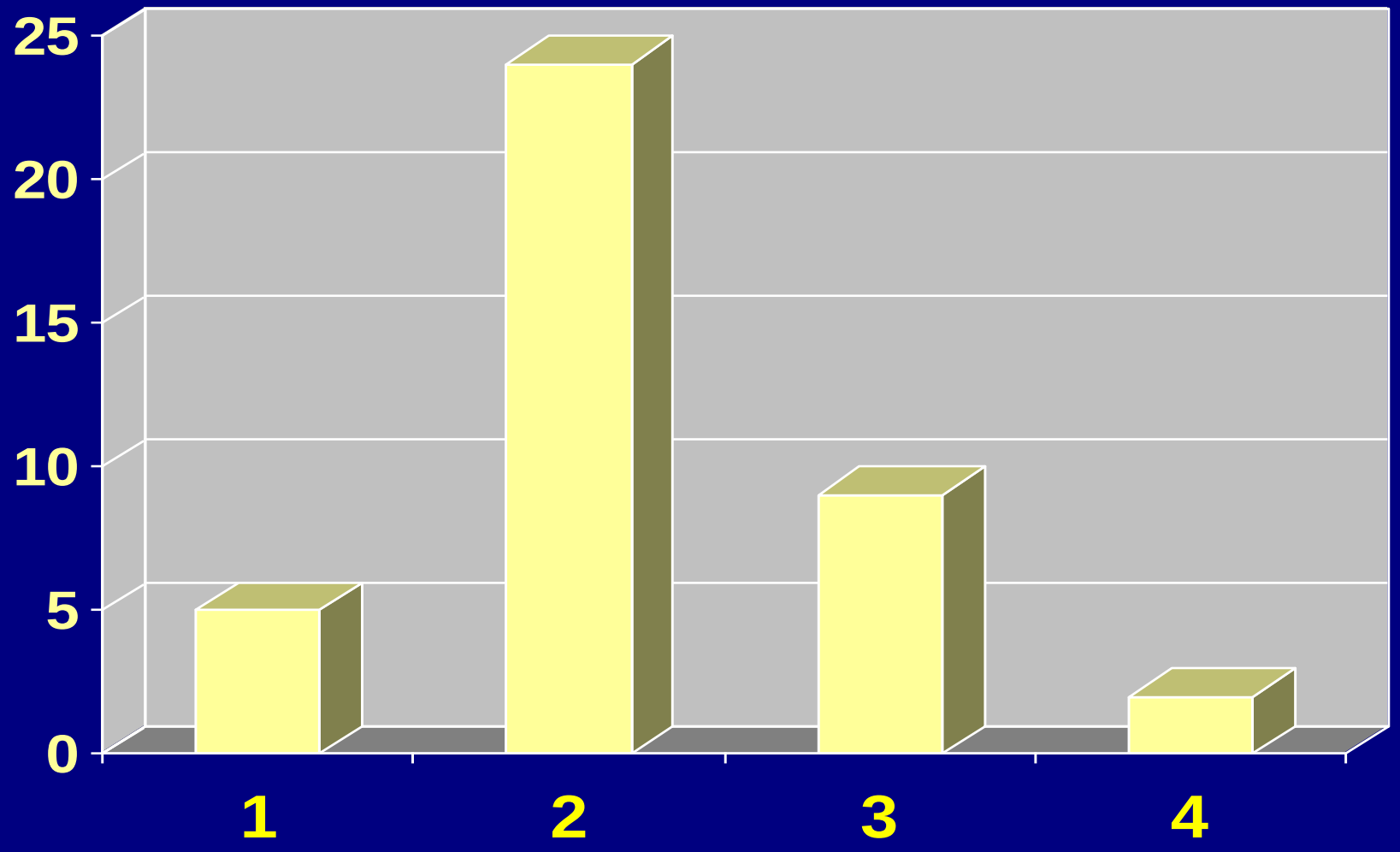
MF stage IIB-IV, SS, PTL-U .

Bexarotene: start 6 weeks after the end of previous non-SDT treatments

PATIENTS' PROFILE

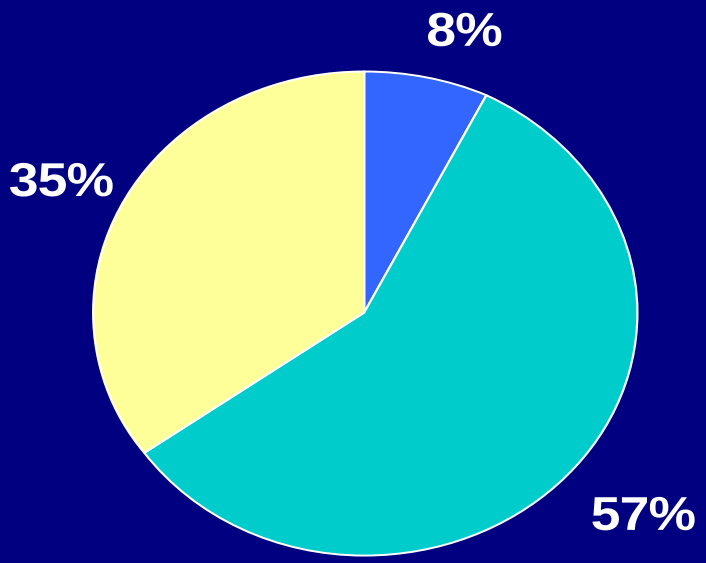
Gender	19F; 21 M
Age (range)	63 (32-82)
Diagnosis	5 SS, 5 PTL-U, 30 MF
MF stages	20 IIB 3 IIIA 2 IIIB 1 IVA1 3 IVA2 1 IVB

NUMBER PREVIOUS TERAPHIES



BEXA-MAINTAINANCE

BEFORE

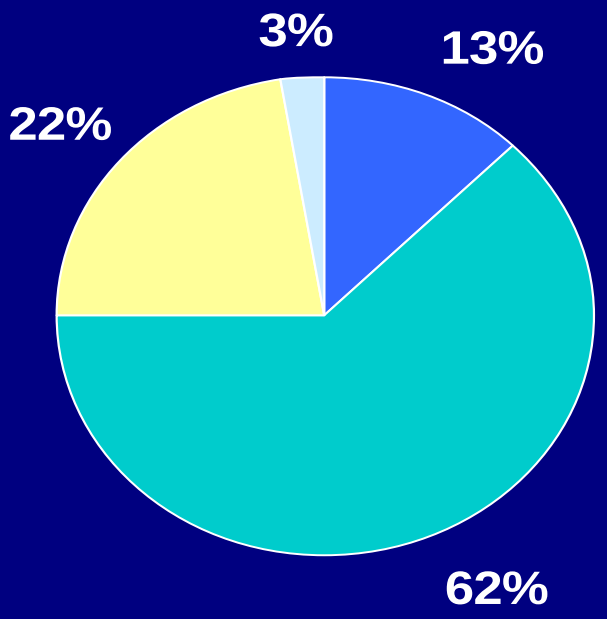


CR: 8%

PR: 57%

RR: 65%

AFTER



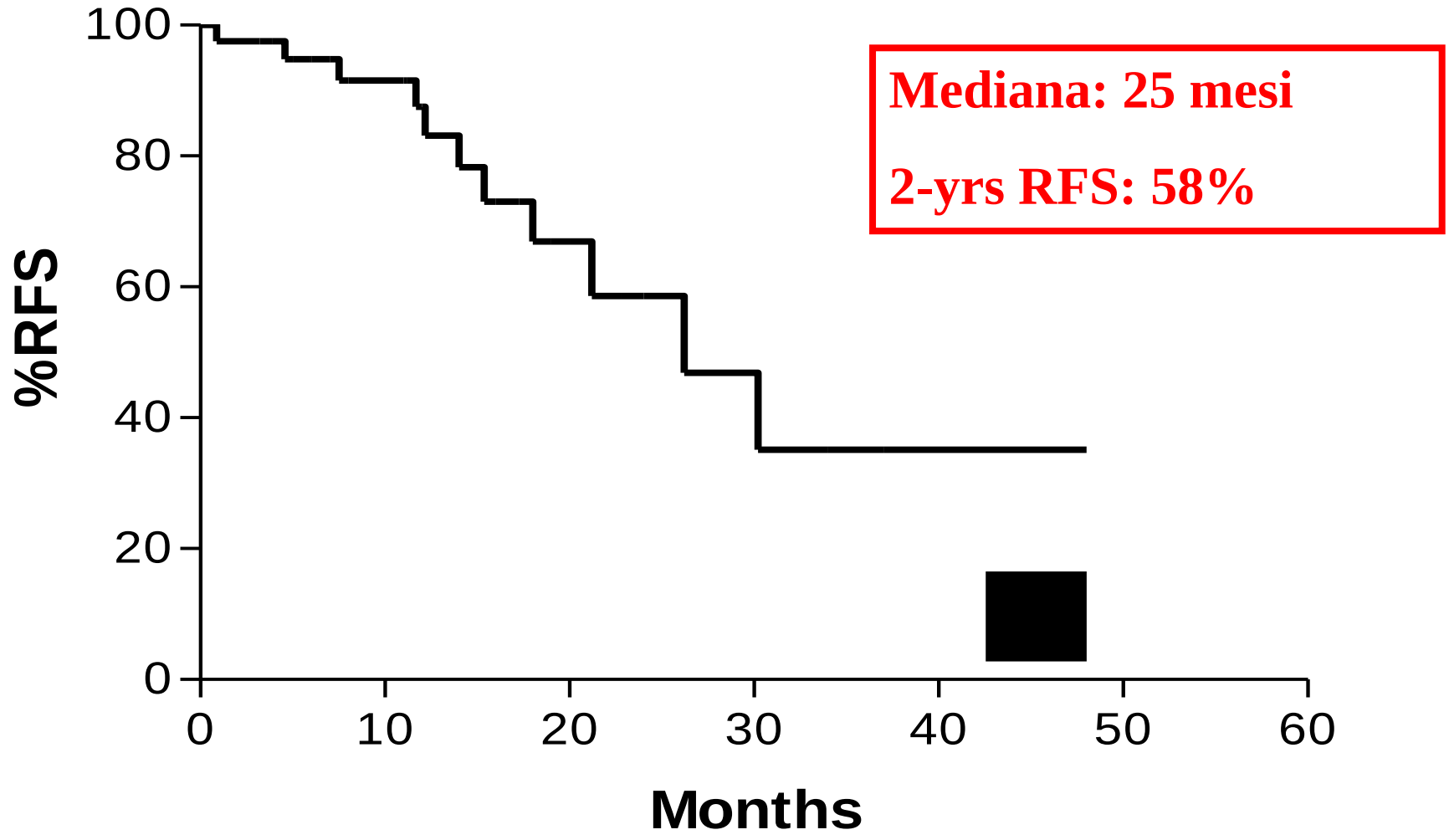
CR: 13%

PR: 62%

RR: 75%

RC
RP
SD
PD

RELAPSE-FREE SURVIVAL



Gemcitabine

75% ORR in front line
[Marchi et al. 2005; Duvic et al. 2006]

Peg-Doxo

56 – 88% ORR (17 - 44% CR)
[Wollina et al. 2003; Pulini et al. 2007; Quereux et al. 2008]

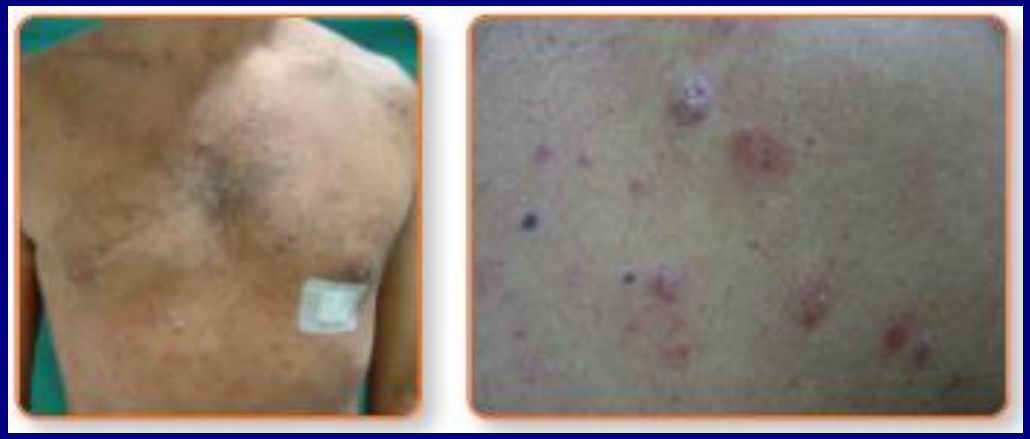
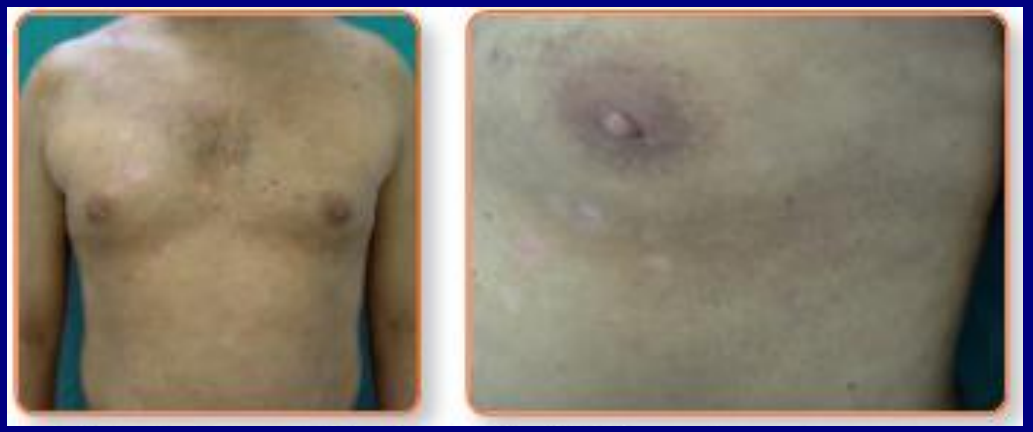
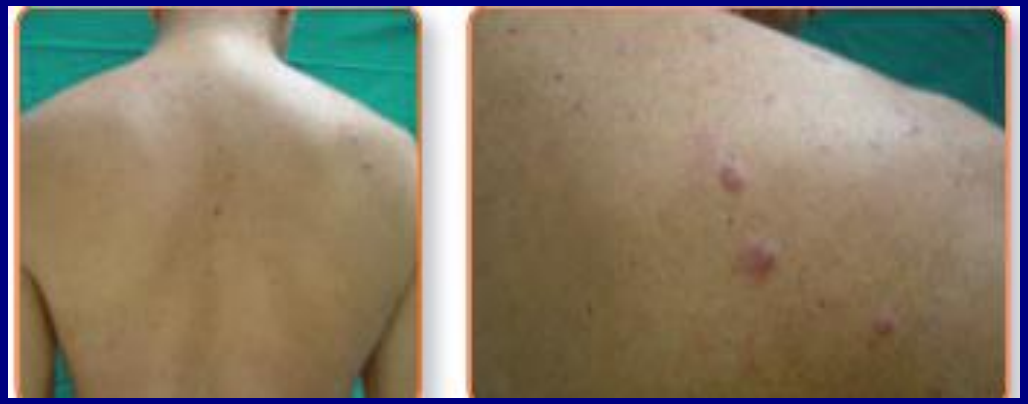
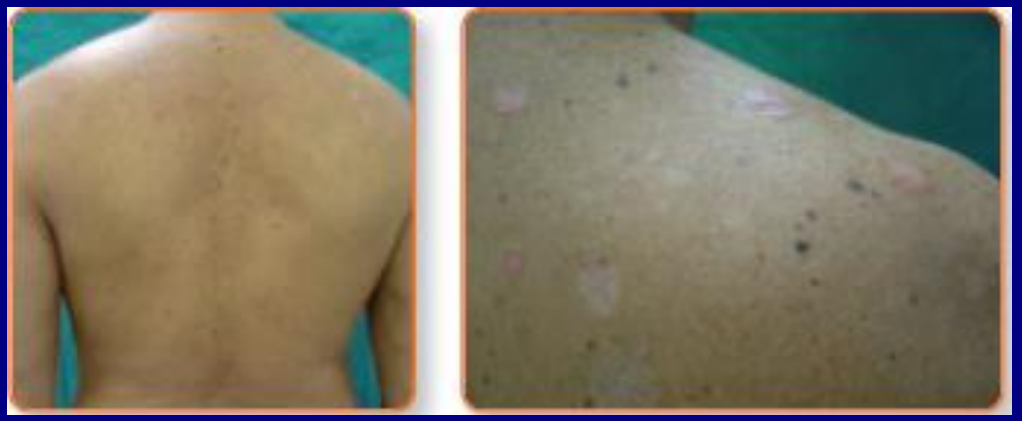
G ITAL DERMATOL VENEREOL 2012;147:573-9

Combination treatment in CTCL: the current role of bexarotene

C. DELFINO [1], V. GRANDI [1], A. PILERI [2], S. RUPOLI [3], P. QUAGLINO [4], R. ALTERINI [5]
G. GOTERI [6], L. CANAFOGLIA [3], N. PIMPINELLI [1]; FOR THE GRUPPO ITALIANO LINFOMI CUTANEI

Peg-DOXO + oral BEXAROTENE: preliminary results

- Peg-Doxo 20 mg/m(2) i.v. every 4 weeks → if SD add Bexarotene 150 mg/m(2)/die p.o. until best response → if response continue with bexa only
- 7 patients (4 MF stage IIB and 3 PTL-NOS, relapsed after or recalcitrant to previous treatments)
- clinical response in 9/11 pts. (3 CR, 2 VGPR, 2 PR; one discontinued after the 1st peg-doxo infusion due to untolerable skin toxicity)
- max. PFS = 23 mos. to date

Ann Hematol
DOI 10.1007/s00277-014-2121-1

ORIGINAL ARTICLE

Long-term outcome of patients with advanced-stage cutaneous T cell lymphoma treated with gemcitabine

Cinzia Pellegrini · Vittorio Stefoni · Beatrice Casadei · Roberto Maglie · Lisa Argnani · Pier Luigi Zinzani

Received: 1 April 2014 / Accepted: 26 May 2014

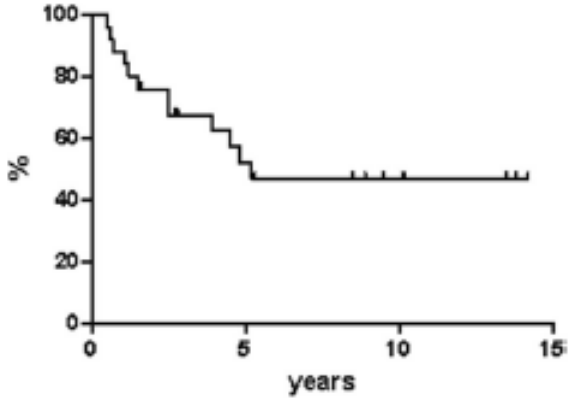


Fig. 1 Overall free survival

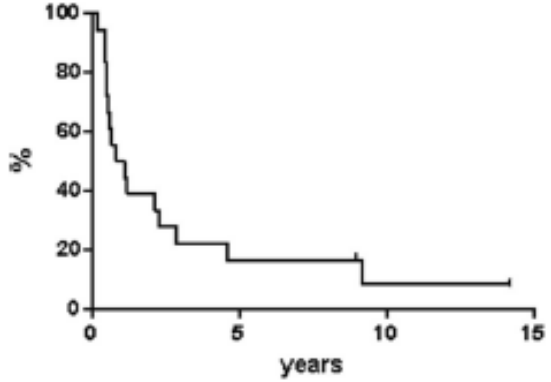


Fig. 2 Progression-free survival

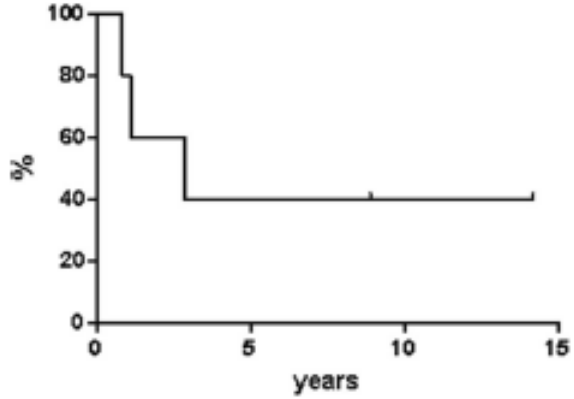


Fig. 3 Disease-free survival

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REVIEW

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Manisha R Panchal
Julia J Scarisbrick

Department Dermatology, University Hospital Birmingham, Birmingham, UK

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FULL PAPER

BJC

British Journal of Cancer (2013) 109, 2566–2573 | doi: 10.1038/bjc.2013.616

Keywords: cutaneous T-cell lymphoma; mycosis fungoides; bexarotene; gemcitabine

Phase II study of gemcitabine and bexarotene (GEMBEX) in the treatment of cutaneous T-cell lymphoma

T Illidge*[,1], C Chan[1], N Counsell[2], S Morris[3], J Scarisbrick[4], D Gilson[5], B Popova[2], P Patrick[2], P Smith[2], S Whittaker[6] and R Cowan[1]

[1]*Manchester Academic Health Science Centre, Institute of Cancer Sciences, University of Manchester, The Christie, Wilmslow Road, Manchester, M20 4BX, UK;* [2]*Cancer Research UK and University College London Cancer Trials Centre, 90 Tottenham Court Road, London W1T 4TJ, UK;* [3]*Guys and St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK;* [4]*University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Medical Centre, Queen Elizabeth Hospital, Birmingham B15 2TH, UK;* [5]*St James's Institute of Oncology, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK and* [6]*St John's Institute of Dermatology, Guys and St Thomas NHS Foundation Trust, Lambeth Palace Road, London SE1 7EH, UK*

Background: Both gemcitabine and bexarotene are established single agents for the treatment of cutaneous T-cell lymphoma (CTCL). We investigated the feasibility and efficacy of combining these drugs in a single-arm phase II study.

Methods: Cutaneous T-cell lymphoma patients who had failed standard skin-directed therapy and at least one prior systemic therapy were given four cycles of gemcitabine and concurrent bexarotene for 12 weeks. Responders were continued on bexarotene maintenance until disease progression or unacceptable toxicity.

Results: The median age was 65 years, stage IB ($n=5$), stage IIA ($n=2$), stage IIB ($n=8$), stage III ($n=8$) and stage IVA ($n=12$), 17 patients were erythrodermic, 17 patients were B1, and 10 patients were both erythrodermic and B1. Thirty (86%) patients completed four cycles of gemcitabine. In all, 80.0% of patients demonstrated a reduction in modified Severity-Weighted Assessment Tool (mSWAT) score although the objective disease response rate at 12 weeks was 31% (partial response (PR) 31%) and at 24 weeks 14% (PR 14%, stable disease (SD) 23%, progressive disease (PD) 54%, not evaluable 9%). Median progression-free survival was 5.3 months and median overall survival was 21.2 months.

Conclusion: The overall response rate of the combination did not reach the specified target to proceed further and is lower than that previously reported for gemcitabine as a single agent.

Table 1. Baseline characteristics, enrolled patients

	GemBex ($n = 36$)[a]
Variable	Median (range)
Age at random assignment, years	65 (38–83)
Pruritis (0–10 continuous scale)	7.5 (0–10)
mSWAT score	103 (13–203)
	No. (%)
Gender	
Male	25 (69.4)
Female	11 (30.6)
ECOG performance status	
0	20 (55.6)
1	16 (44.4)
Clinical stage at study entry	
Ib	5 (13.9)
IIa	2 (5.6)
IIb	8 (22.2)
III	8 (22.2)
IVa	13 (36.1)

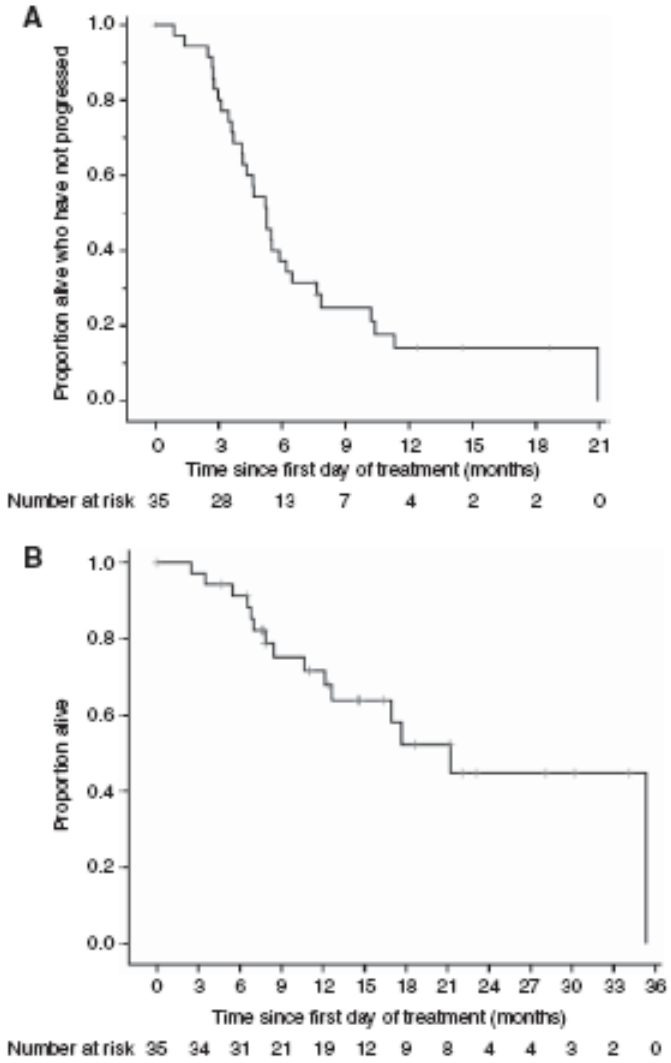

Figure 4. (A) Progression-free and (B) overall survival curves, as-treated population.

Gem 1000 mg/mq i.v. days 1,8 every 21 (4 cycles) + Bexa 300 mg/mq/die

Weaknesses:

a. 36.1% pts in stage IV

b. heavily pretreated

c. poorly tolerated Bexa dosage

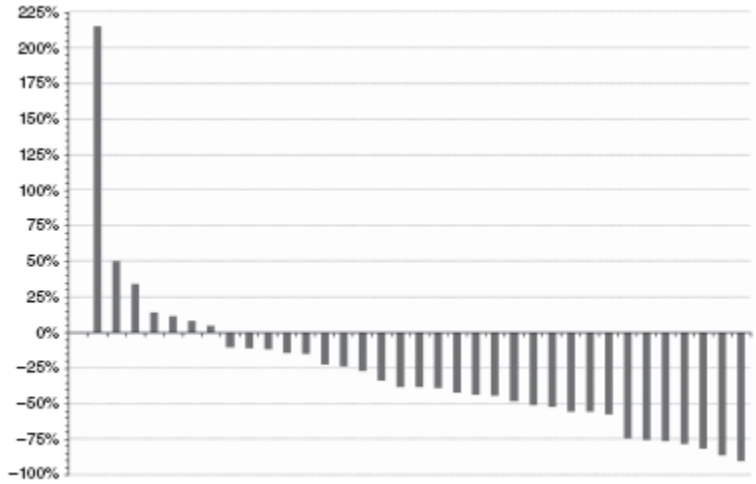

Figure 3. Waterfall plot of percentage change from baseline in mSWAT score at the end of combination treatment, as-treated population.

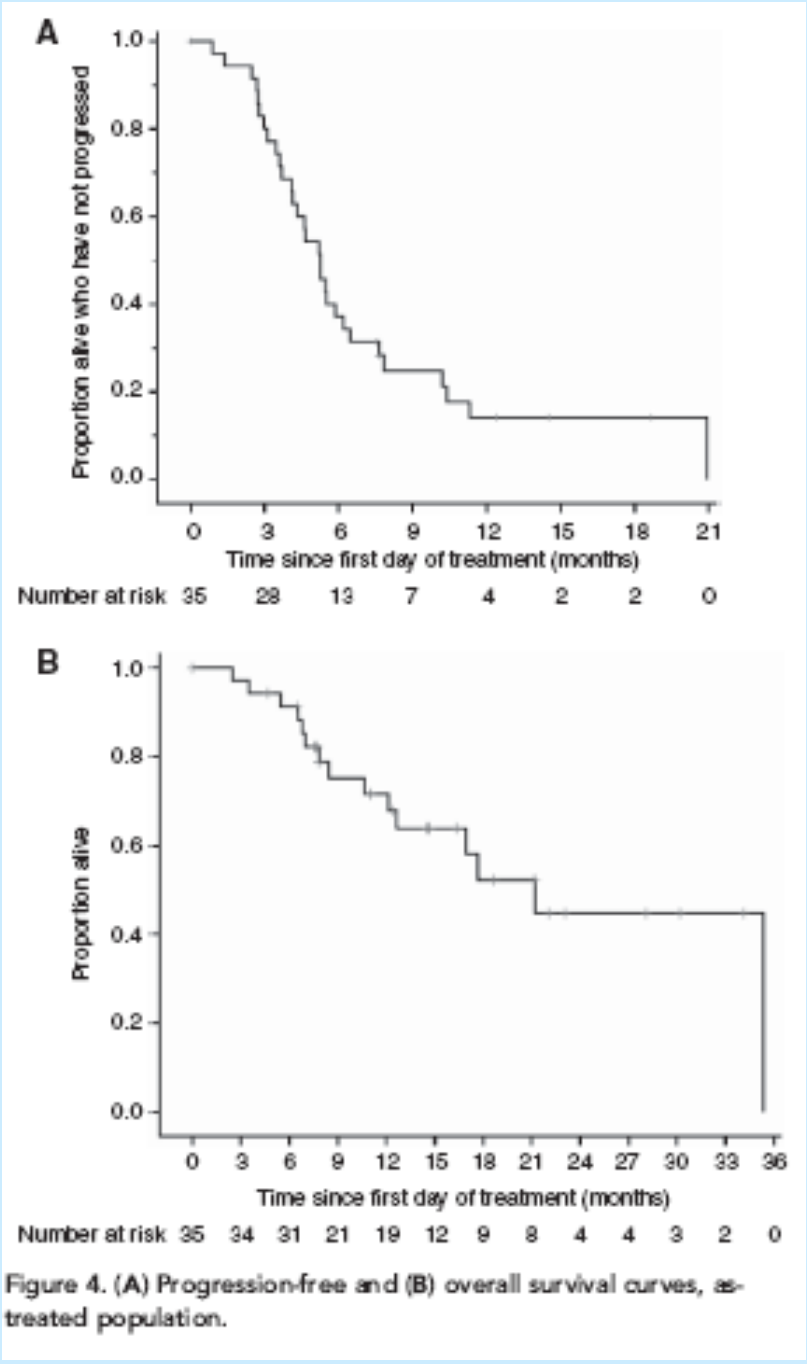

Figure 4. (A) Progression-free and (B) overall survival curves, as-treated population.

MONOCENTRIC PILOT STUDY:

9 patients (6 MF stage IIB, 3 PTL-U)

Gemcitabine (1200 mg/m^2 i.v. days 1,8 every 28) + Bexarotene (150 mg/m^2/die p.o.) until best response, then Bexa only until progression.

8/9 (88.8%) ORR – 2 CR, 4 VGPR e 2 PR; 1 SD.

Median PFS = 19 months (max 26) to date

proposal of prospective, multicenter study under evaluation by FIL board