Pralatrexate Plus Bexarotene in Relapsed/Refractory Cutaneous T-cell Lymphoma

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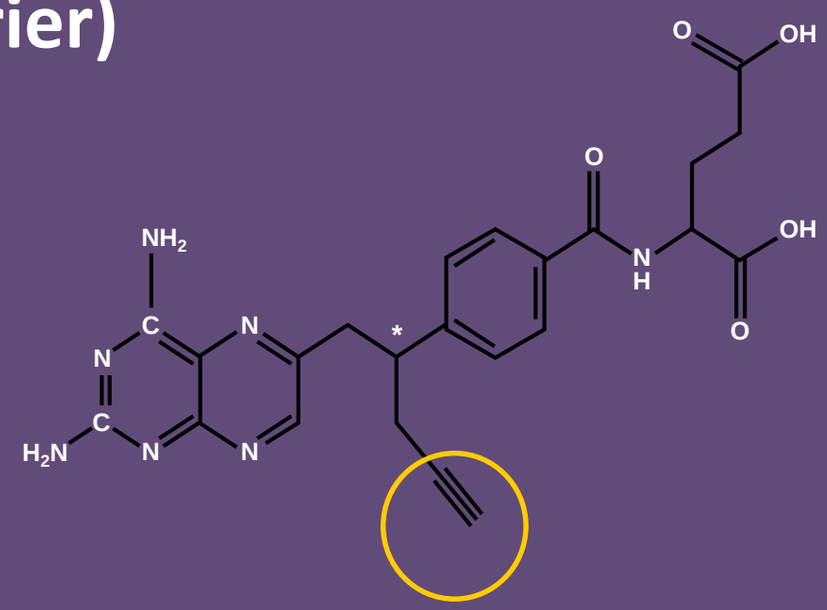
Pralatrexate: Mechanism of Action

- **Rationally designed antifolate for preferential uptake and retention by tumor cells**

  Uptake via RFC-1 (reduced folate carrier)

  Retention due to polyglutamation by

  FPGS (folylpolyglutamyl synthetase)



10-propargyl derivative of 10-deazaaminopterin

- **TARGET: DHFR inhibition**

  Blocks DNA synthesis → tumor cell death

RFC, reduced folate carrier
FPGS, folylpolyglutamyl synthetase
DHFR, dihydrofolate reductase

Pralatrexate Clinical Trials

PTCL – PROPEL (N=111)

Efficacy and safety in patients with relapsed or refractory PTCL & MF-LCT led to pralatrexate approval in the US at 30mg/m2 6 of 7 weeks. Durable responses associated with prolonged survival suggest use in 2nd line PTCL.

O'Connor et al. JCO 2011: 29, 1182-9.

CTCL -Dose de-escalation trial (N= 54)

Heavily pre-treated patients with reftactory or relapsed CTCL at 30 mg/m^2, 20 mg/m^2, 15 mg/m^2 & 10 mg/m^2 weekly. Intravenous push over 30 sec to 5 min for 3 of 4 weeks.

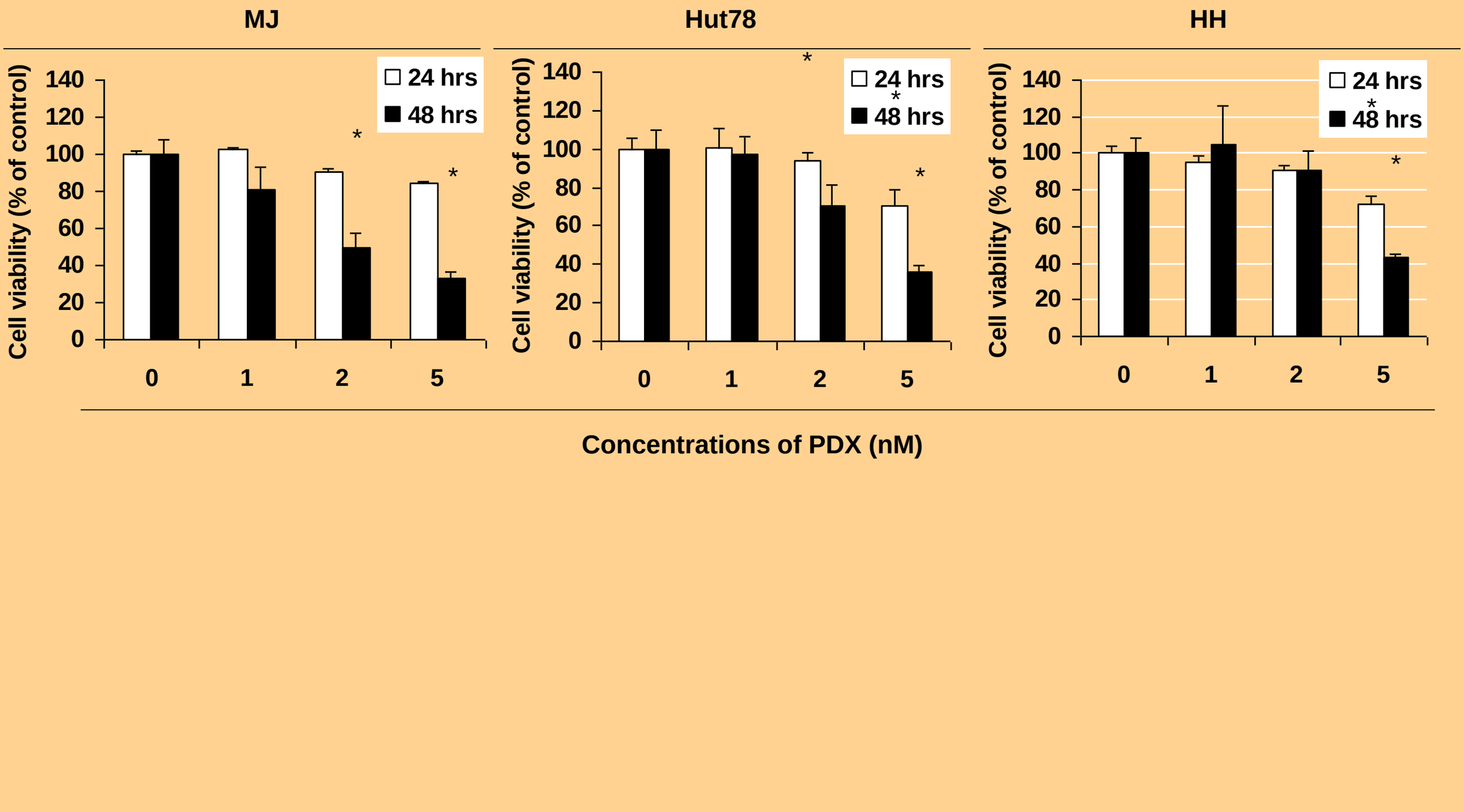
29 pts on15 mg/m2 3/4 weeks (ORR 45%)

Horowitz et al. Blood 2012:119:4115

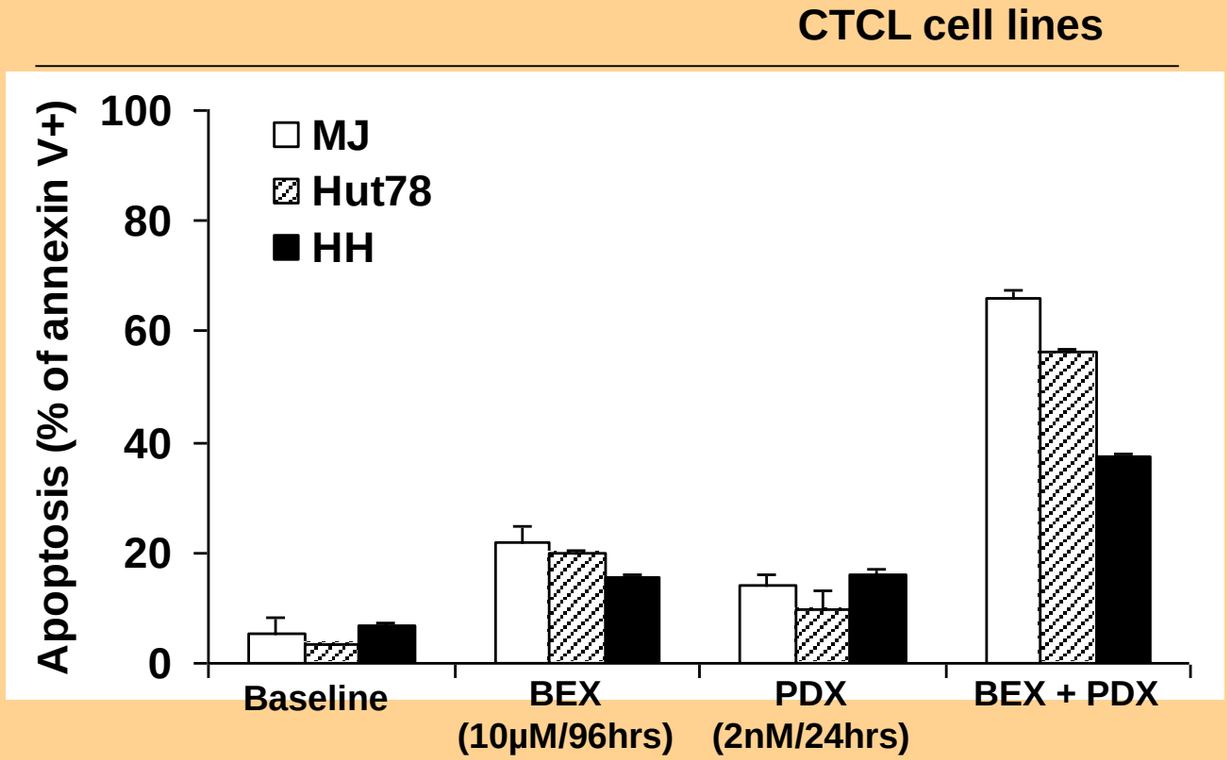
Praletrexate single agent response rate - 4/12 (33%)MDA

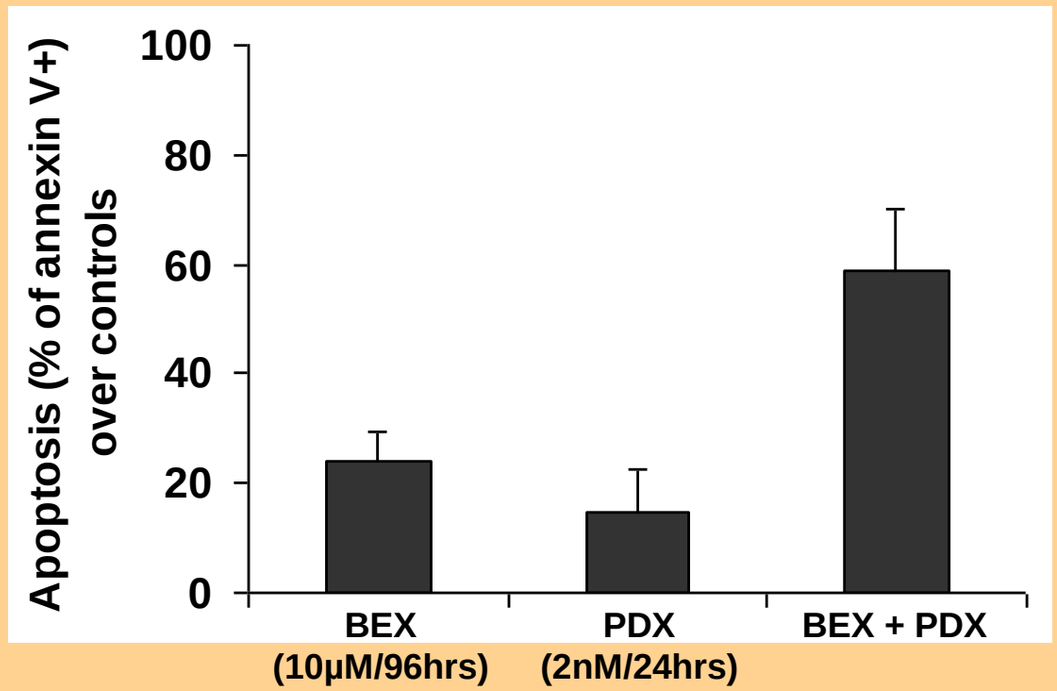
Pt ID	Age	Sex	Race	Starting dose (mg/m^2)	# of cycles	Response
1	55	F	Black	30	7	**PR**
2	73	M	White	30	23	**PR**
3	47	M	White	30	2	PD
4	72	M	White	20	5	SD
5	52	F	White	20	1	SD
6	77	M	White	20	6	SD
7	71	F	White	15	2	PD
8	57	F	White	15	10	**PR**
9	80	M	White	15	13	**PR**
10	68	M	White	10	1	SD
11	36	M	Black	10	7	SD
12	73	M	White	10	2	SD

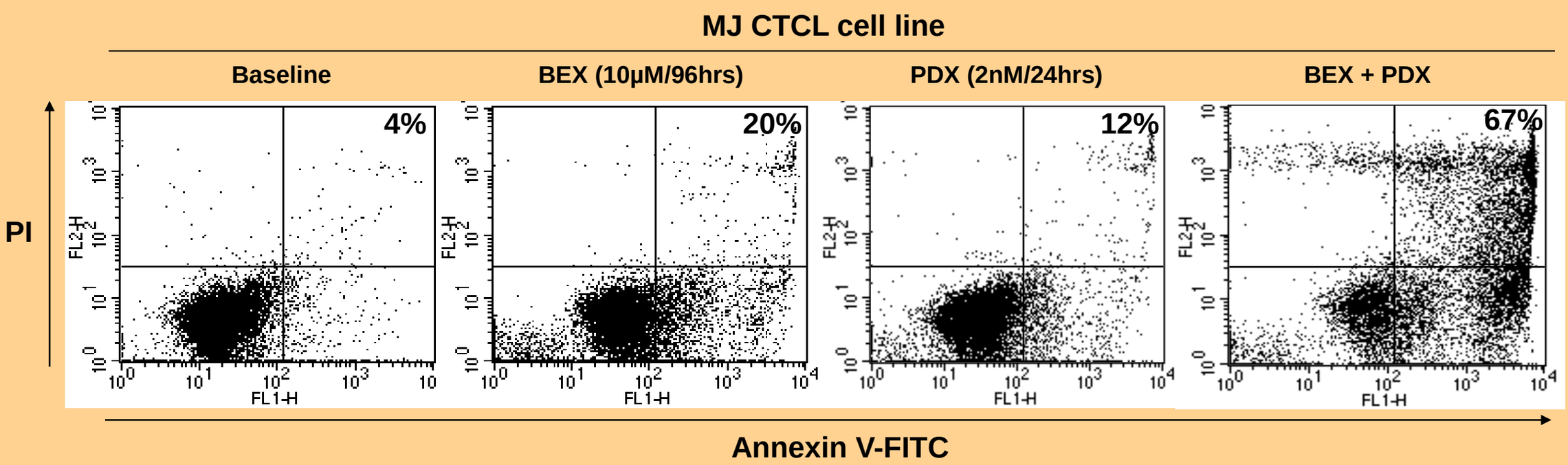
PDX inhibits cell growth of CTCL cell lines At 24 and 48 hours



PDX + bex causes apoptosis in cell lines and SS patients' Sézary cells

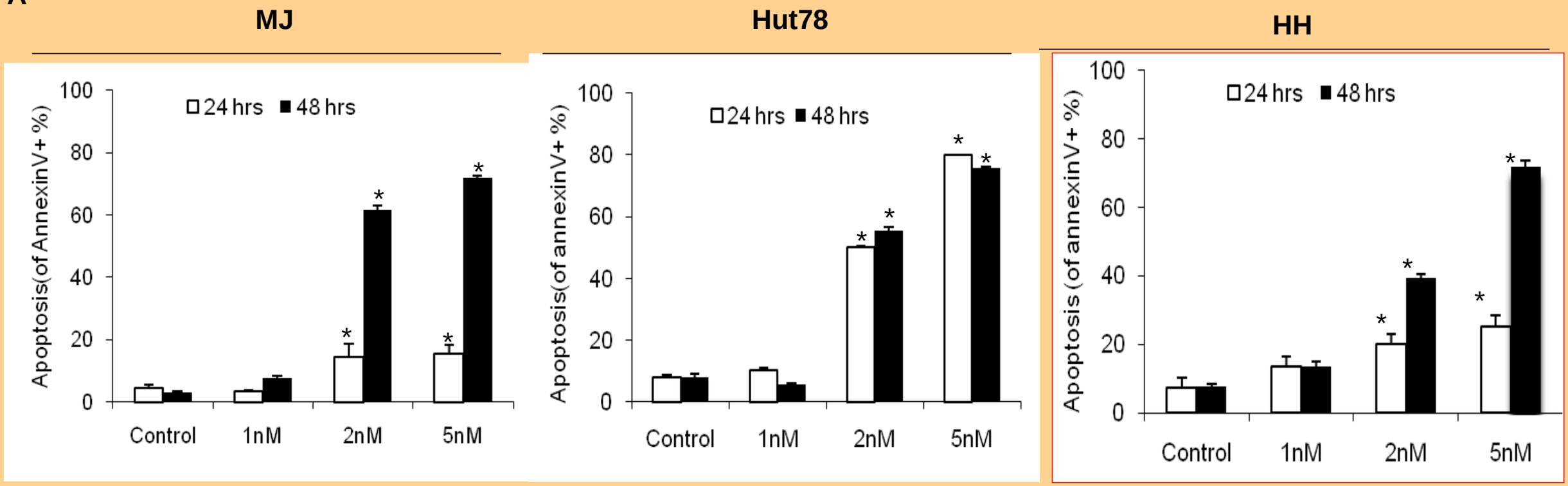






PDX induces apoptosis in a dose and time-dependent manner

A



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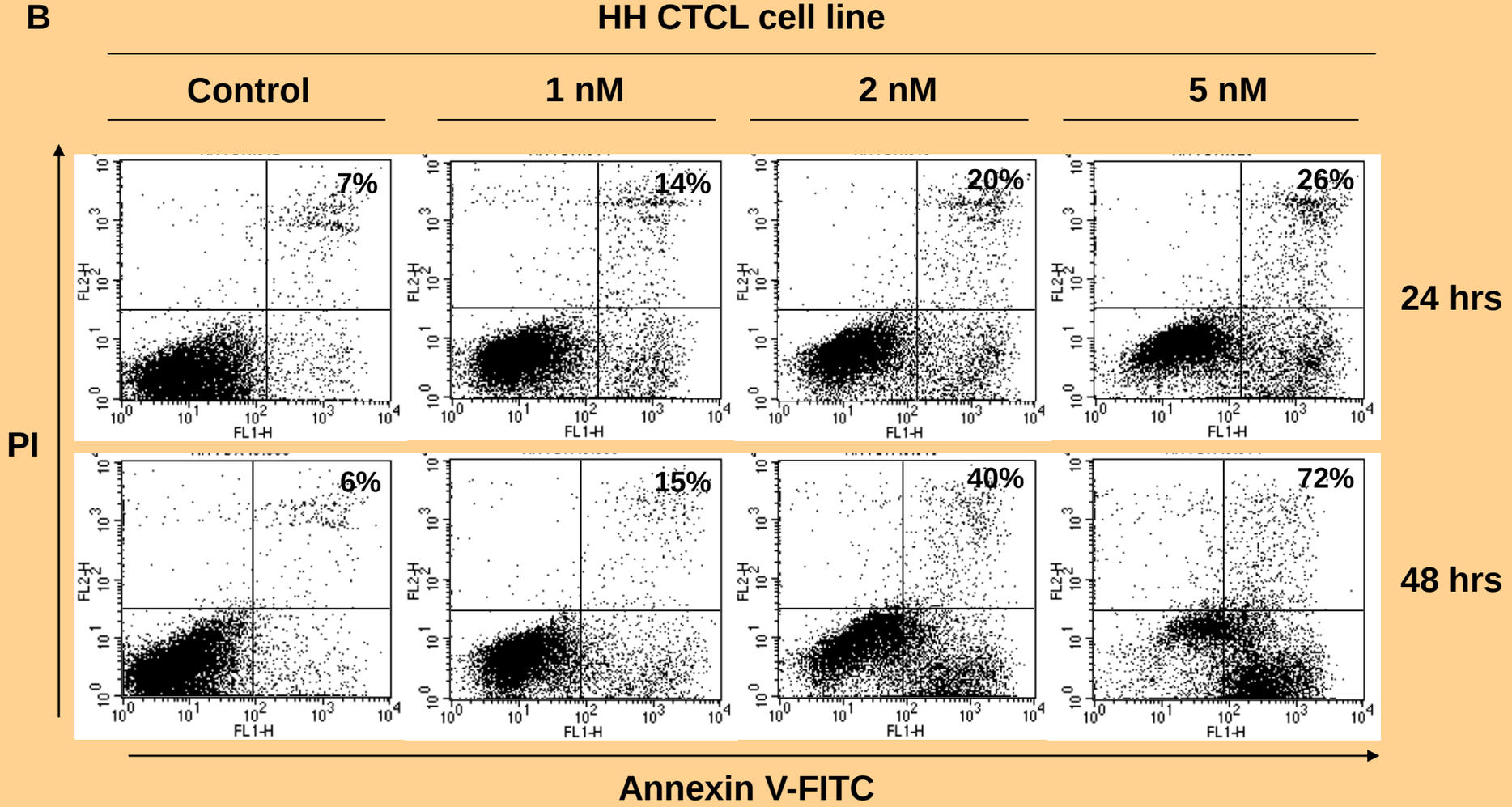
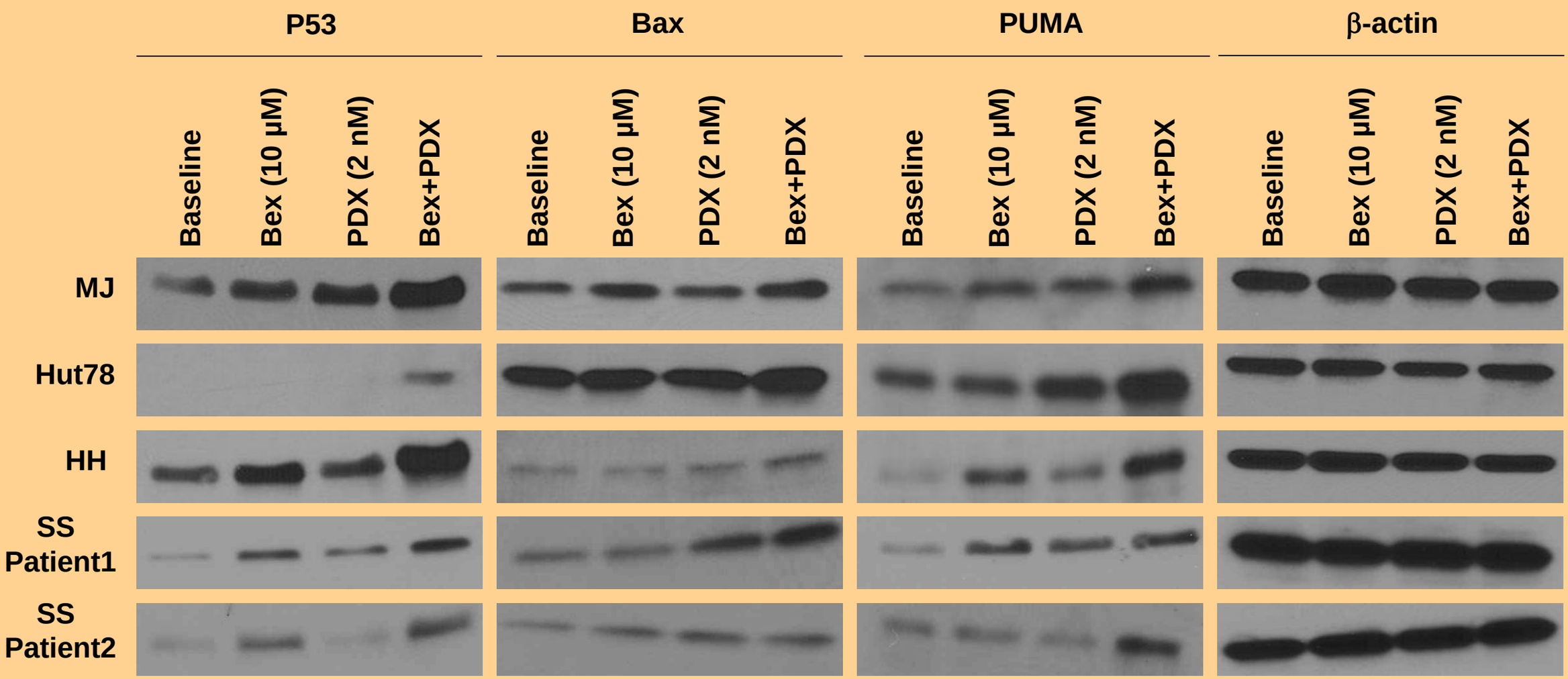
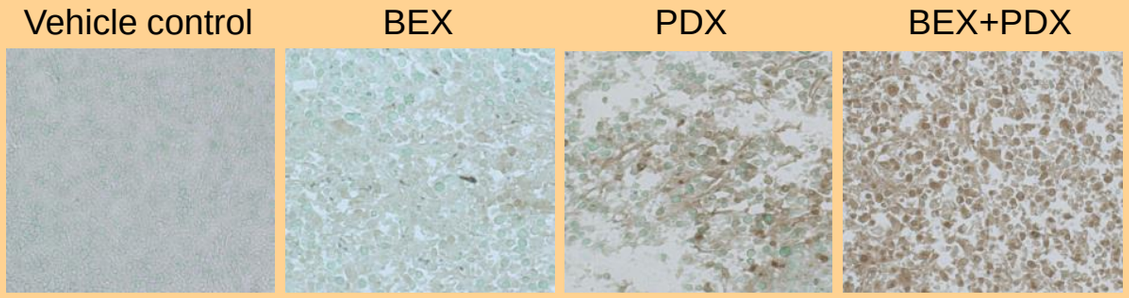
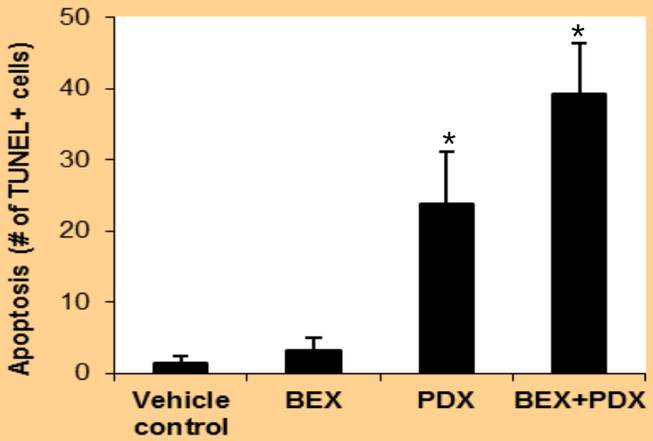


Synergistic effect of PDX and BEX on p53/Bax/PUMA signaling in CTCL cell lines and SS patients' Sézary cells

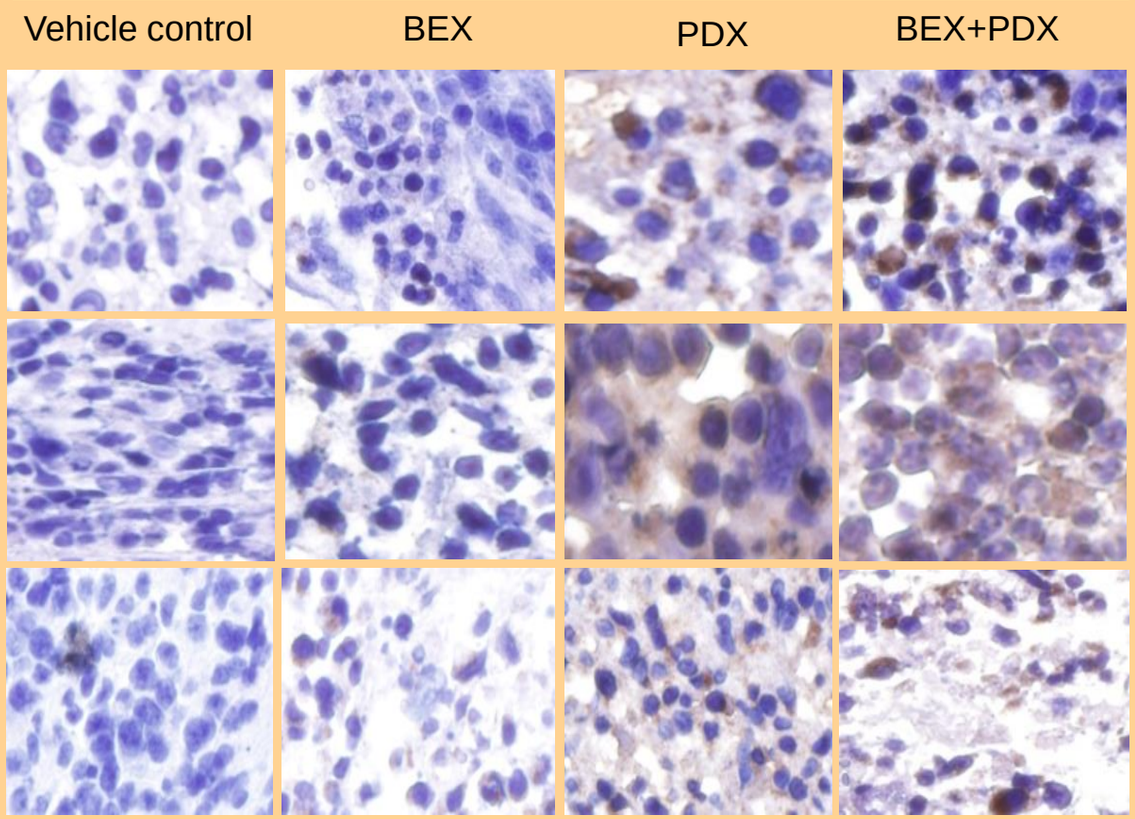


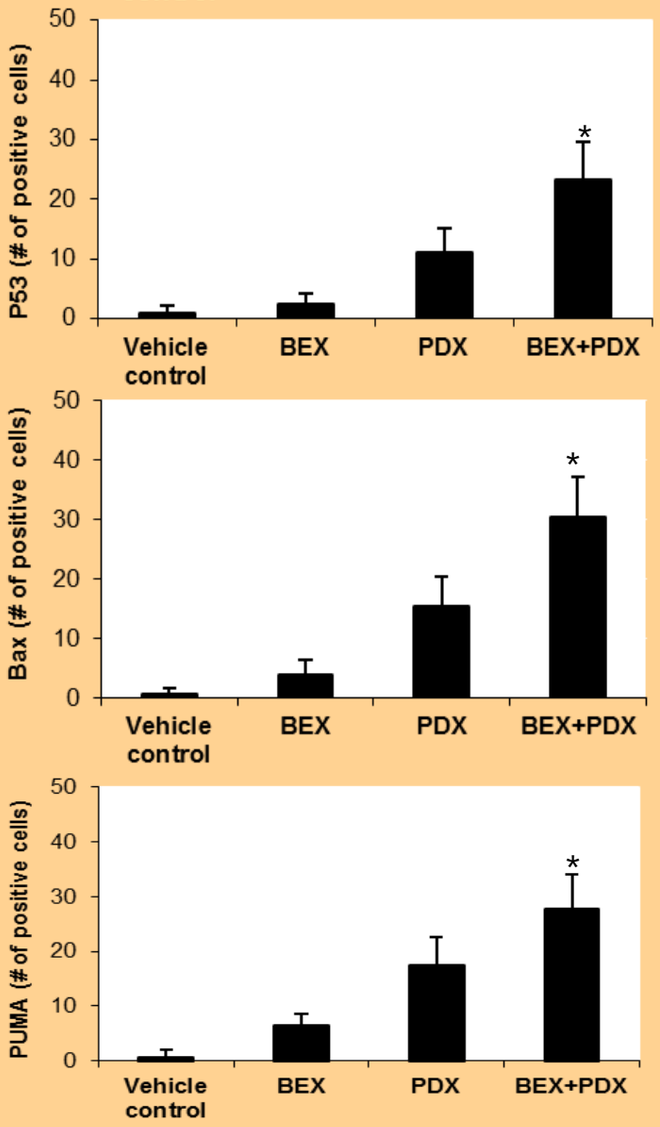
TUNEL Assay



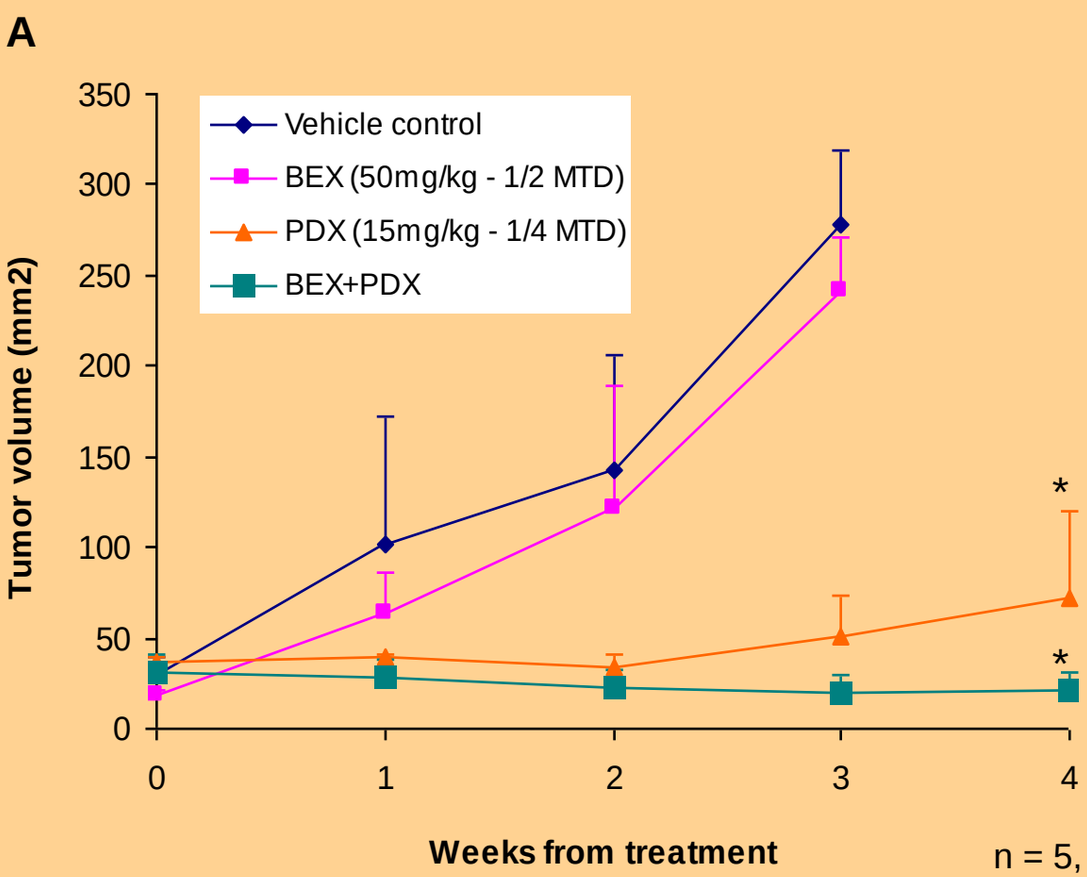


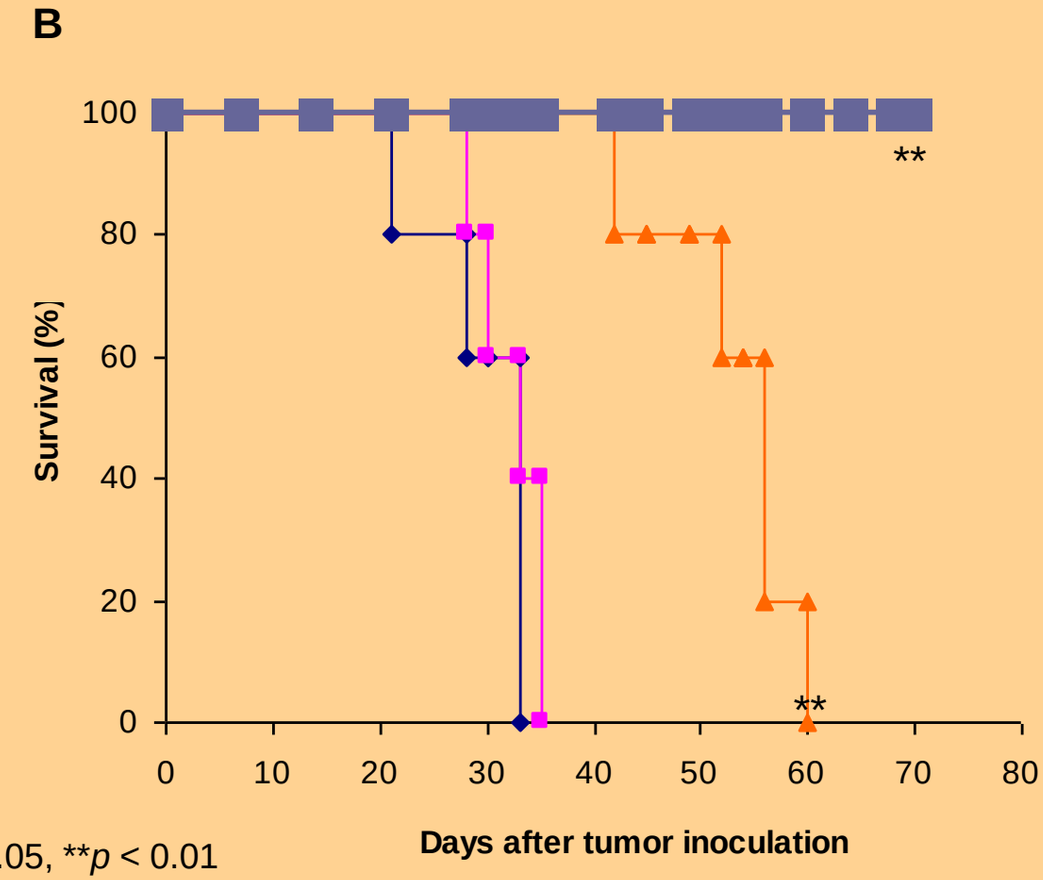
IHC





HH CTCL xenograft





n = 5, * $p < 0.05$, ** $p < 0.01$

Schedule: qd3
(d1/d7/d14)

Phase I/II Dose Finding Open Label Multicenter Trial of Oral Bexarotene in Combination with Pralatrexate

PRIMARY END POINTS: Determine the maximum tolerated dose (MTD) and recommended dose of pralatrexate plus bexarotene with concurrent vitamin B_{12} and folic acid supplementation when administered to adult MF patients who have failed prior systemic treatment

Secondary End Points: Determine safety profile of pralatrexate plus oral bexarotene when administered to patients with relapsed/refractory CTCL.

Collect preliminary efficacy data – global w mswat
Determine the pharmacokinetic (PK) profile of pralatrexate plus bexarotene in patients who undergo plasma PK sampling

Abstract Co-authors

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- Rakshandra Talpur MD & Chunlei Zhang, MD at MDAnderson

14 patients in multicenter trial treated at MD Anderson

- **Cohort 1**: 15 mg/m^2/week pralatrexate + 150 mg/m^2/day bexarotene

  1 patient treated at our site (2 at other sites) 0/3 DLTs

- **Cohort 2a**: 15 mg/m^2/week pralatrexate + 300 mg/m^2/day bexarotene

  3 patients treated at our site: 2 w DLTs

  ≥ Grade 3 neutropenia and ≥ Grade 3 thrombocytopenia

- **Expansion cohort:** 15 mg/m^2/week pralatrexate + 150 mg/m^2/day bexarotene. 8 additional MDACC patients were treated at MTD

Talpur et al Clin Lymphoma Myeloma Leuk. 2014 Aug;14(4):297-304

Phase 1/II dose-finding, open-label, multicenter study of pralatrexate plus bexarotene

- **Standard 3 + 3 dose-escalation design for determination of the MTD**

  <u>Cohort 1: 15 mg/m^2 pralatrexate + 150 mg/m^2 bexarotene</u>

  Cohort 2a: 15 mg/m^2 pralatrexate + 300 mg/m^2 bexarotene

  Cohort 2b: 10 mg/m^2 pralatrexate + 150 mg/m^2 bexarotene

  Cohort 3: 10 mg/m^2 pralatrexate + 300 mg/m^2 bexarotene

- **The cohort determined to be the optimal dose/schedule to be expanded to 30 patients.**

Patient Demographics

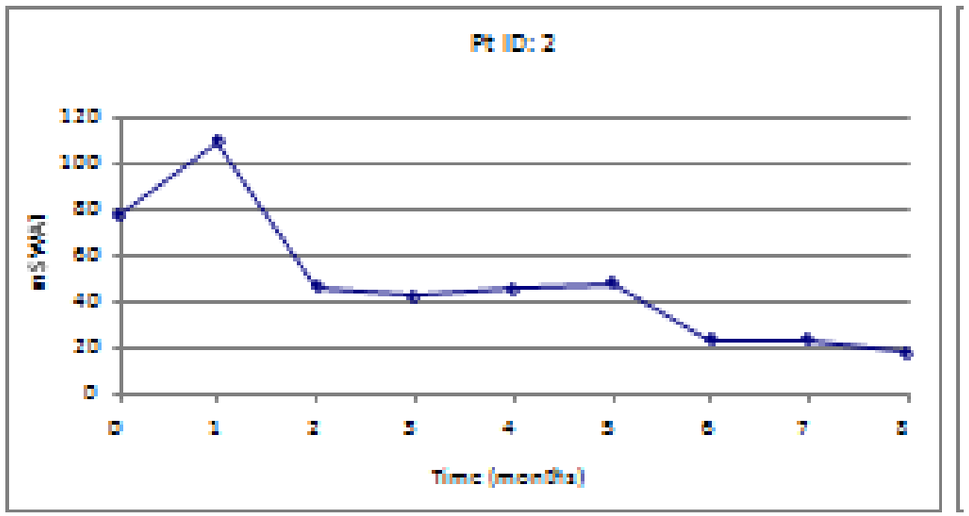
Parameter	Patients (N = 14)
Gender, n (%) Female Male	 8 (57) 6 (43)
Race, n (%) White Black Asian	 5 (36) 8 (57) 1 (7)
Age (years) < 65 ≥ 65 Median Minimum – Maximum	 7 (50) 7 (50) 63.5 41 – 82
CTCL Staging IB IIB IVA_1 (B1) IVA_2 (LN+) IVB (BM+ T4N3B2)	 1 (7) 3 (21) 1 (7) 8 (57) 1 (7)

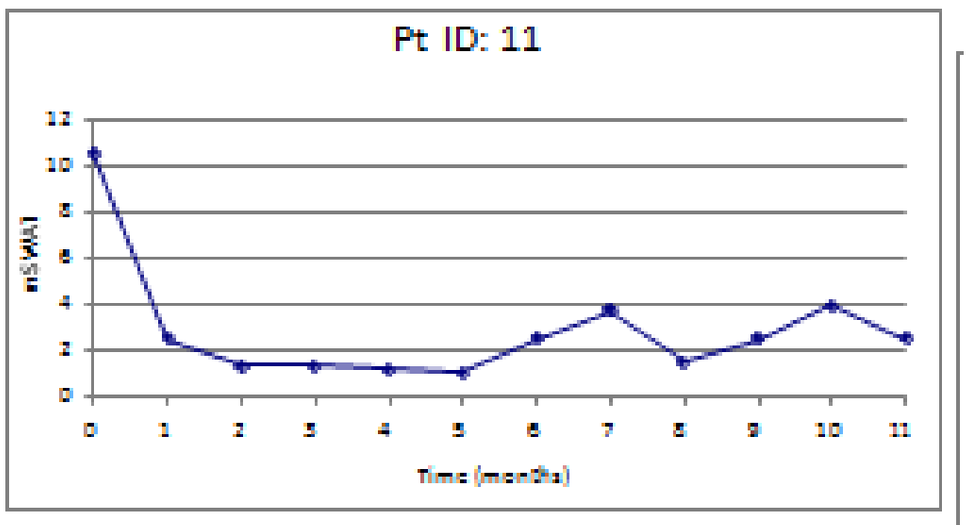
Prior Therapies in 14 patients

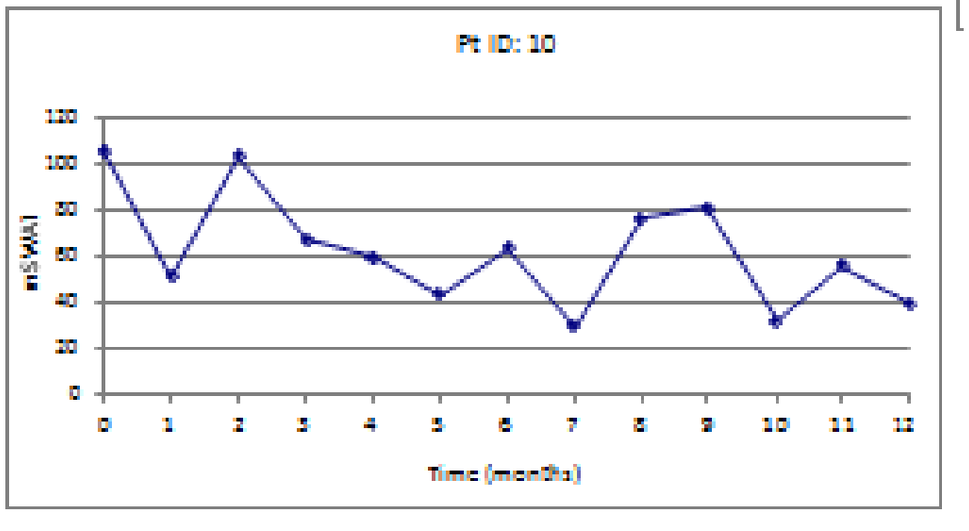
Median Number of prior therapies	
Median (range)	6 (2-8)
Number of systemic prior therapies	
Median (range)	3 (1-7)
Prior systemic therapy	
Bexarotene/retinoid	**11 (79%)**
Multi-agent chemotherapy	3 (21%)
Interferon	3 (21%)
Histone deacetylase Inhibitor	1 (7%)
Prior non-systemic therapy	
Light therapy (PUVA/NBUVB)	7 (50%)
Corticosteroid	12 (86%)
TBSEB	2 (14%)
Local XRT	4 (29%)

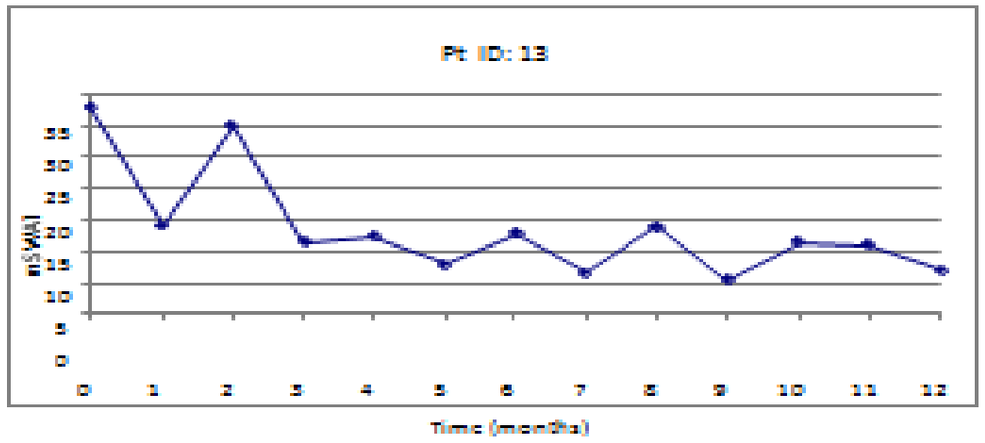
Mswat responses
7 PDX + BEX Responders

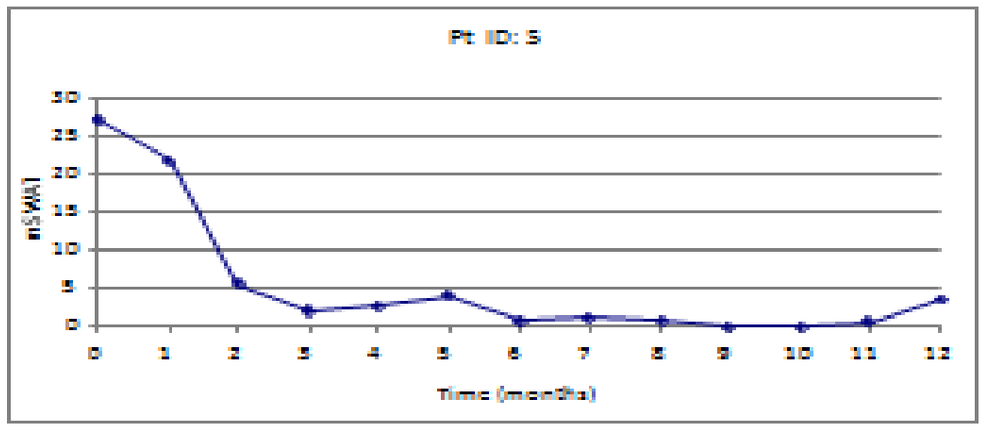
Leukemia & Lymphoma 2015

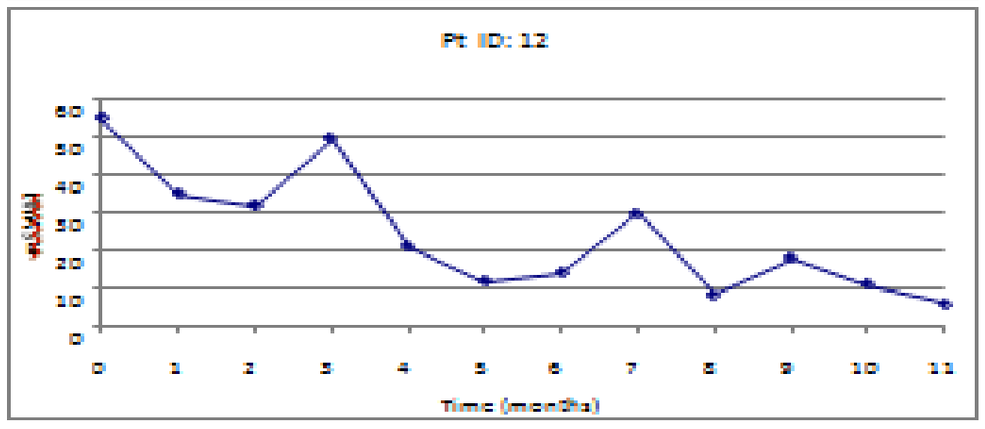


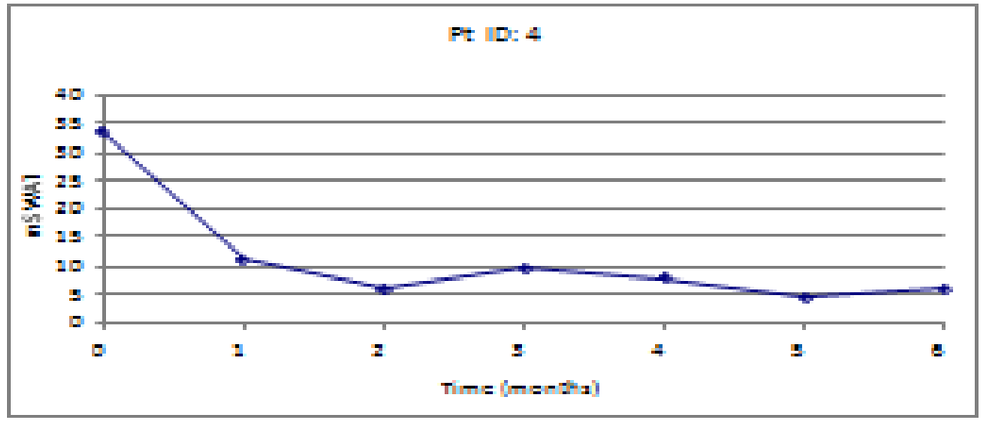












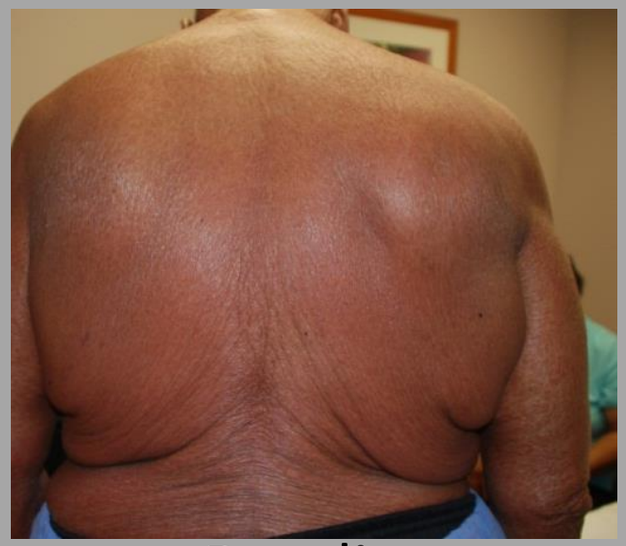
Pralatrexate + bexarotene Response 7/14 (50%)

Pt ID	Age	Sex	Race	Stage	Starting dose of bexarotene (mg/m^2)	Starting dose of pralatrexate (mg/m^2)	# of cycles	Resp
1	77	F	White	IIB	300	15	2	SD
2	41	M	Black	IVA_2	300	15	9	**PR**
3	55	M	Black	IVA_2	300	15	5	SD
4	82	M	White	IIB	150	15	9	**PR**
5	73	F	Black	IVA_2	150	15	**13**	**PR**
6	51	F	Hisp	IB	150	15	6	SD
7	49	F	Black	IVA_2	150	15	1	SD
8	66	M	White	IVA_2	150	15	2	SD
9	66	F	Black	IVA_2	150	15	1	PD
10	42	F	Black	IVA_1	150	15	**21**	**PR**
11*	71	F	White	IVA_2	150	15	**32**	**PR**
12	58	M	White	IIB	150	15	**21**	**PR**
13*	65	M	Black	IVA_2	150	15	**33**	**PR**
14	62	W	Black	IVB	150	15	5	SD

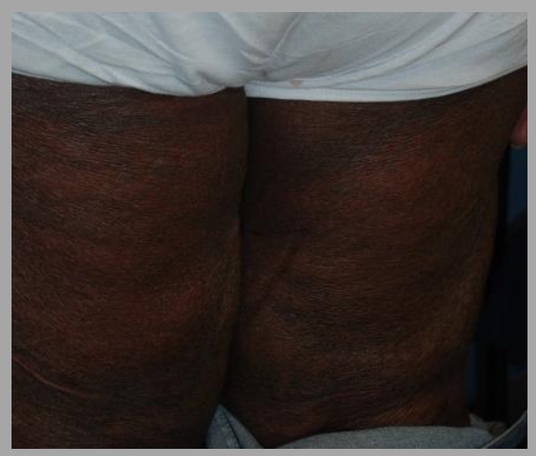
Cohort 1 (Pt # 13) (Pralatrexate 15 mg/m2 /Bexarotene 150 mg/m2)

- 64 y/o AA male with MF stage IVA2(T2N4B0M0) MR in nodes to 5 cycles of CMED
- Pral/ bex PR of skin at cycle 10 and CR at cycle 22.
- Bex reduced 375 mg to 300 mg at cycle 3 for Neutropenia G3 & Pral to 10 mg/m2 cycle 23 for skin sores Gr3
-

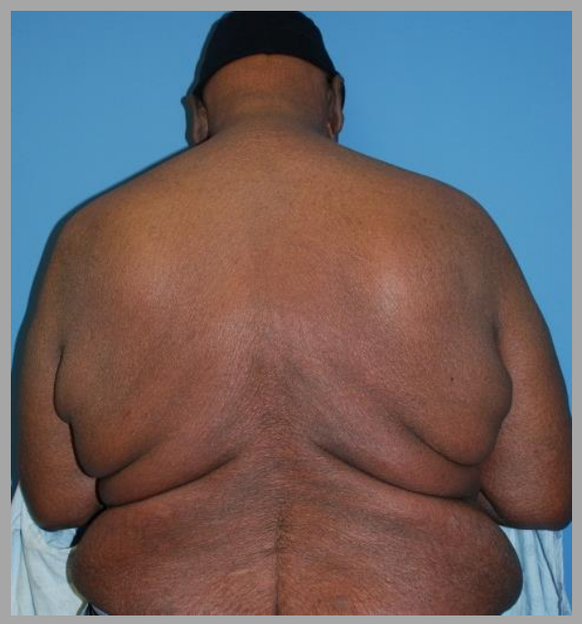
Baseline



Baseline

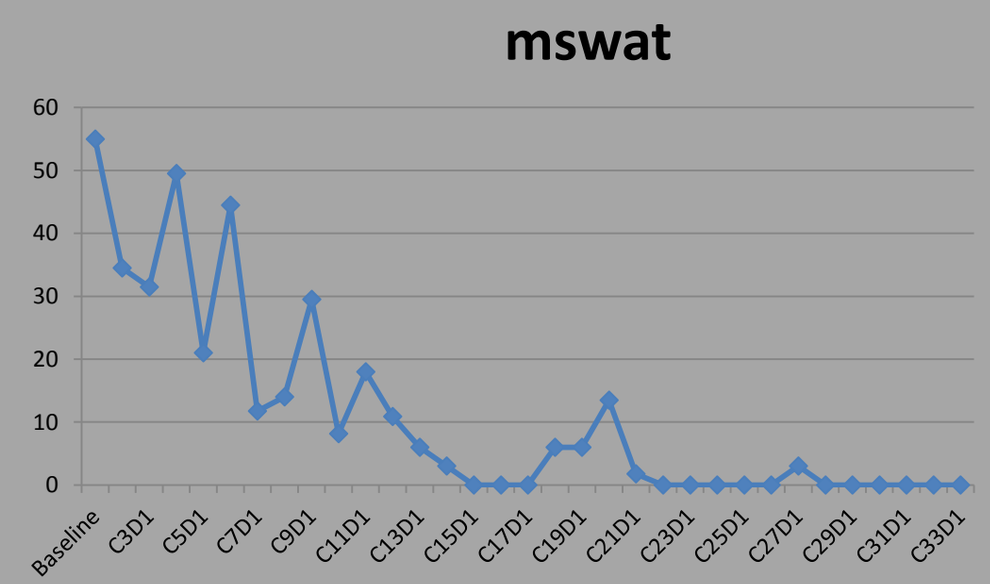


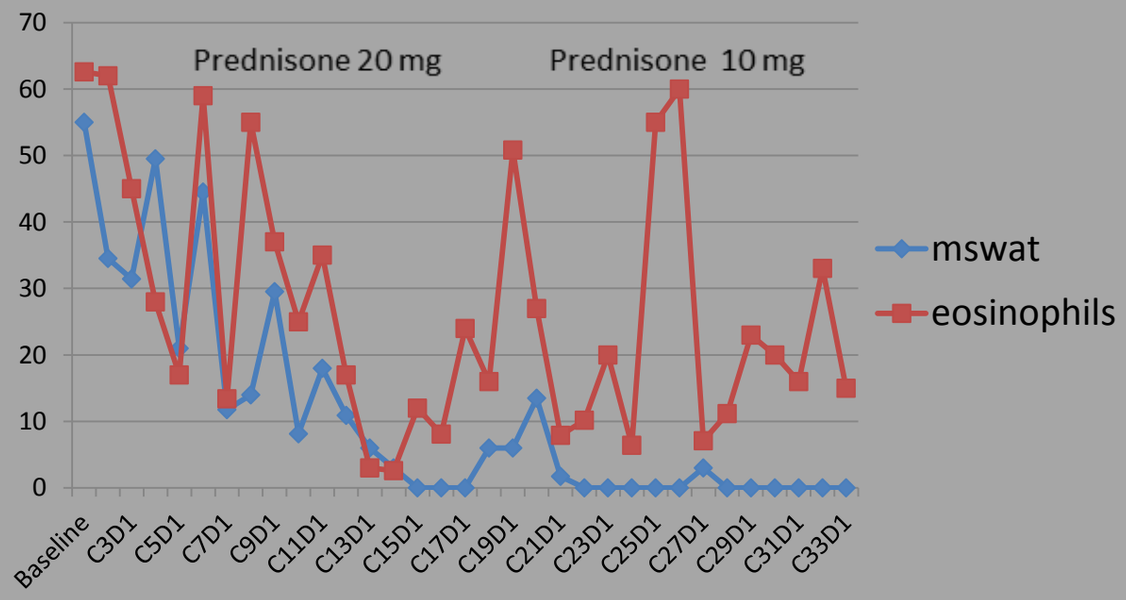
End of cycle 33



End of cycle 33

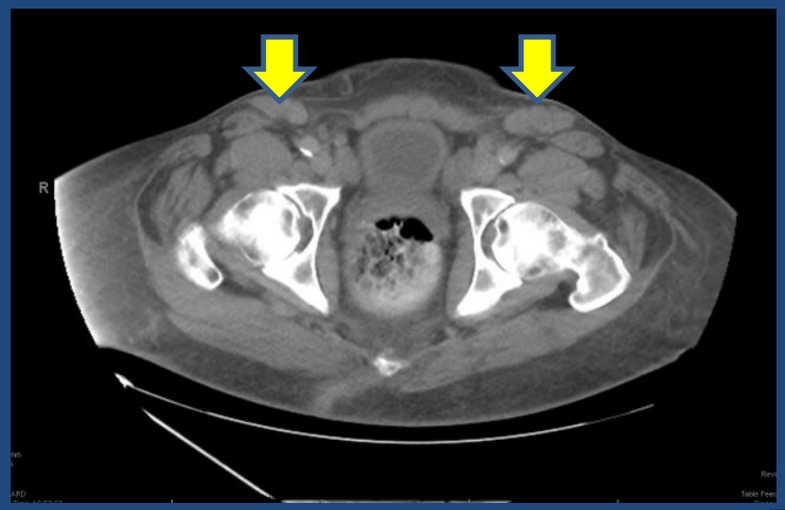
Skin CR > 1 year and MR in nodes



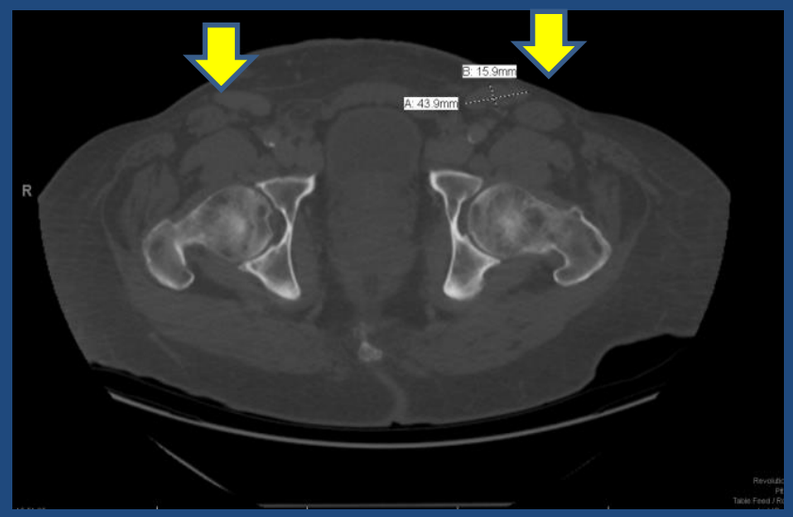


Response in Inguinal Lymph Nodes

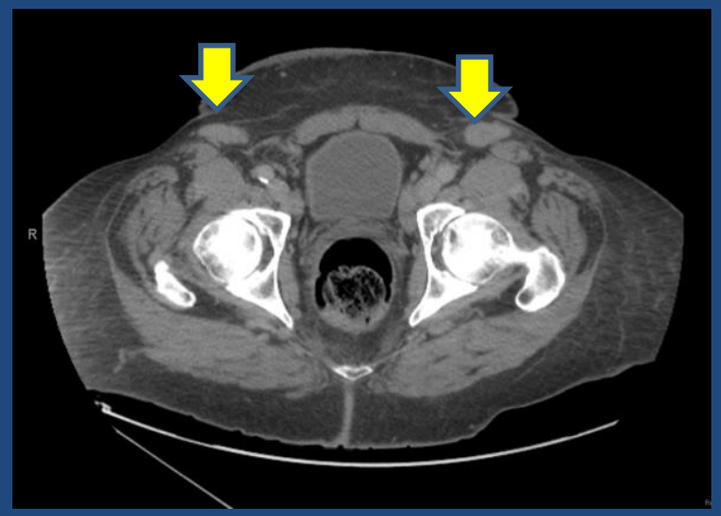
Baseline

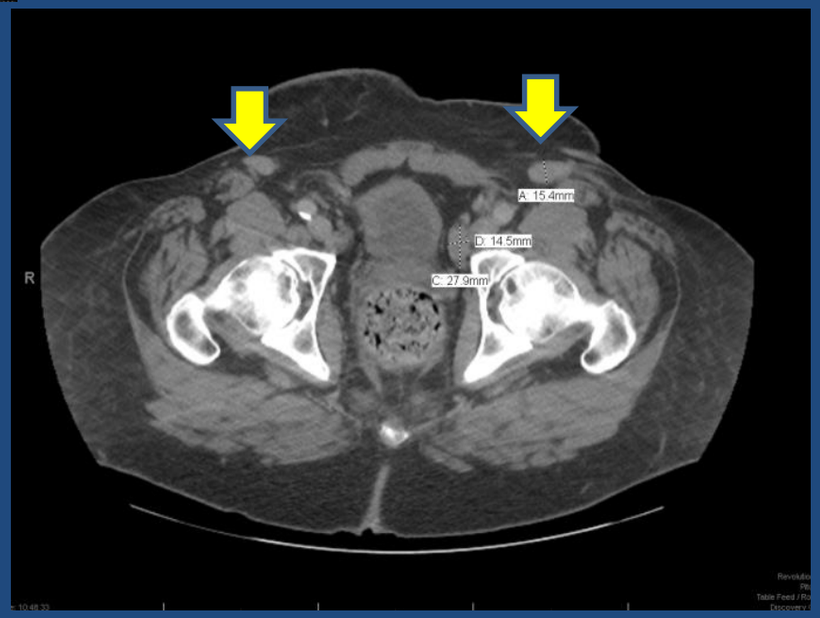


Cycle 10 Day1 (PR in skin)



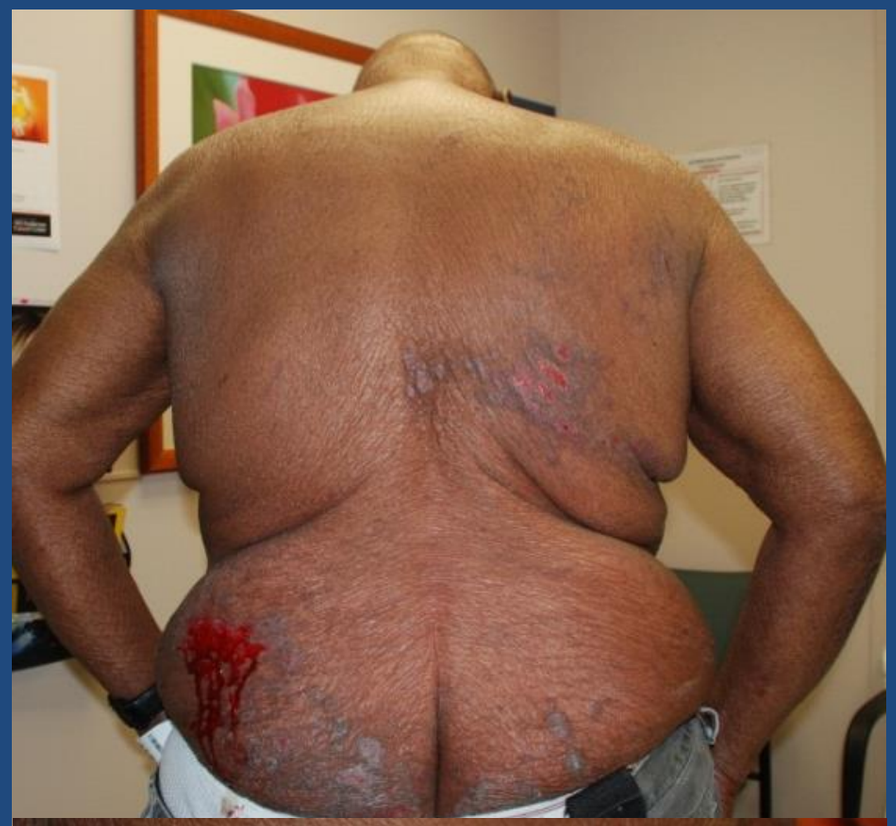
Cycle 15 Day 1 (CR in skin)

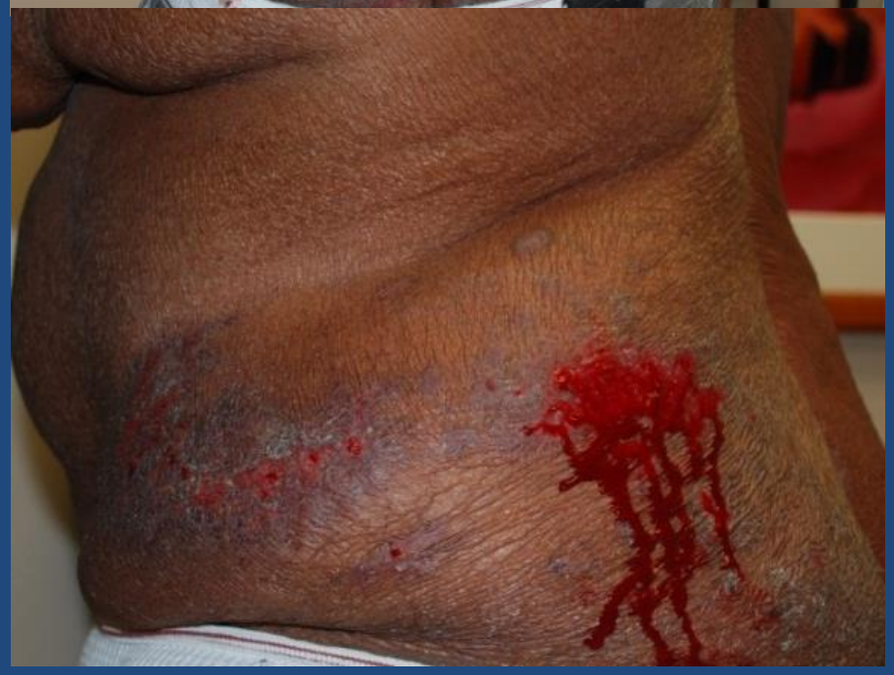


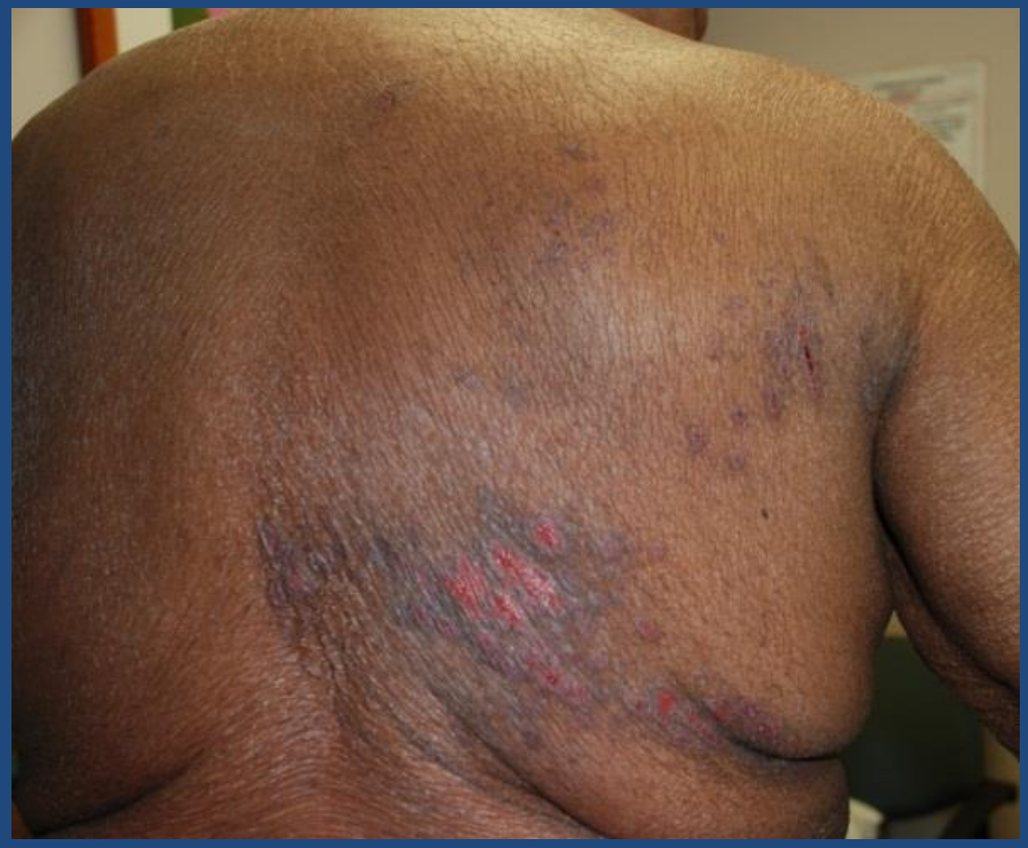


End of Treatment Cycle 32

Skin necrosis on 15 mg/m2 pralatrexate 150 mg/m2 bex on Cycle 12 Day 1

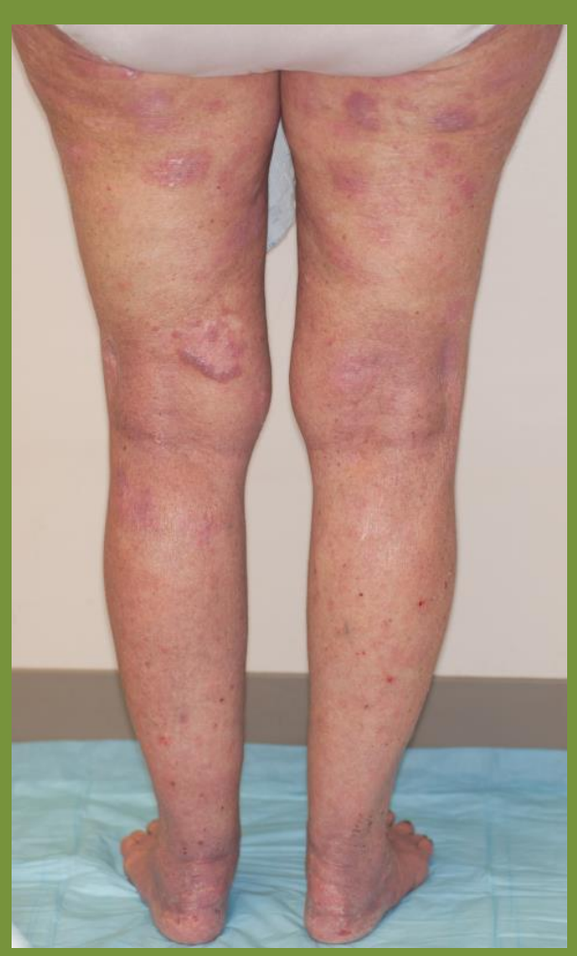




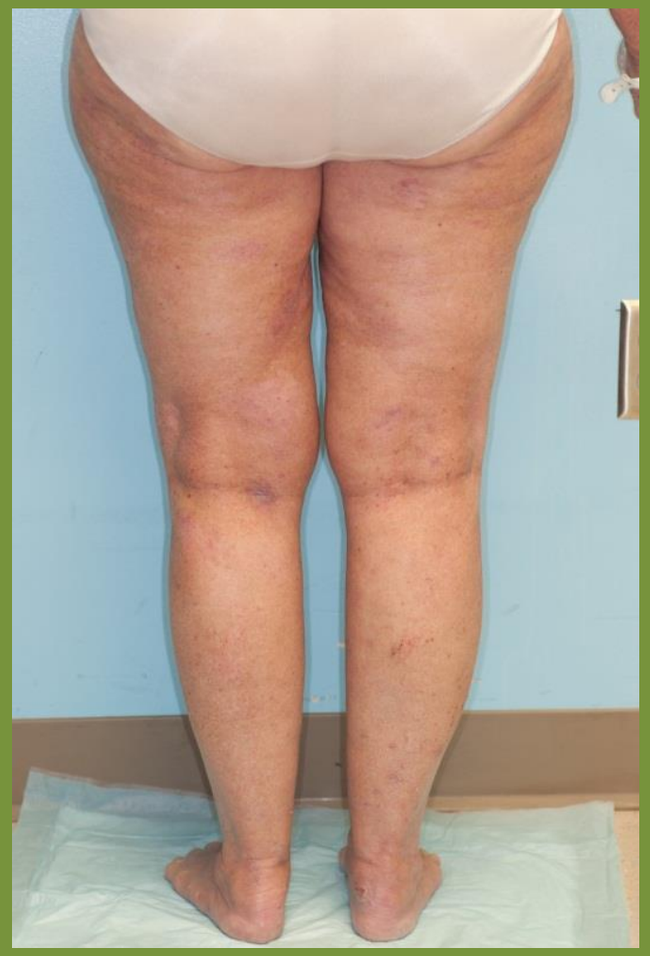


Case 2: Cohort 1 (pt # 11) Bexarotene 150 mg/m2 + Pralatrexate 15 mg/m2

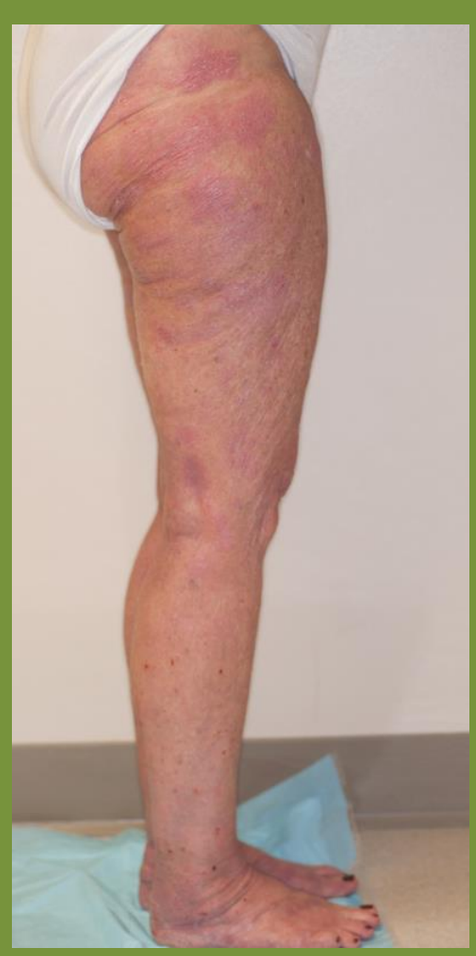
- 72- y/o WF stage IVA (T2N3B0M0) LARGE CELL TRANSFORMATION
- refractory to multiple systemic therapies.
- Pralatrexate 15 mg/m^2 and oral bexarotene 225 mg/m^2 with dose reduction to 10 mg/m2 QOW for neutropenia.
- BL mSWAT of 27.94% reduced to 2.8%. PR skin. Small nodes not biopsied.
- On combination therapy for 32 cycles or 2 years 6 months



Baseline



Cycle 15 D3



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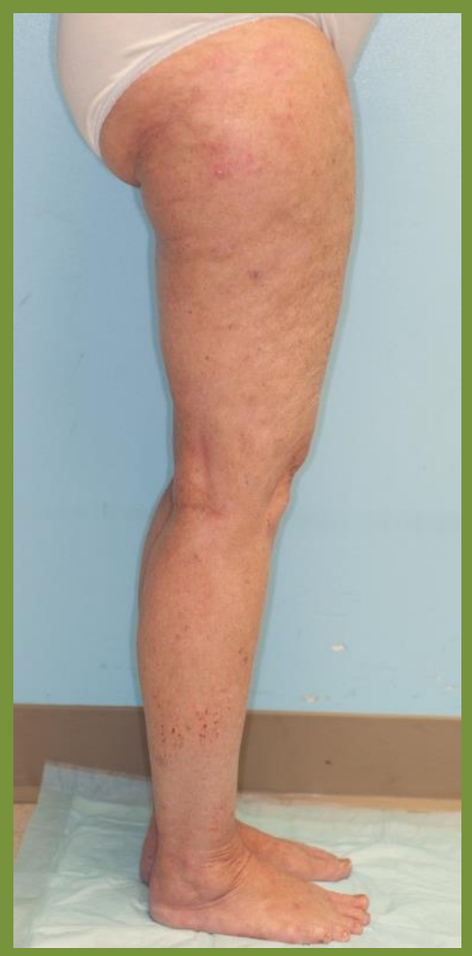
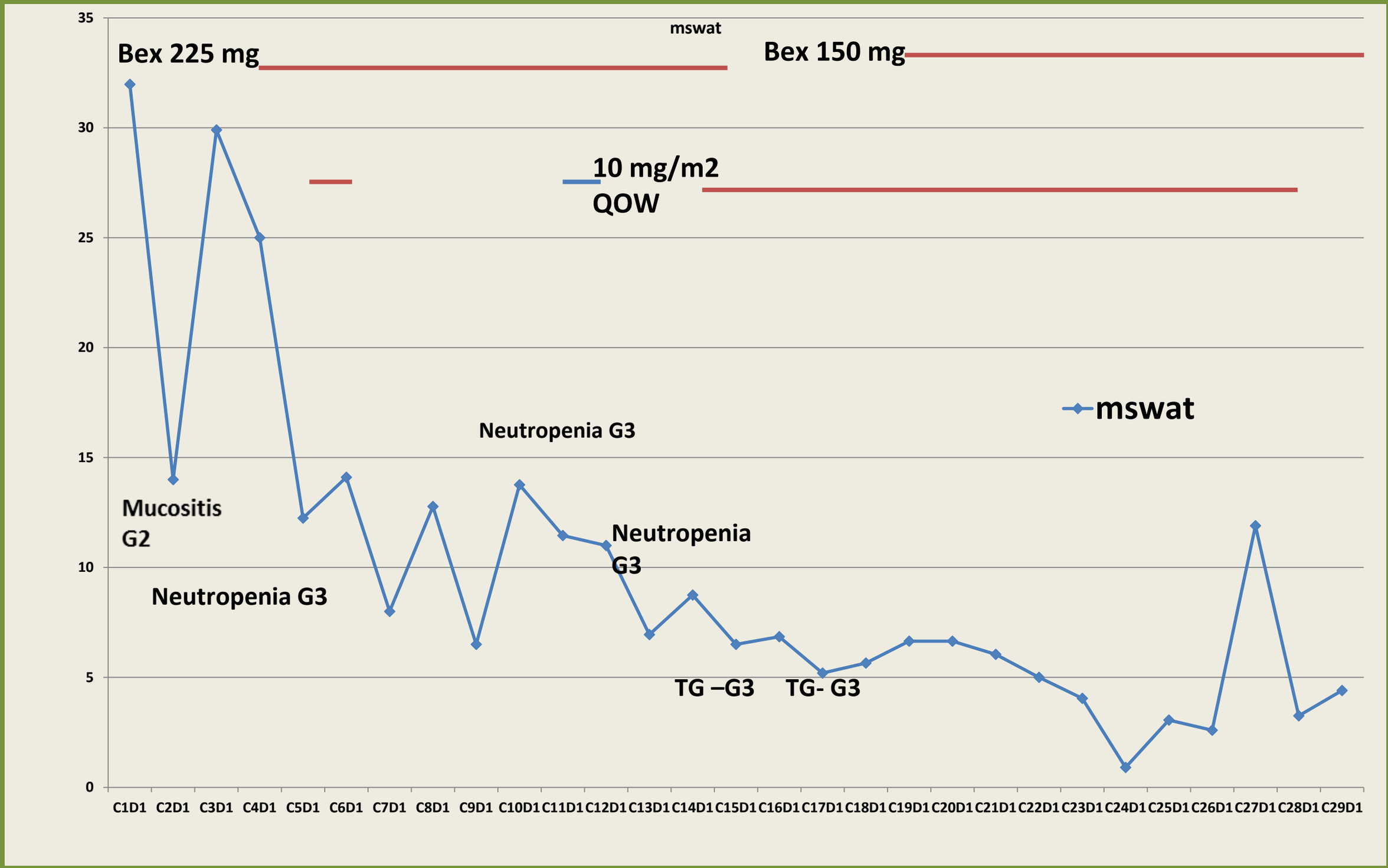


Cycle 15 D3

Skin Response to mSWAT
Praletrexate/bexarotene (case 2, pt 11)

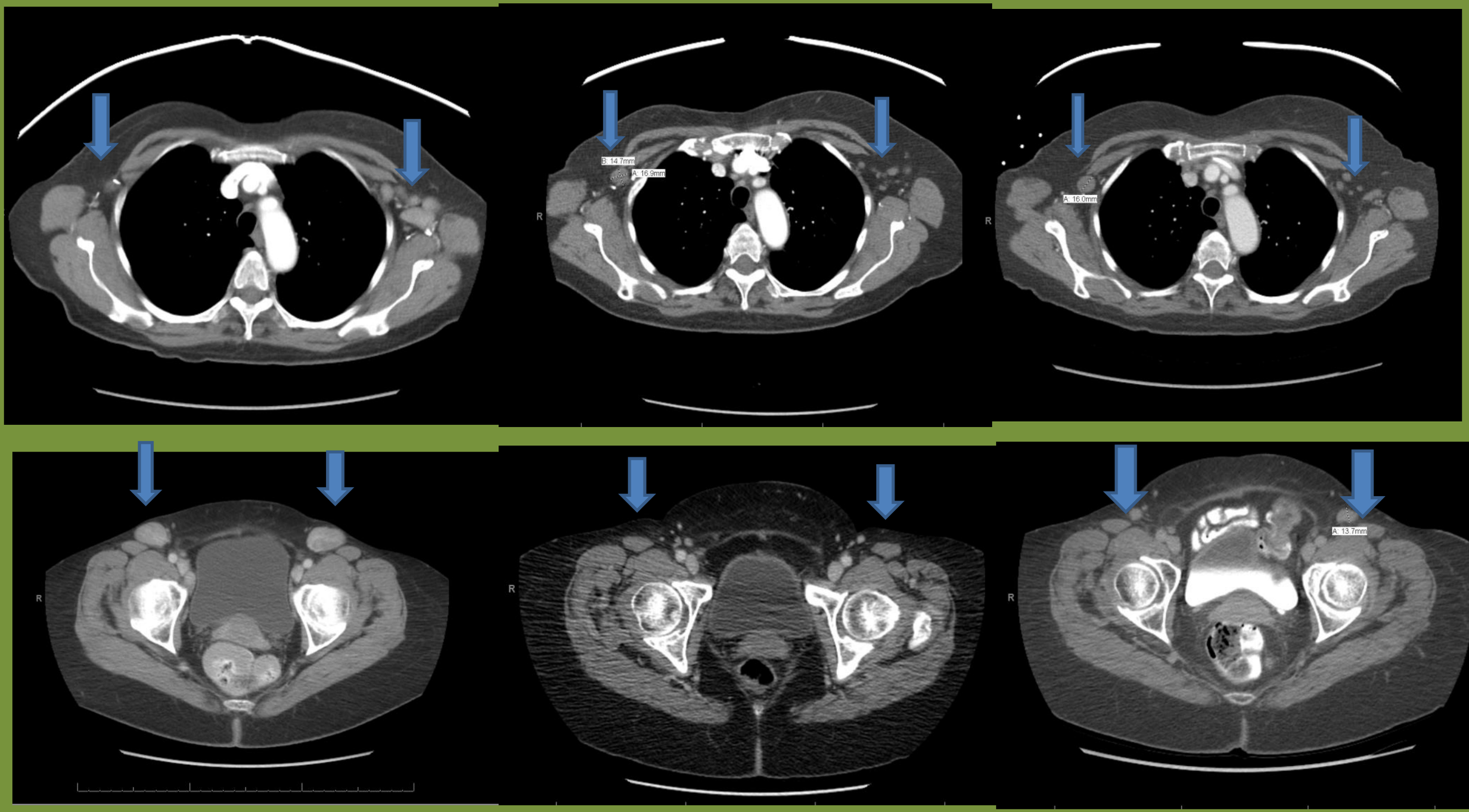


Decrease in nodes: PR at C7D1 and C16 D1

Baseline

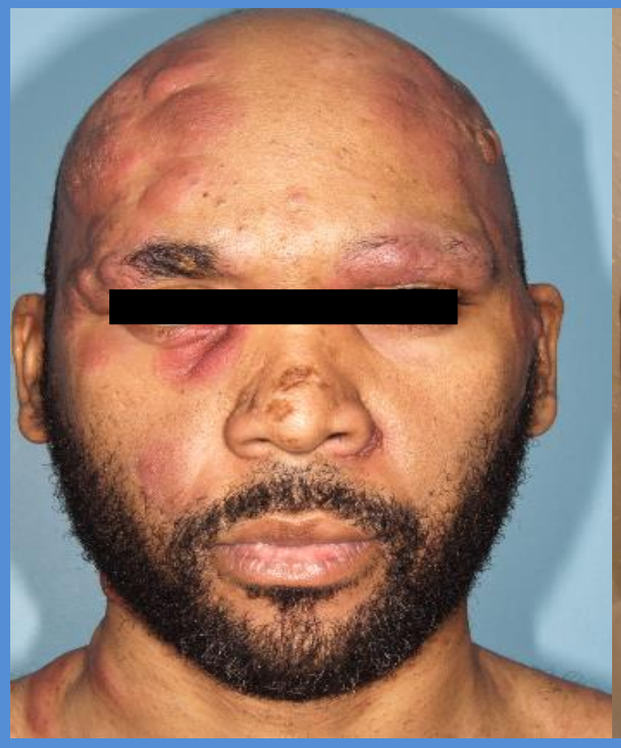
Cycle 7 Day 1

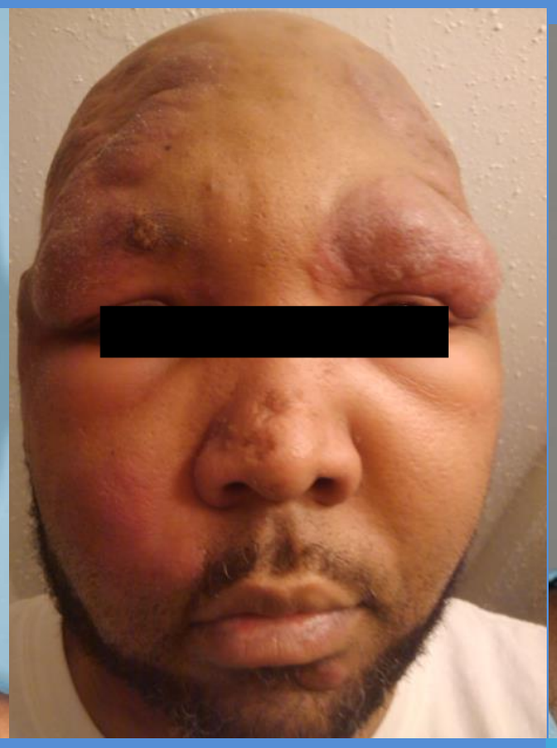
Cycle 16 Day 1

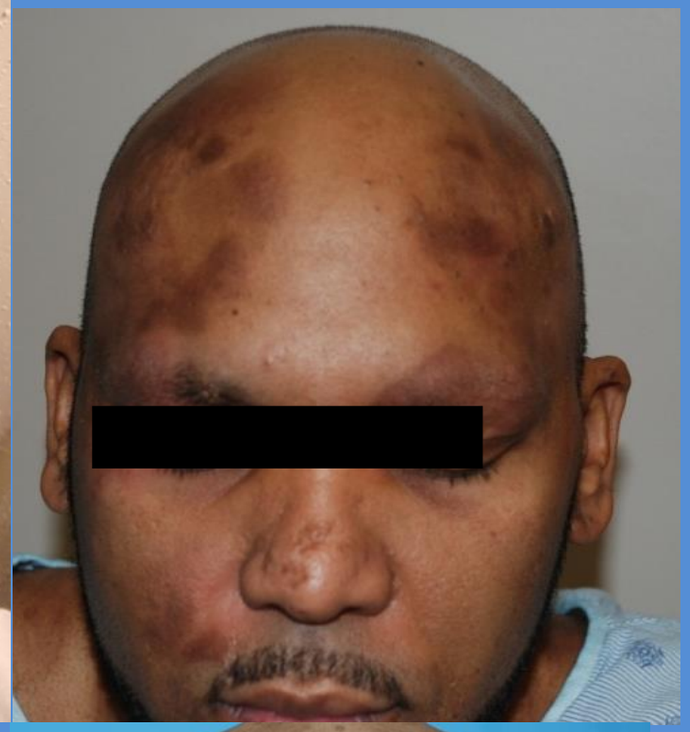


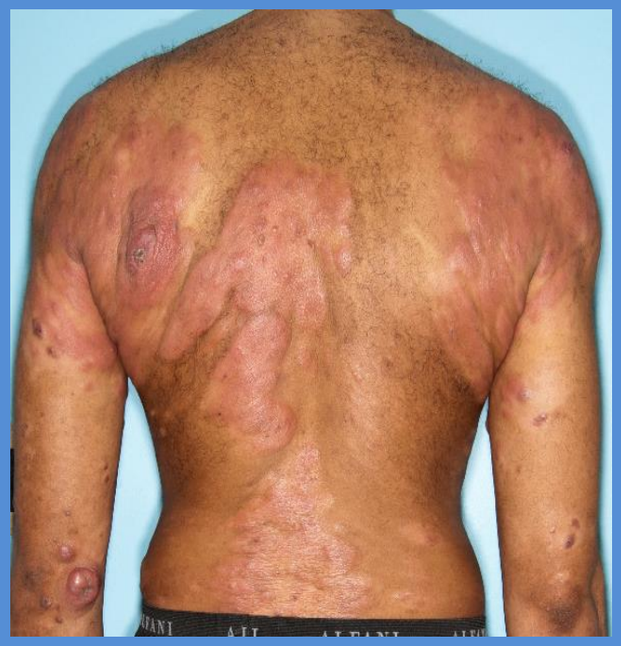
Case:3- Cohort 2 (Pt # 2) 300 mg/m2 (675 mg) Bexarotene + 15mg/m2 Pralatrexate 40 year old AA male - MF stage IVA_2(T3N3M0B0).

PD Liposomal Doxyrubicin: mSWAT score 78.3%, decreased to 29% by 5 cycles



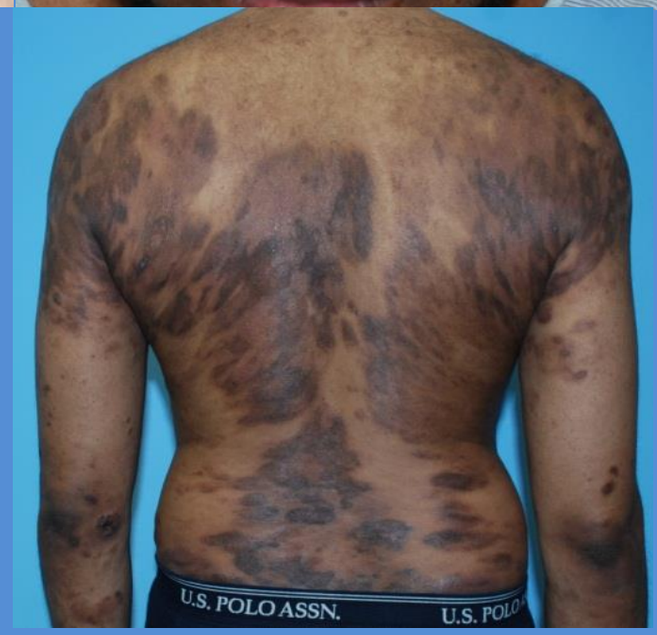






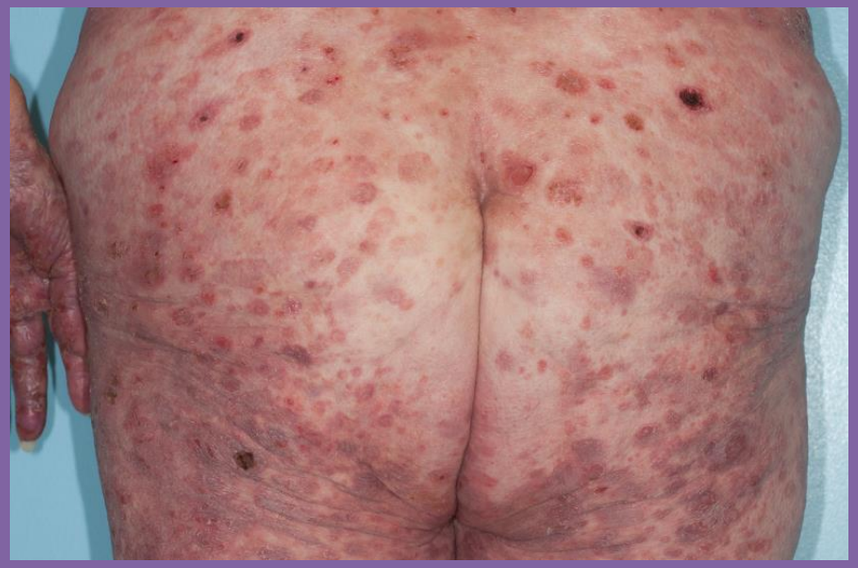
Baseline

Disease Flare

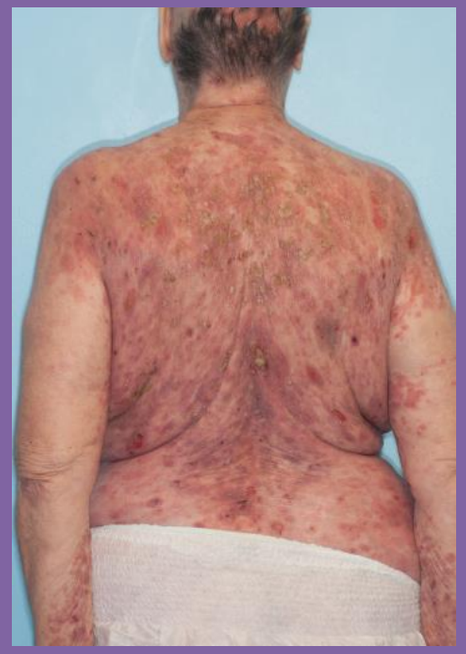


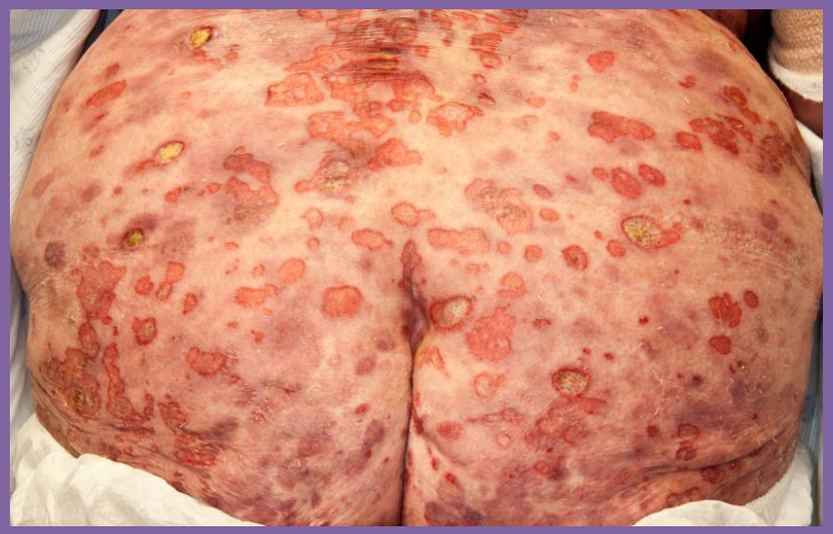
Cycle 6 Day 1

Case 4: Cohort 2 pt # 1 - Pralatrexate 15 mg/m2 + Bexarotene 300 mg/m2

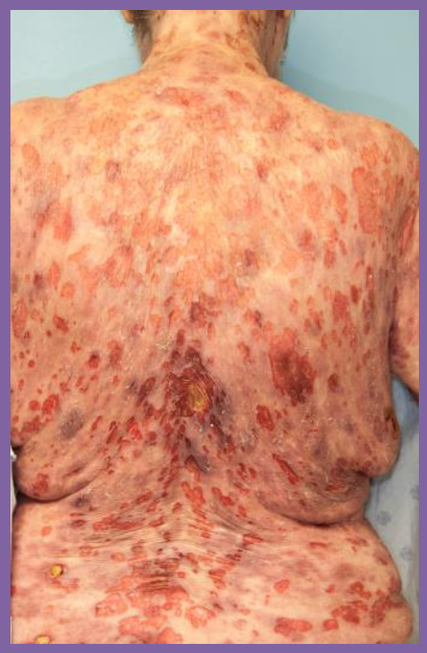


Baseline





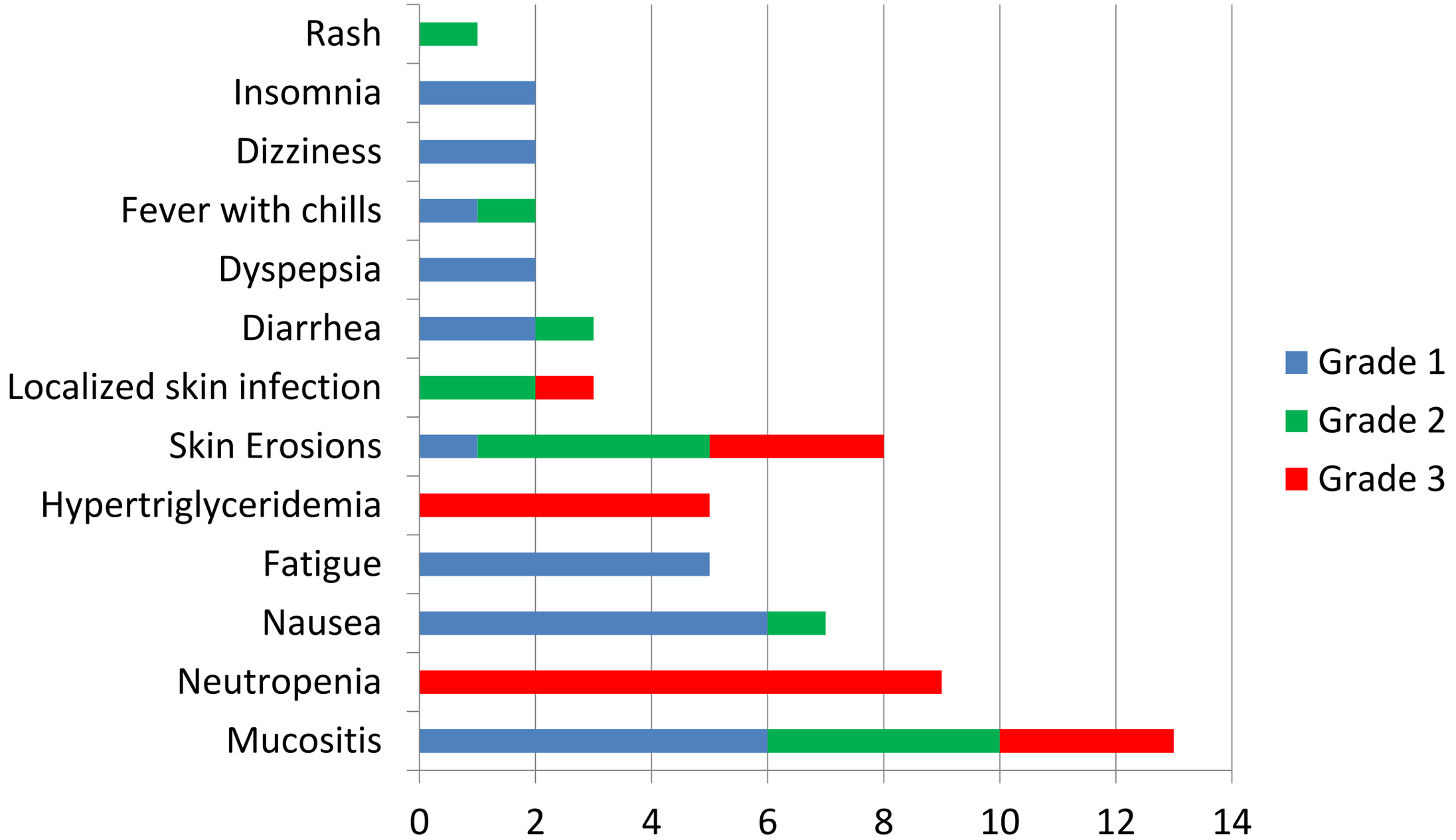
End of Study



End of Study

77 y/o WF stage IIB on cohort 2 pral 29.7 mg + Bex 600 mg. C1D1 DLTs were hypotension, neutropenia. Held 2 doses. C2D1 developed grade 3 mucositis, generalized skin ulcers and new skin lesions PD

Number of patients (n=14) with Adverse Events by Grade



Dose Limiting Toxicity during Cycle 1

Grade 3- 4 (Dose limiting toxicities) (N= 5)

1. Neutropenia (5)
2. Hypertriglyceridemia (1)
3. Leukopenia (1)
4. Thrombocytopenia (1)
5. Groin ulceration (skin erosions) (1)

Conclusions

- MTD 150 mg/m^2 of bexarotene and 15 mg/m^2 of pralatrexate is well-tolerated
- Capable of giving long term durable responses in advanced CTCL patients including those with large cell transformation.
- Response 50% vs pralatrexate alone 33% PRs
- Management of Skin ulceration and mucositis is possible with dose reduction and oral leucovorin.

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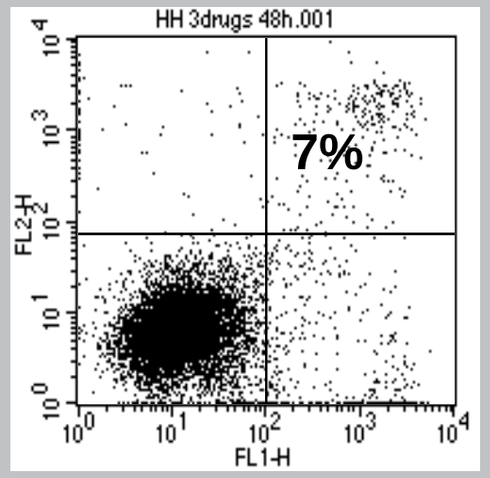
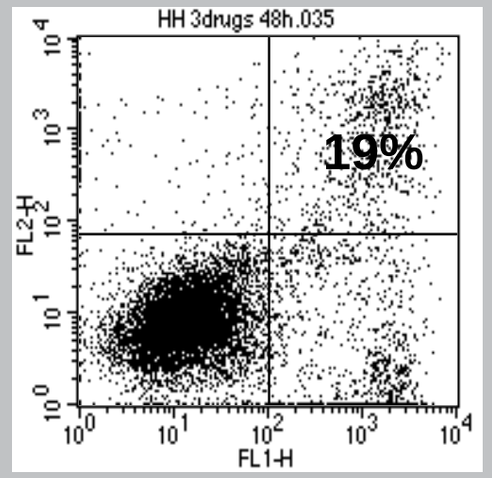
Depsipeptide (Romidepsin) and PDX (Pralatrexate) induce apoptosis in CTCL cell lines (48hrs)

HH

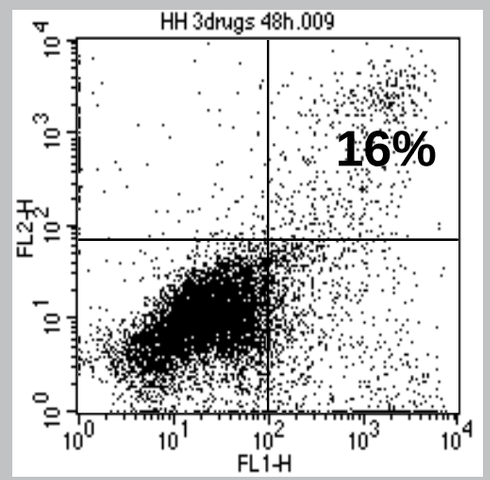
control



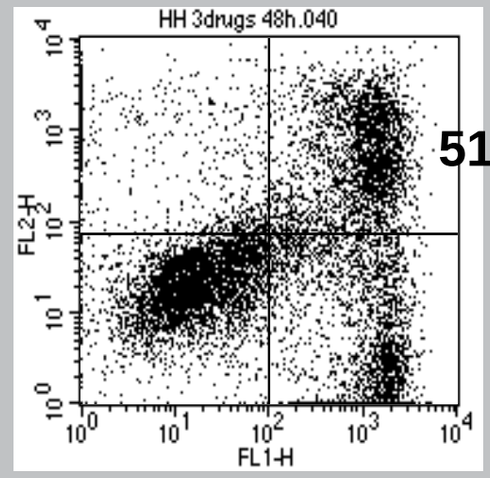
Depsipeptide 1nM



PDX 5nM

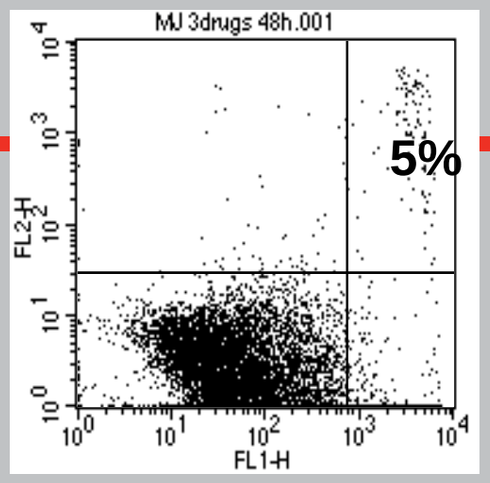


DP 1nM+PDX 5nM

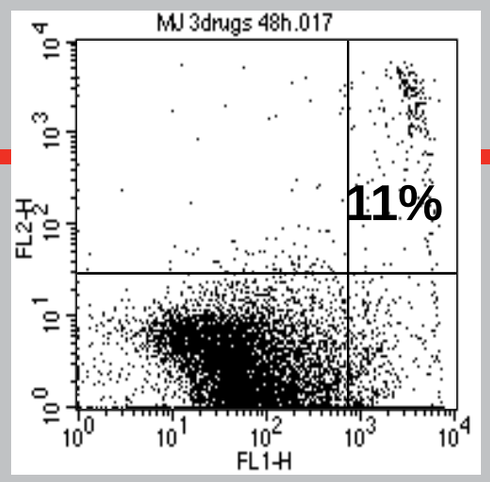


MJ

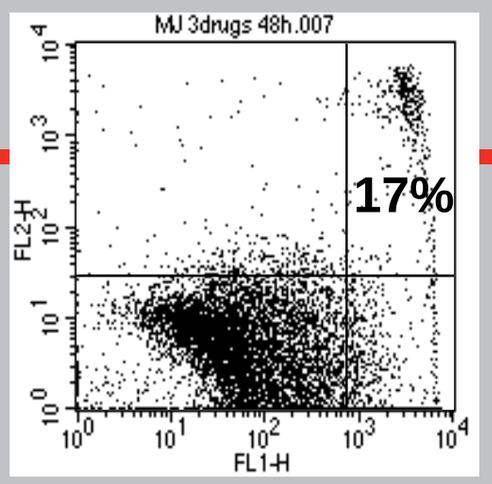
control



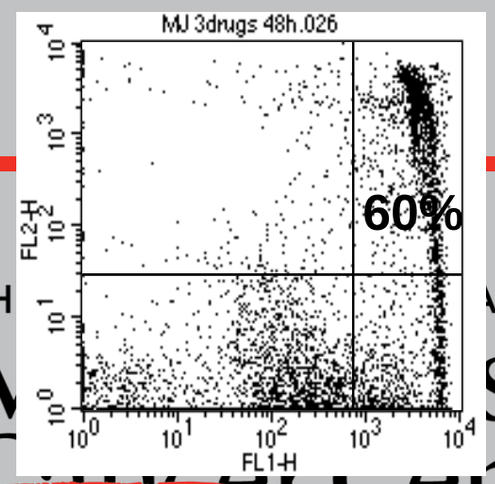
Depsipeptide 1nM



PDX 2nM



DP 1nM+PDX 2nM



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PDX +BEX Synergy

PDX at 1-5 nM induces apoptosis in a time- and dose-dependent manner in three CTCL cell lines

• PDX selectively triggers apoptosis in SS patients' CD4+ T cells compared to normal CD4+ T cells.

•

PDX combined with BEX exerts a synergistic pro-apoptosis effect in CTCL cells.

• Synergistic pro-apoptosis is associated with up-regulation of tumor suppressor p53 and the p53-regulated pro-apoptosis proteins Bax and PUMA.

• These findings support the ongoing phase 1 clinical trial of PDX/BEX and provide the rationale for future studies of this combination in CTCL patients.

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Pralatrexate Plus Bexarotene in Relapsed/Refractory Cutaneous T-cell Lymphoma

Madeleine Duvic, MD
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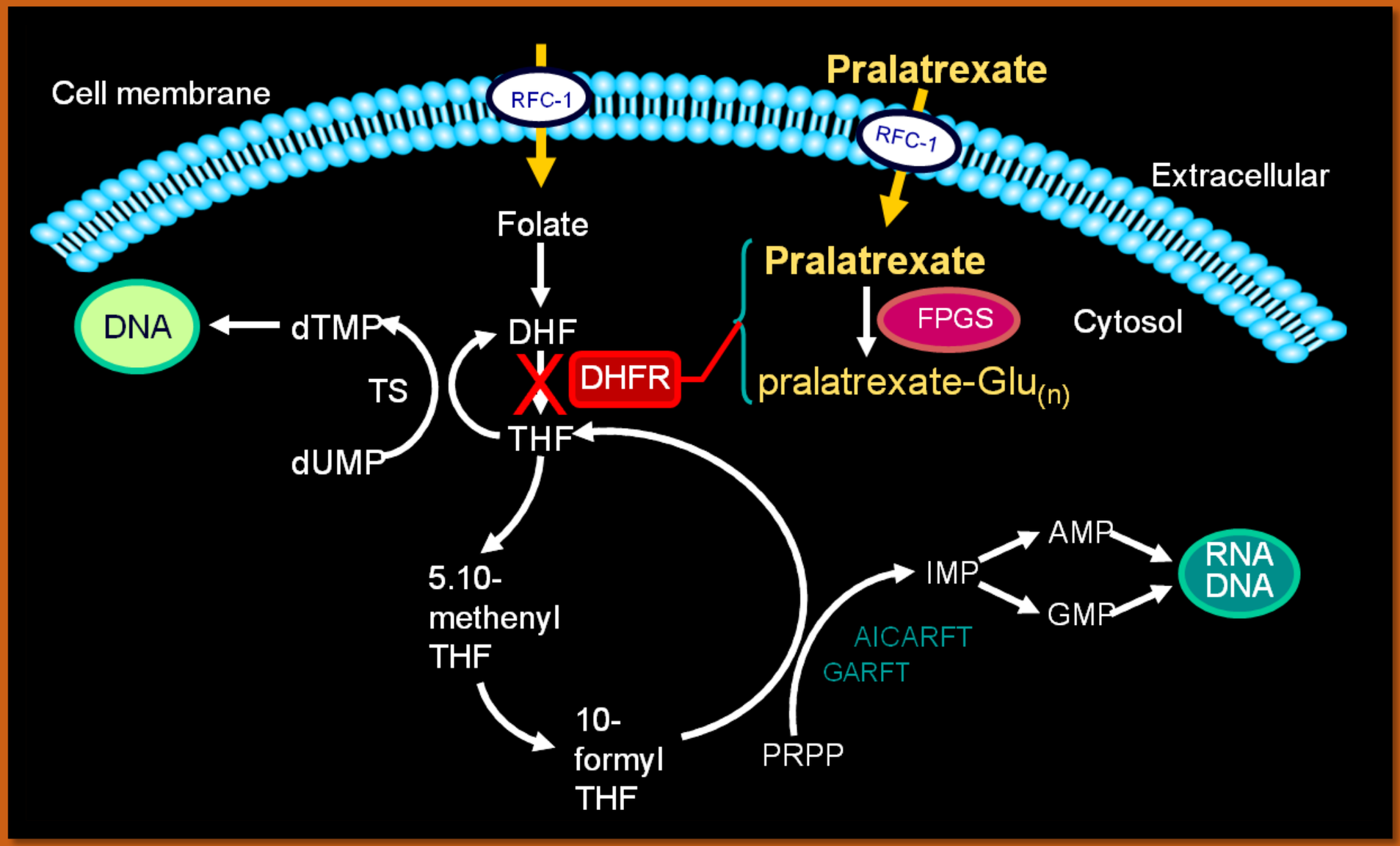
University of Texas MD Anderson Cancer Center

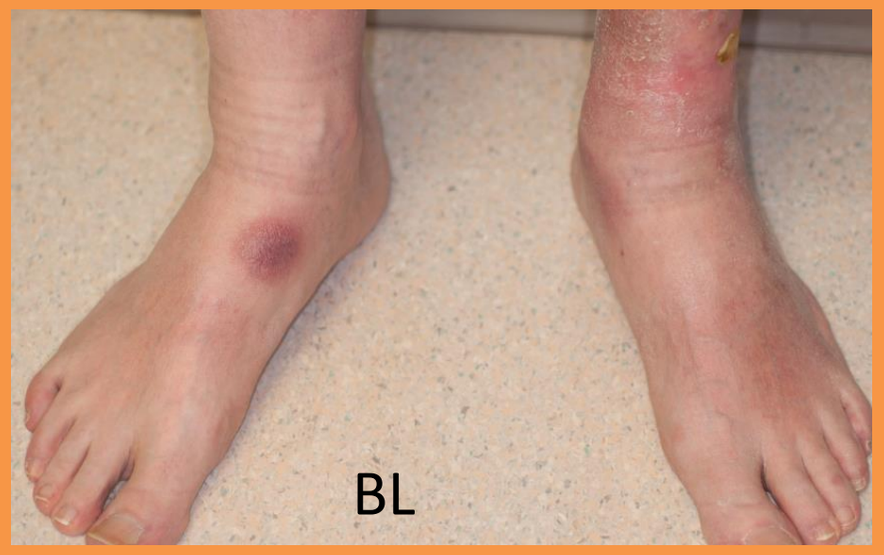
Pralatrexate: Mechanism of Action

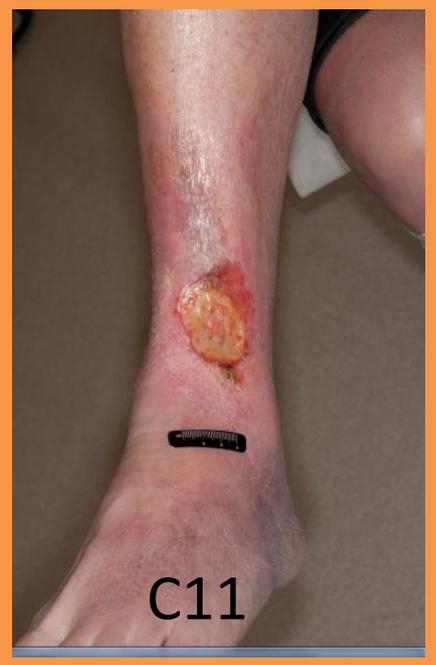


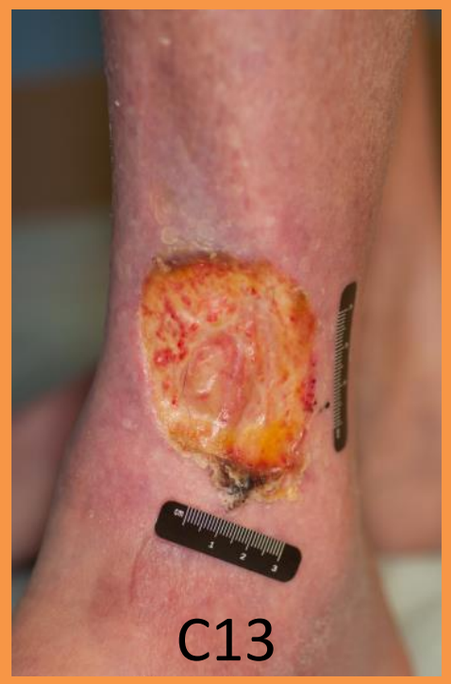
	DHFR inhibition K_i (pM)	Influx V_{max}/K_m	FPGS activity V_{max}/K_m
Pralatrexate	**13.4**	**12.6**	**23.2**
Methotrexate	**5.4**	**0.9**	**2.2**

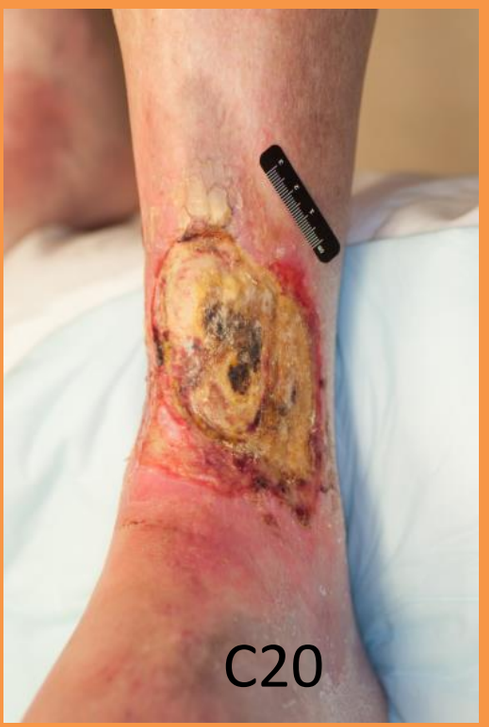
> 10-fold Improvement in influx and polyglutamation

Case # 5-Cohort 1 (pt # 11) (Bexarotene 150 mg/m2 + Pralatrexate 15 mg/m2)



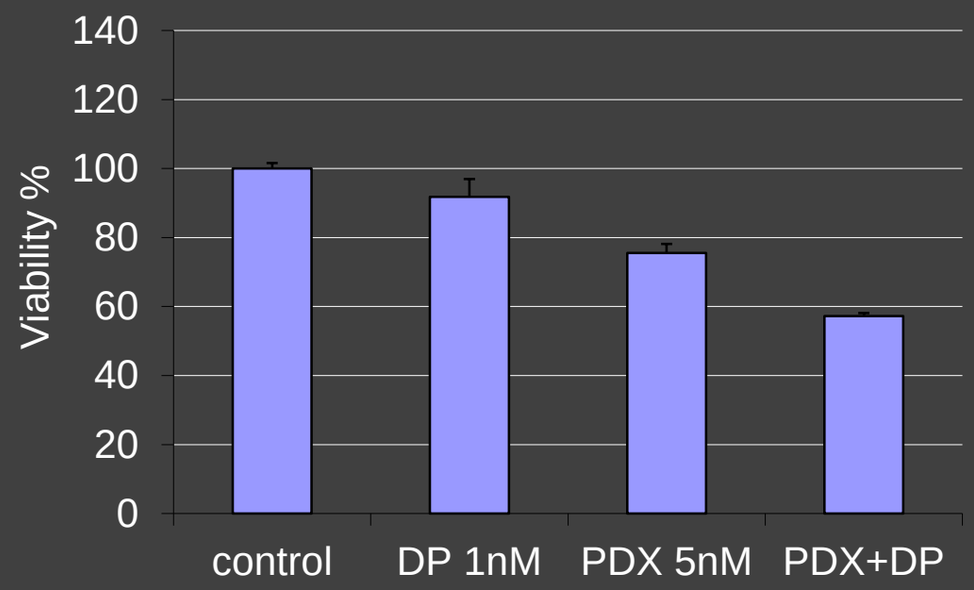


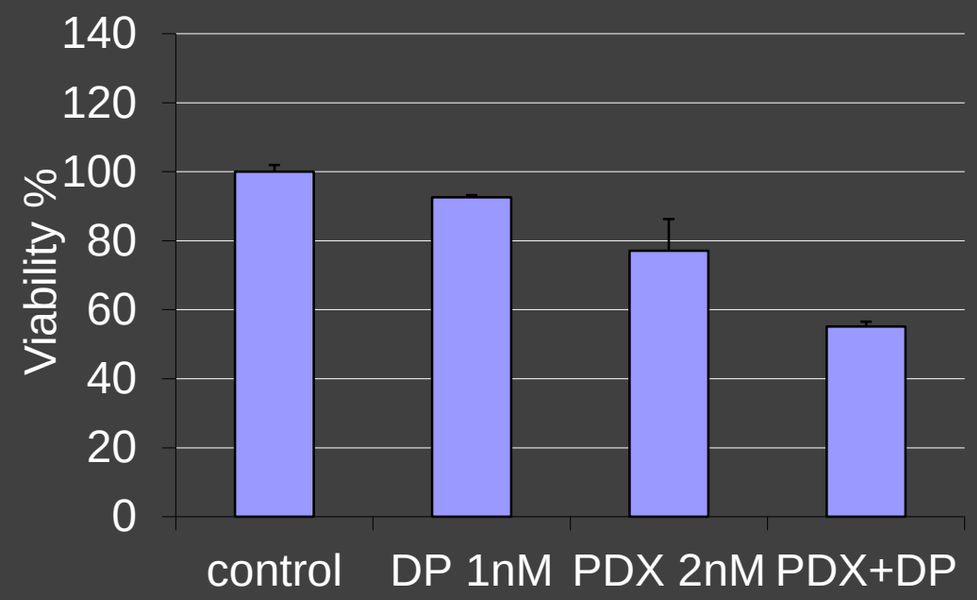




- 59-y/o WM with mycosis fungoides stage IIB
- intially acral lesion thought to be CD4 positive small to medium pleomorphic T-cell lymphoma and was treated multiple times with local radiation to the left foot tumors and was on bexarotene.
- Study entrance had tumors and plaques on lower extremities with mswat of 10.5.
- Pralatrexate reduced to 10mg/m2 QOW secondary grade 3 mucositis .
- Achieved partial response at cycle 5
- Chronic ulcer on left leg exposed to prior radiation kept getting larger and patient was taken off due to progressive disease after receiving 21 cycles of pralatrexarte.

Depsipeptide (Romidepsin) and PDX (Pralatrexate) inhibits cell growth in CTCL cell lines (MTS 48hrs)





Response Assessments

- Modified severity weighted adjustment tool (mSWAT) done prior to every cycle
- Computed tomography (CT) scans at screening for all patients and subsequently according to response to treatment
- Flow cytometry at baseline and every other cycle with blood involvement and within 4 weeks of response/progression for patients without blood involvement
- Pruritus severity prior to every cycle
- Lactate dehydrogenase (LDH) prior to every cycle

Criteria for Integrated Response Evaluation

Complete Response	• 100% clearance of disease in all areas (skin, blood, viscera, lymph nodes)
Partial Response	• 50% disease reduction in all involved areas
Stable Disease	• < 25% increase to < 50% reduction in mSWAT score from baseline • Fails to attain criteria for CR, PR, or PD
Progressive Disease	• ≥ 25% increase in mSWAT score from baseline • In patients with CR or PR, ≥ 25% increase of mSWAT score from the sum of nadir and 50% baseline mSWAT score