Cutaneous Lymphoma

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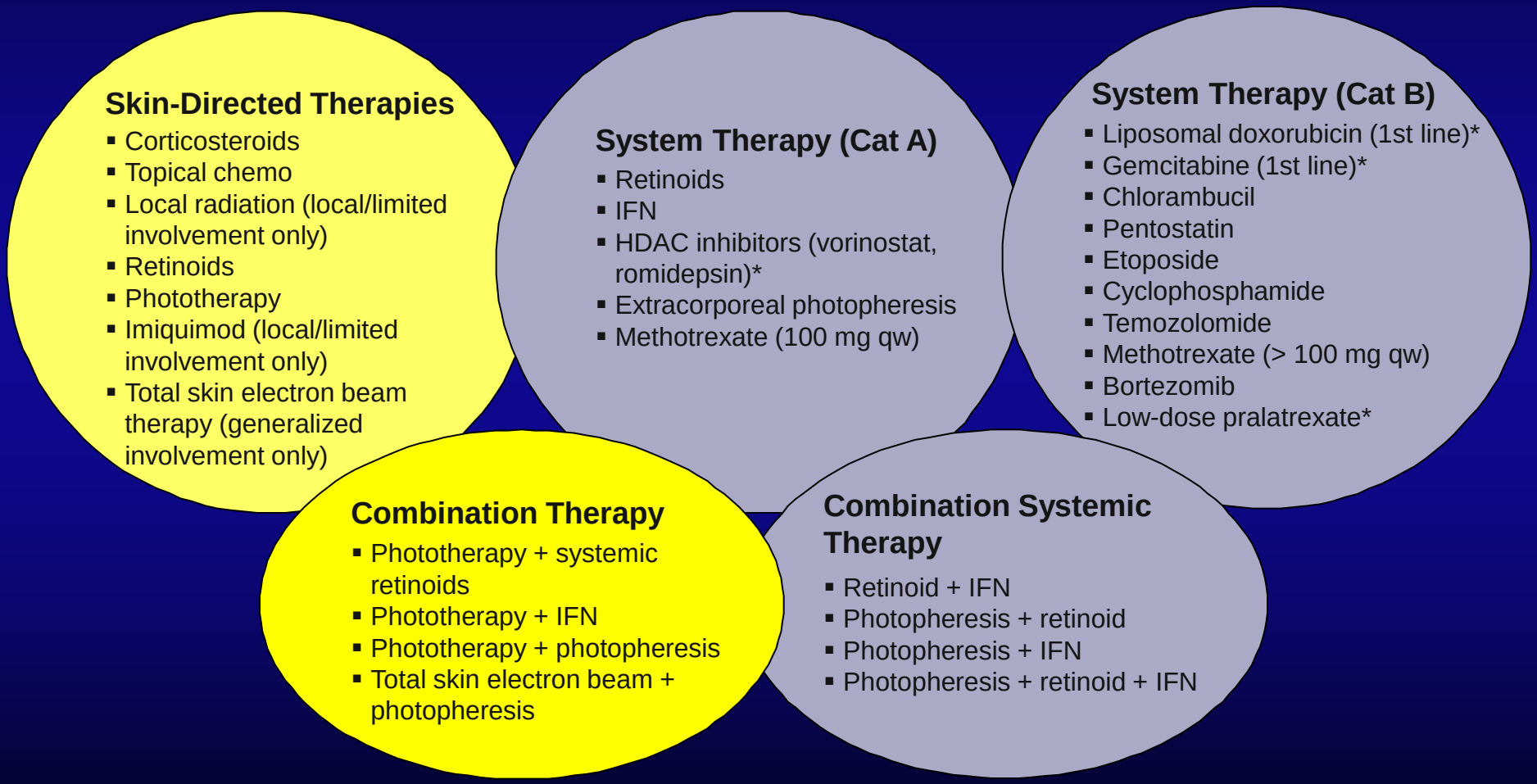
WHO-EORTC classification of cutaneous lymphoma - T cells

- Cutaneous T-cell and NK-cell lymphomas
  - Mycosis fungoides
  - MF varants and subtypes
    - Follicolotropic MF
    - Pagetoid reticulosis
    - Ganulomatous slack skin
- Sézary syndrome
- Adult T cell leukemia/lymphoma
- Primary cutaneous $CD30^+$ lymphoproliferative disorder
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T cell lymphoma
- Extranodal NK-T cell lymphoma, nasal type
- Primary cutaneous peripheral T cell lymphoma unspecified

NCCN Suggested Treatment Regimens for MF and Sézary Syndrome



*Preferred options for LCT MF and stage IV non-Sézary/visceral disease (aggressive growth characteristics).

NCCN. Clinical practice guidelines in oncology: non-Hodgkin's lymphomas. v.2. 2013.

Therapy for Early-Stage CTCL

- Topical chemotherapy
  - Mechlorethamine (Nitrogen Mustard)
    - Used since 1950's
    - Commercial formulation (Valchlor®)*
      - 0.02% gel
      - Applied 1-4 times daily
    - Response:
      - Response rate: 69% (by SWAT score)
      - Median time to response -> 26 weeks
        - † Complete response -> 19%
      - Duration of response -> 90% at 10+ months
    - Adverse reactions
      - Skin irritation (25%)
      - Dispigmentation (6%)
      - Skin cancer

*** FDA labeled indication for CTCL.**
Lessin et al. JAMA Dermatol 2013 149:25-32

Therapy for Early-Stage CTCL

- Retinoids
  - Bexarotene gel (Targretin®) *
    - Topical gel
    - Partial response - 42%
    - Complete response - 21%
  - Isotretinoin (Accutane®)#
    - Oral
    - Response rate - 40-45%
- Topical steroids
  - Medium to high potency
  - Overall response rate
    - T1 disease
      - CR 63%
      - PR 31%
    - T2 disease
      - CR 25%
      - PR 57%

*** FDA labeled indication for CTCL**
 # Non-FDA indication (clinical)

Hoppe et al. *J Clin Oncol.* 1987;5:1796–1803.
Ramsay et al. *J Am Acad Dermatol.* 1988;19:684–691.
Vonderheid et al. *J Am Acad Dermatol.* 1989;20:416–428.
Duvic. *Dermatol Online J.* 2001;7:3.
Zackheim et al. *J Am Acad Dermatol.* 1990;22:802–810.
***Physicians' Desk Reference.* 2003.**

Phototherapy in Early-Stage CTCL

- Psoralen with UVA irradiation (PUVA)
  - Response rates
    - Stage IA - 79% to 88%
    - Stage IB - 52% to 59%
    - Patch disease - 90%
    - Plaque disease - 76%
    - Overall response rates of 50%
  - FFP ~2.5 years
  - Generally well tolerated
  - Adverse reactions:
    - Psoralen can cause nausea, need to protect eyes from light
    - Associated with secondary skin cancers

Duvic et al. *J Am Acad Dermatol.* 1996;35:573–579.

Herrmann et al. *J Am Acad Dermatol.* 1995;33:234–242.

Roenigk et al. *J Invest Dermatol.* 1990;95 (suppl 6):198–205.

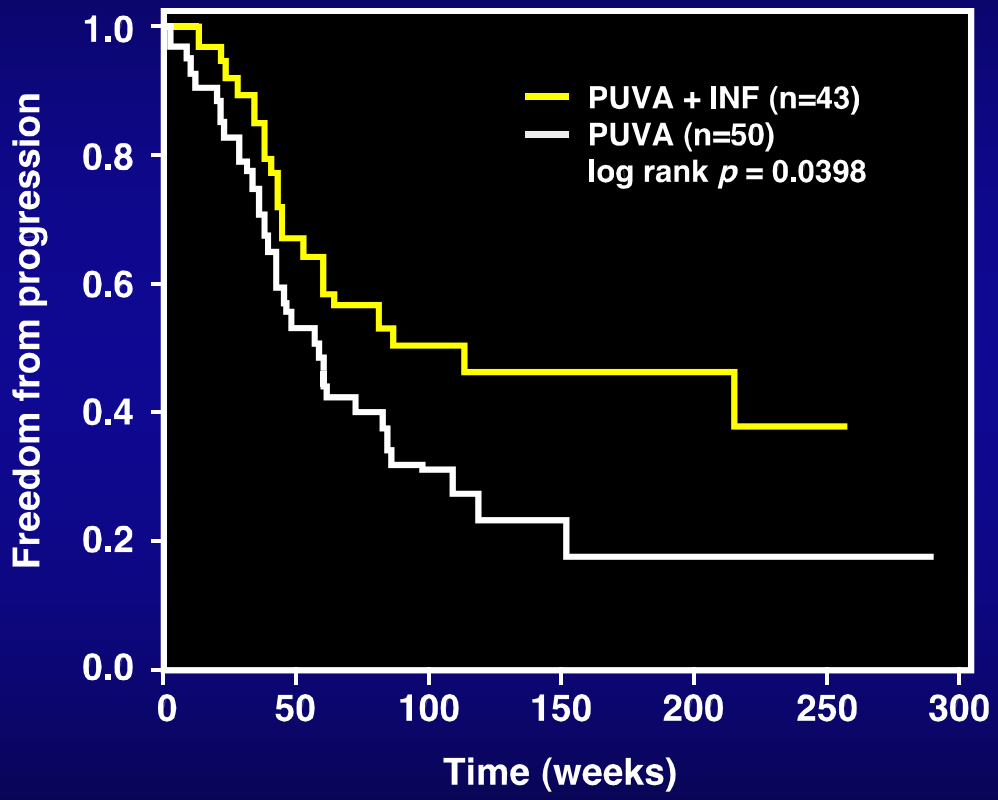
Baron et al. *Dermatol Ther.* 2003;16:303–310.

Ramsay et al. *Arch Dermatol*. 1992;128:931–933.

Rampino et al. *Radiol Med*. 2002;103:108–114.

PUVA + Interferon-α

- Study of 96 patients with stage I and II MF
- Response
  - PUVA - 72%
  - PUVA + INF - 80%
- Less UVA exposure in PUVA + INF treatment



Stadler et al, 2006 JCO 24(suppl):7541

Phototherapy in Early-Stage CTCL

- UVB irradiation
  - Remissions - 71% (25 of 35) of patients after a median treatment of 5 months
  - Median duration - 22 months
  - No patients with plaque-stage disease had remission
  - No nausea/? Less secondary skin cancer
- Electron beam irradiation
  - Can control depth of penetration of electrons
    - Most of the radiation delivered to top 5 mm
  - Effective in thick generalized plaques or tumors
  - Response rate of 55-95% in IA/IIA disease
  - Total body E-beam
    - T2: CR 76% with 15 yr FFR of ~15%
    - T3: CR 44% with 10 yr FFR ~15%
  - Increased DFS but not OS

Duvic et al. *J Am Acad Dermatol.* 1996;35:573–579.

Herrmann et al. *J Am Acad Dermatol.* 1995;33:234–242.

Roenigk et al. *J Invest Dermatol.* 1990;95 (suppl 6):198–205.

Baron et al. *Dermatol Ther.* 2003;16:303–310.

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Rampino et al. *Radiol Med*. 2002;103:108–114.

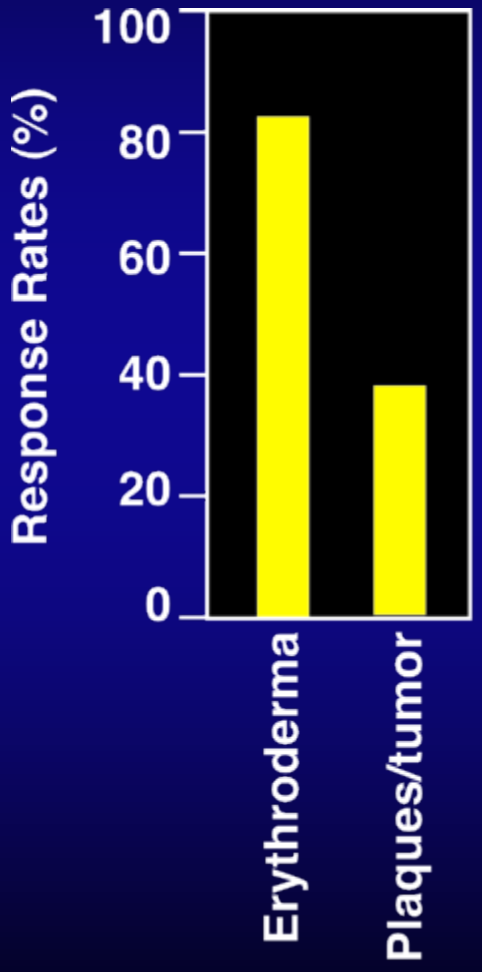
Systemic/Phototherapy for CTCL - Photophoresis (ECP)

- Removal and exposure of white blood cells to UVA light in the presence of psoralen and re-infusing back into patient
- ~10% of white cells treated
- Given on 2 consecutive days monthly

THERAKOS™ CELLEX™ Photopheresis System

Extracorporeal Photopheresis (ECP)

- ECP more effective for erythroderma than for plaques and tumor disease (CTCL-1)
  - » More effective when circulating Sezary cells
- Median time to response was 2-4 months
- Median duration of response varied
  - » CTCL-1 > 14 months



Therakos - data on file

Extracorporeal Photopheresis (ECP)

- Retrospective review of the largest series of ECP treatment
  - 16 studies
  - 411 total patients
  - Responses
    - Overall response - 60%
    - Partial response - 36%
    - Complete response - 18%
- Combined with immunostimulatory agents (INF-α)
  - ORR - 75% (35/47 pts)
  - Median survival - 66 months

Knobler R et al. Transfus Apher Sci 2003; 28:81-89
Suchin KR et al. Arch Dermatol 2002; 138:1054-60

Management of Late-Stage (IIB–IVB)/Refractory CTCL

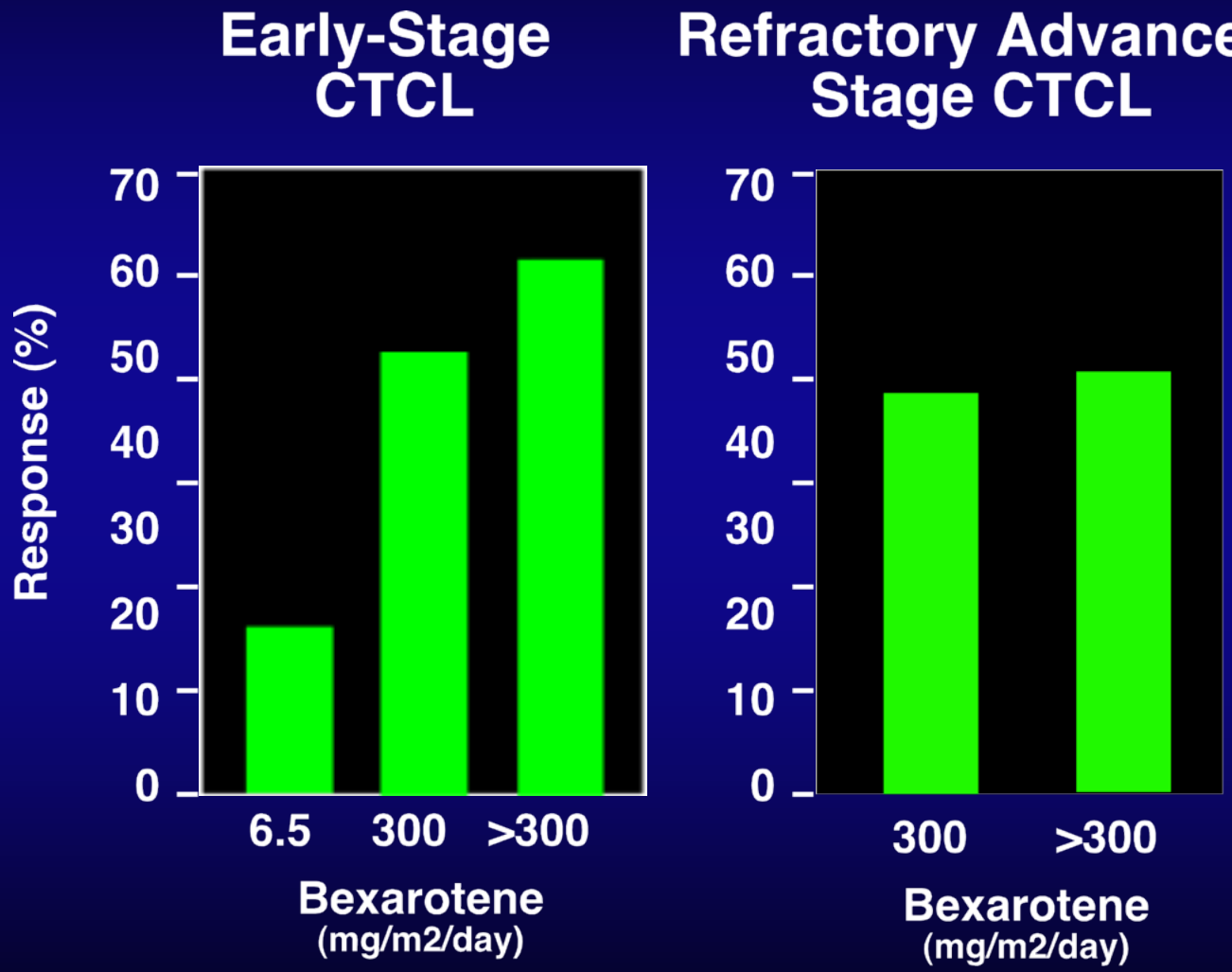
- Chemotherapy
  - Gemcitabine (*Gemzar*)#
  - Liposome-encapsulated doxorubicin (*Doxil*)*
  - Cladribine (*Leustatin*)*
  - Methotrexate
  - Pralatrexate
  - Pentostatin
  - Cyclophosphamide
  - Temozolomide
  - Etoposide
- Retinoids
  - Bexarotene
  - Isotretinoin
- Histone deacetylase (HDAC) inhibitor
  - Vorinostat
  - Romidepsin
- Interferon
  - Interferon – alpha
  - Interferon - gamma
- Others
  - Bortezomib
  - Brentuximab vedotin
  - Alemtuzumab (CamPath)

Gemcitabine treatment of CTCL

- Treatment
  - Gemcitabine 1200 mg/m^2 IV on days 1, 8, 15.
  - Repeated every 28 days (x 3 cycles)
- Response
  - Overall response -> 70.5%
    - Complete response -> 11.5%
    - Partial response -> 59%
  - Median response duration -> 15 months (range 6 to 22 months)
- Toxicity
  - Anemia, low white cell count, low platelet count
  - Hair loss (mild)
  - Increased liver enzymes

Zinzani et al. J Clin Oncol 2000, 18:2603-2606

Responses in Patients With CTCL Treated With Oral Bexarotene



Response based on the physician's global assessment

Duvic et al. *Arch Dermatol*. 2001;137:581–593.

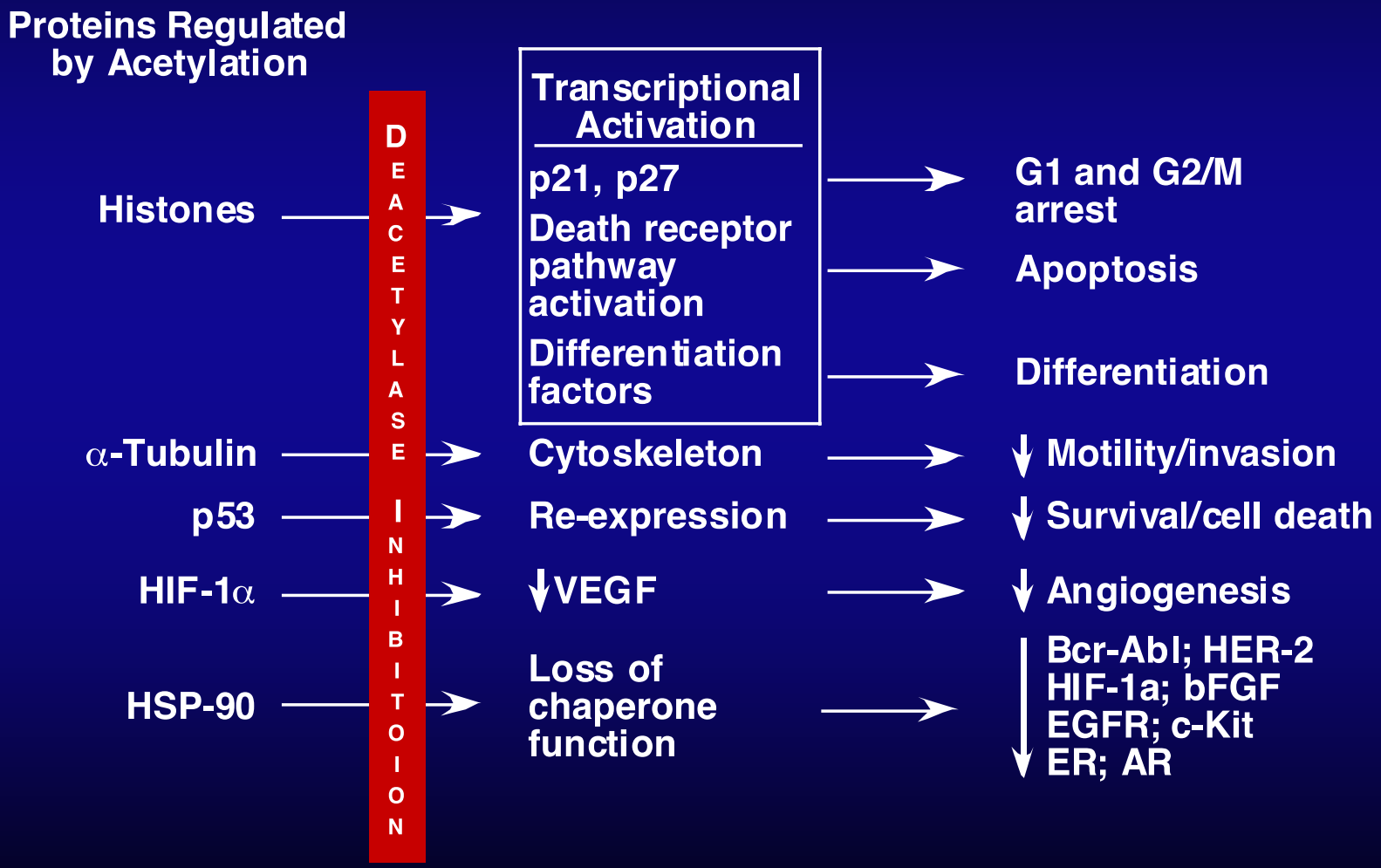
Summary of Phase 2/3 Experience With Oral Bexarotene

- Responses are dose dependent
- Time to maximum response is several months
- Treatment complicated by hypertriglyceridemia and hypothyroidism
  - » Hypertriglyceridemia treated with fibrate or statin (NOT gemfibrozil)
  - » Often started on Synthroid
- Hypertriglyceridemia and hypothyroidism resolved with bexarotene stopped

Talpur et al. *J Am Acad Dermatol.* 2002;47:672–684.

Sherman et al. *N Engl J Med*. 1999;340:1075–1079.

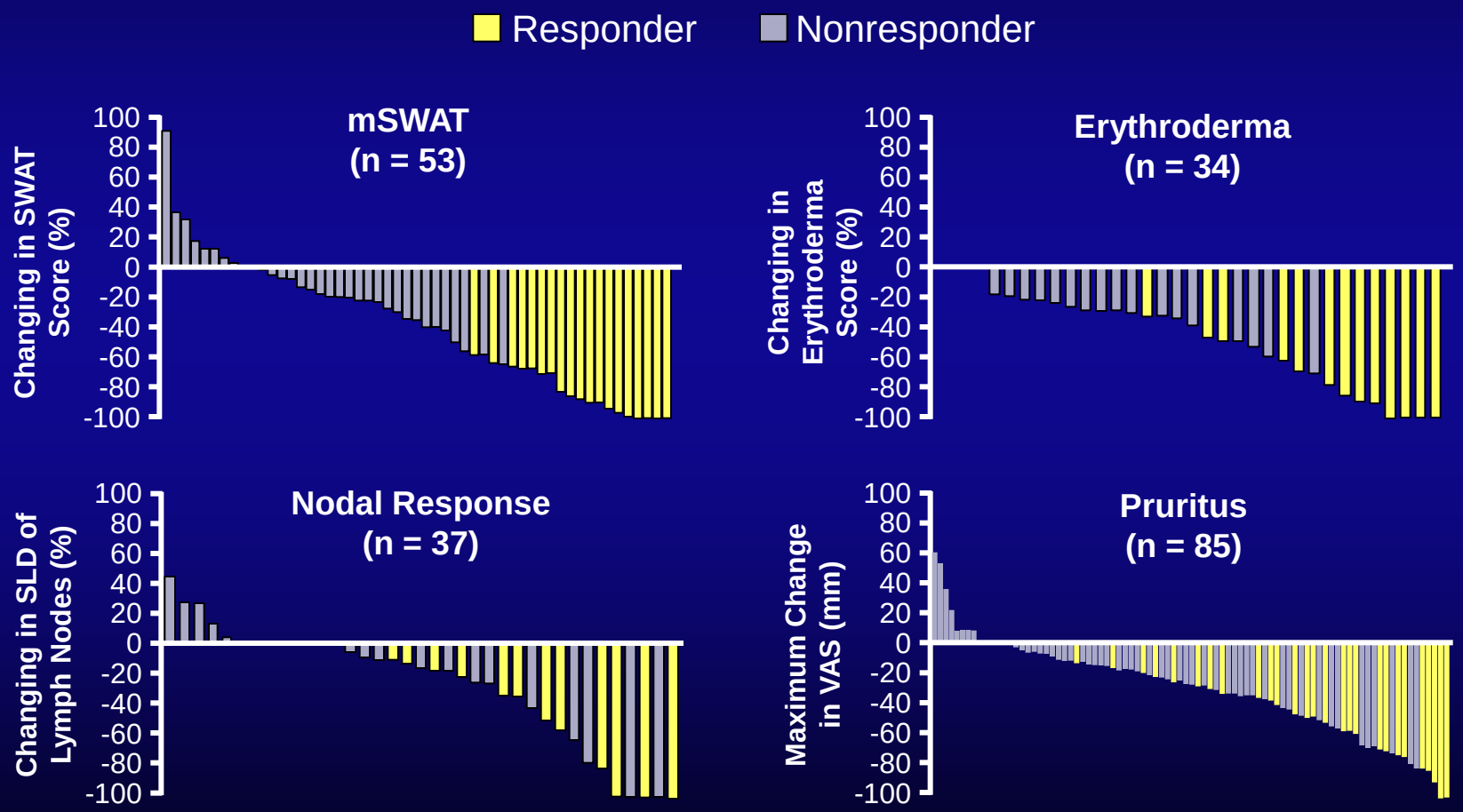
Multiple Proteins Are Regulated by Acetylation/Deacetylation



Romidepsin – histone deacetylase inhibitor

- Treatment
  - » Romidepsin 14 mg/m2 over 4 h IV weekly for 3 weeks
  - » Repeat every 4 week
- Median time to response -> 2 months
- Median duration of response -> 11-15 months

Pivotal Open-Label Phase II Study of Romidepsin in Refractory CTCL



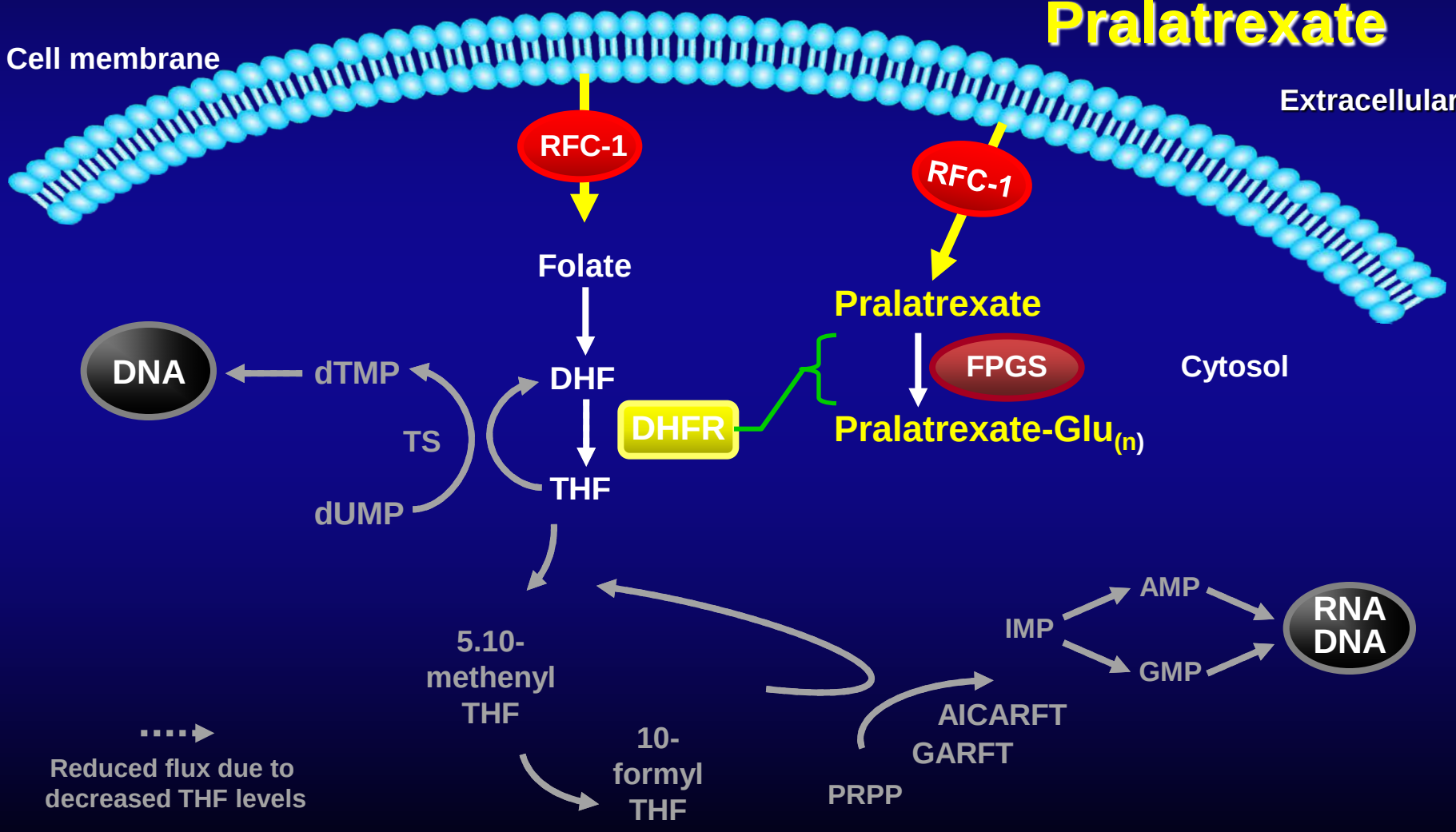
Whittaker SJ, et al. J Clin Oncol. 2010;28:4485-4491.

ZOLINZA™ (vorinostat) Study 1: Clinical Results

- Histone deacetylase (HDAC) inhibitor
- Response rate
  - Overall response rate -> 29.7%
  - Stage IIB and higher CTCL -> 29.5
- Median times to response was ~ 55 days (range 28 to 171 days)
- Median duration of response not reached but estimated at ~6 months

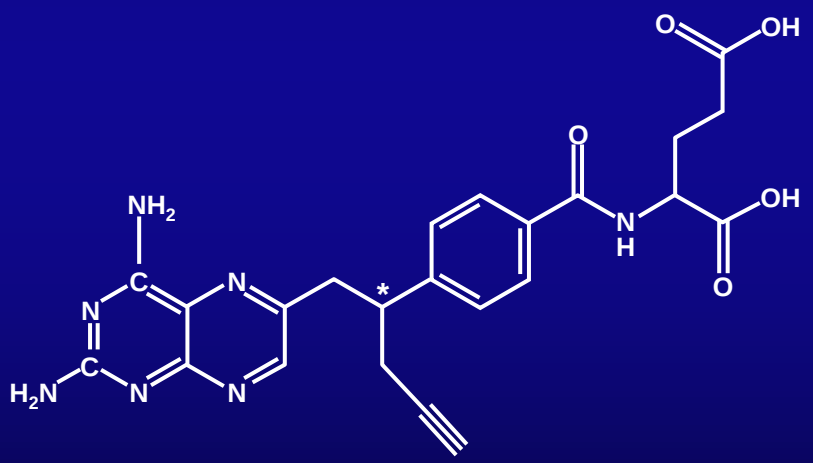
Pralatrexate Mechanism of Action

Rationally designed antifolate to improve cellular uptake and retention



Pralatrexate

- Treatment schedule
  - » 15 mg/m2 weekly for 3 of 4 weeks
- Response rate
  - » Overall -> 41%
  - » Partial response -> 35%
- Side effects
  - » Mouth sores –> 54%
  - » Fatigue -> 43%
  - » Skin toxicity -> 28%
  - » Edema -> 26%
  - » Anemia -> 22%
  - » Fevers -> 22%



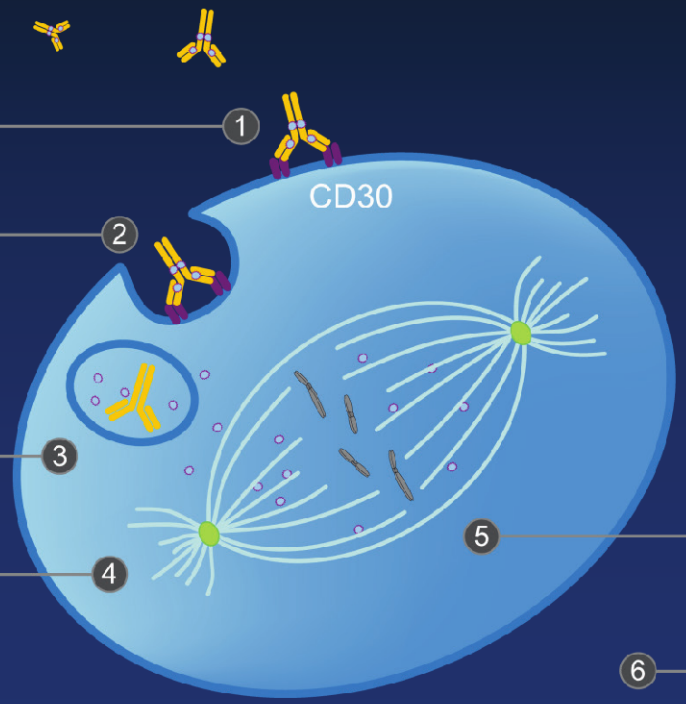
Horwitz et al. Blood 2012. 119:4115-4122

Krug LM, et al. *Clin Cancer Res*. 2000;6:3493-3498.

Brentuximab Vedotin Mechanism of Action

Brentuximab vedotin antibody-drug conjugate (ADC)

- Monomethyl auristatin E (MMAE), microtubule-disrupting agent
- Protease-cleavable linker
- Anti-CD30 monoclonal antibody



1. Brentuximab vedotin binds to CD30
2. Brentuximab vedotin-CD30 complex is internalized and traffics to lysosome
3. MMAE is released
4. MMAE disrupts microtubule network
5. G2/M cell cycle arrest
6. Apoptosis

ALCANZA: ORR4, PFS, CR, and Change in Symptom Burden

Endpoint	Brentuximab Vedotin (n = 64)	Methotrexate or Bexarotene (n = 64)	Difference (95% CI)	*P* Value
ORR4, n (%)	36 (56.3)	8 (12.5)	43.8 (29.1 to 58.4)	< .0001
CR, n (%)	10 (15.6)	1 (1.6)	14.1 (-4.0 to 31.5)	.0046*
Median PFS, mos	16.7	3.5	--	< .0001*†
Mean max. reduction in Skindex-29 symptom domain, points	-27.96	-8.62	-18.9 (-26.6 to -11.2)	< .0001*

***Adjusted *P* value from weighted Holm's procedure.**
†HR: 0.270 (95% CI: 0.169-0.430).

- PFS significantly improved for subgroups defined by pt characteristics (baseline ECOG PS of 0, sex, age < 65 yrs, geographical region), disease characteristics (MF and pcALCL, skin involvement, baseline skin tumor score), and treatment (bexarotene and methotrexate)

Kim YH, et al. ASH 2016. Abstract 182.

Combination Chemotherapy for Advanced MF/SS

- Combination chemotherapy
  - » Small studies
  - » Various regiments
  - » +/- electron beam irradiation or nitrogen mustard
- Retrospective analysis
  - » 24 studies involving 331 patients
  - » Response rate
    - – Complete responses - 38%
    - – Partial responses - 43%
  - » Duration - 5 to 41 months
- Unclear if improved survival

Bunn et al. 1994; Ann Int. Med. 121:592-602

WHO-EORTC classification of cutaneous lymphoma - B cells

- Cutaneous B-cell lymphoma
  - » Primary cutaneous marginal zone B-cell lymphoma
  - » Primary cutaneous follicle center lymphoma
  - » Primary cutaneous diffuse large B cell lymphoma, leg type
  - » Primary cutaneous diffuse large B cell lymphoma, other
    - – Intravascular large B cell lymphoma
- Precursor hematologic neoplasm
  - » CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)

Primary cutaneous B cell lymphoma - survival

Cumulative Survival