

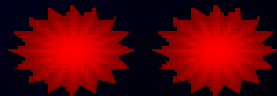
Histone Deacetylase Inhibitors

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Director, Division of Medical Oncology
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Winship Cancer Institute
Atlanta, USA.

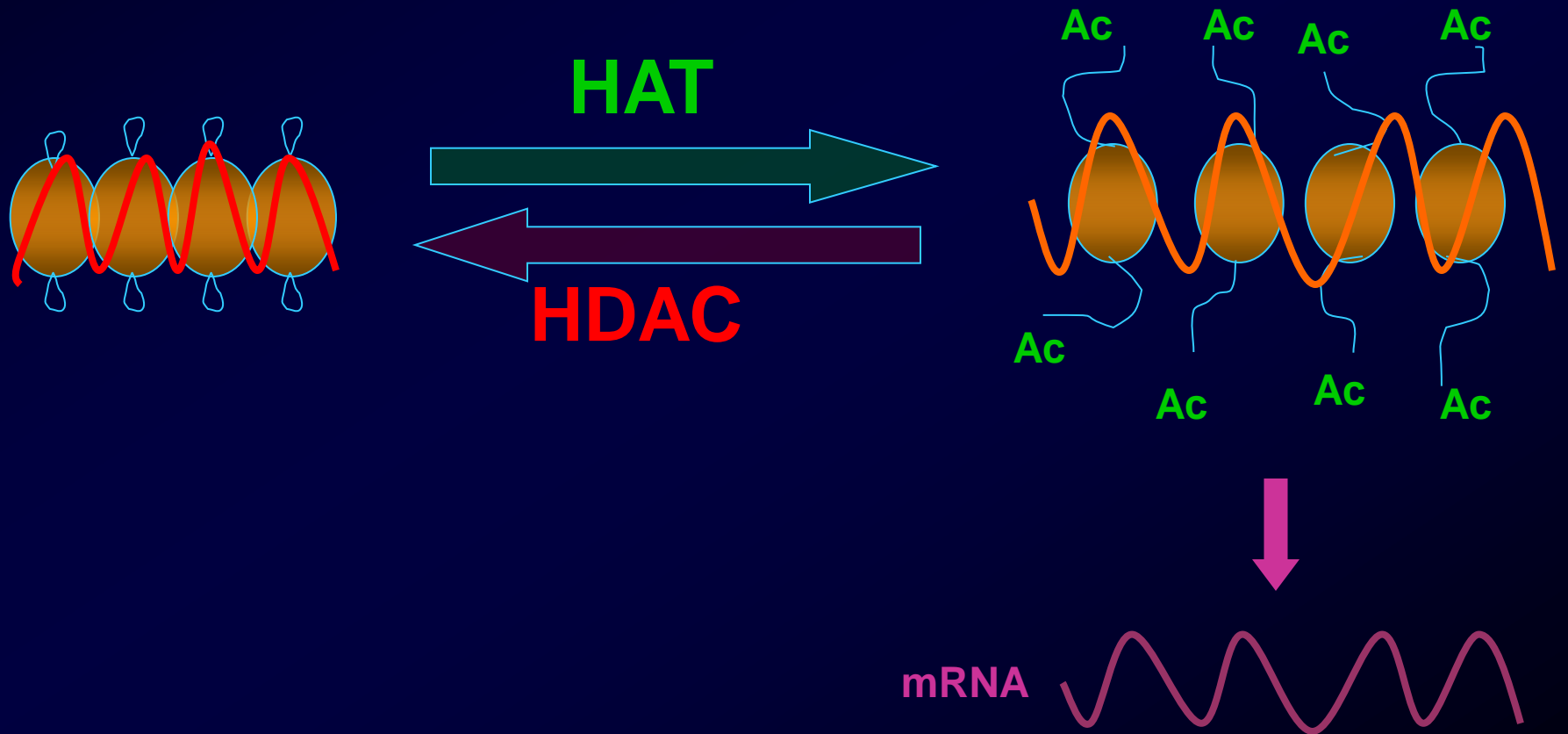


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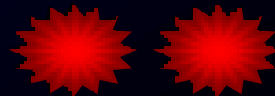
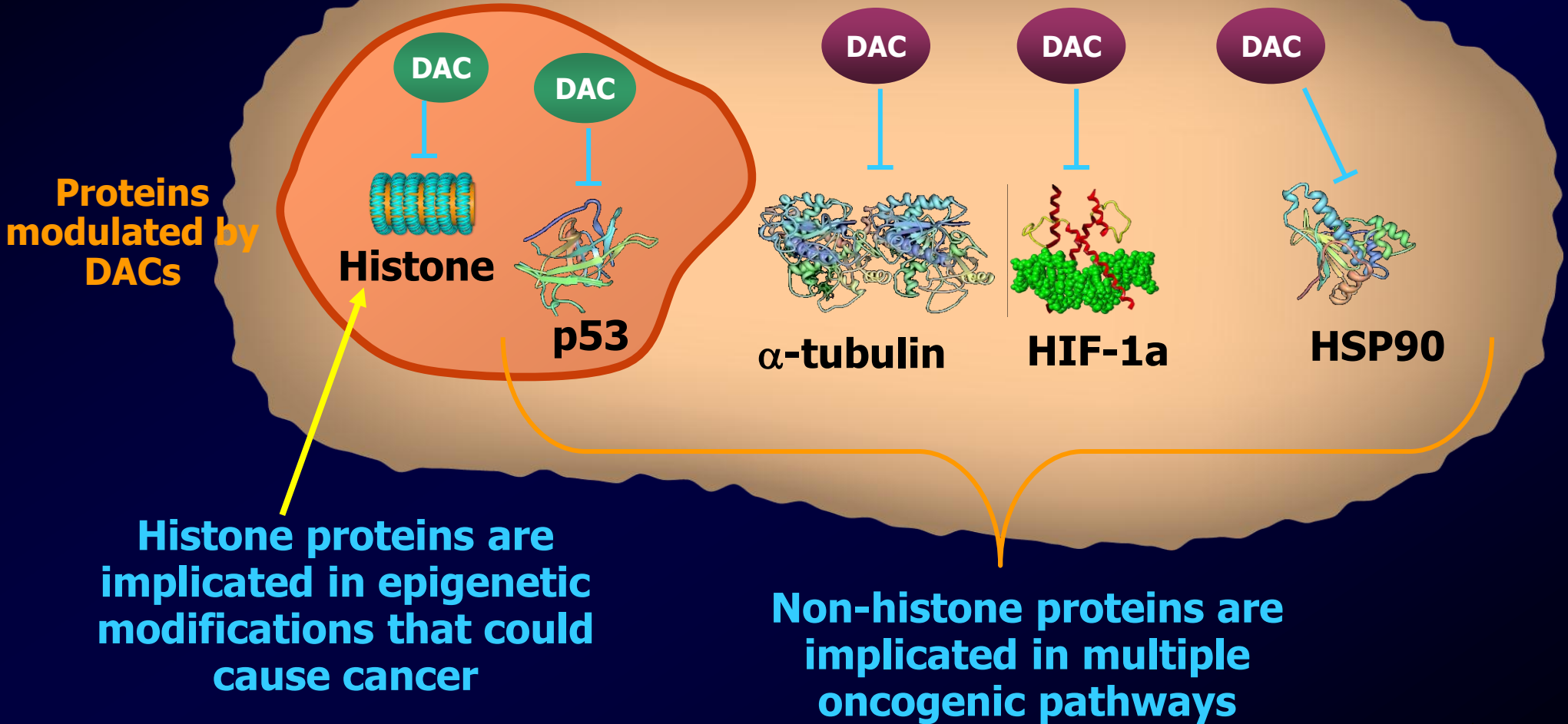
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Histone Acetylation

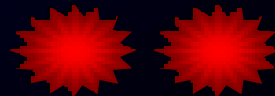


DACs are Implicated in Cancer by Modulating Histone and Non-Histone Proteins Involved in Oncogenesis



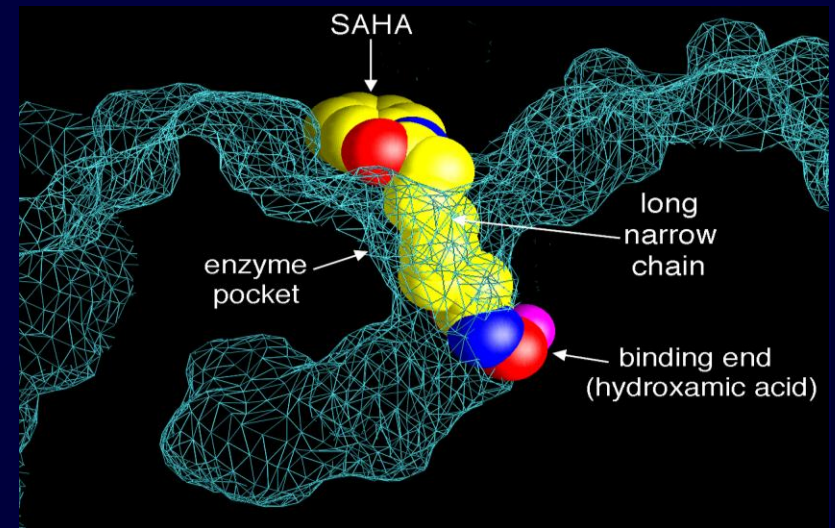
HDAC Inhibitors in Solid Tumors: Monotherapy

Author	Agent	Disease	Response
Traynor	Vorinostat	NSCLC	0/13
Krug	Vorinostat	Mesothelioma	2/13
Ramalingam	Belinostat	Mesothelioma	0/13
Blumenschein	Vorinostat	Head & Neck	0/14
Chew	Vorinostat	Breast	0/13



SAHA/Vorinostat (Suberoylanilide Hydroxamic Acid)

- **Small molecule (MW < 300)**
- **Binds inside the catalytic site of HDAC**
 - **Blocks substrate access to the active zinc ion**
- **Part of a new class of drugs that target select members of class I and II HDACs**

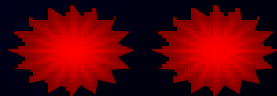


Marks PA, et al. *Nat Rev Cancer*. 2001;1:194-202; Villar-Garea A, et al. *Int J Cancer*. 2004;112:171-178.



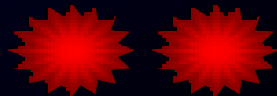
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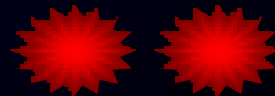
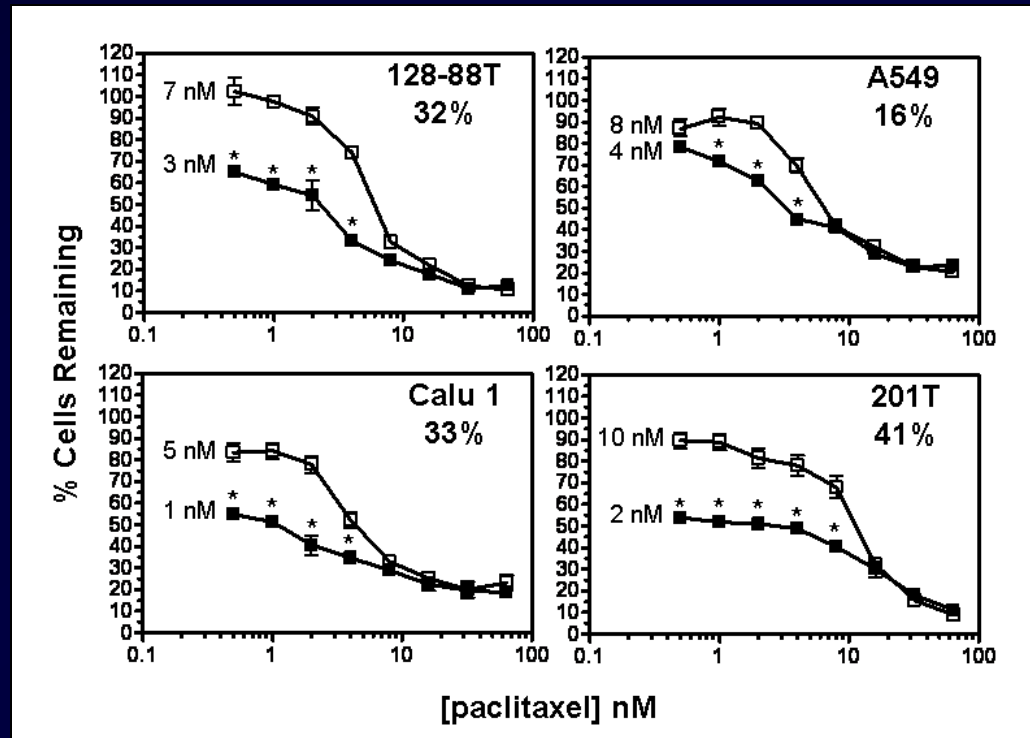


Vorinostat: Early Clinical Experience

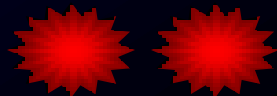
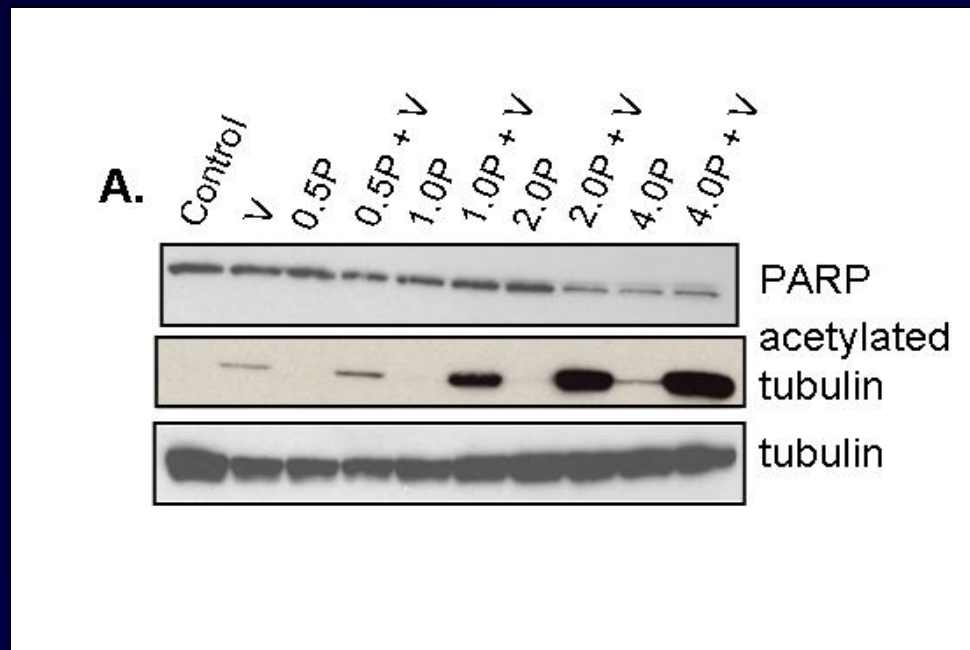
- Tolerated at doses up to 400 mg PO QD (2 weeks on, 1 week off)
- Common toxicities
 - Nausea, emesis, fatigue, thrombocytopenia
- Approved for treatment of refractory CTCL
- Disease stabilization noted in NSCLC patients



Vorinostat Enhances Anti-cancer Properties of Paclitaxel



Vorinostat Enhances Tubulin Acetylation in NSCLC Cell Lines



Vorinostat + Chemotherapy

Cancer Therapy: Clinical

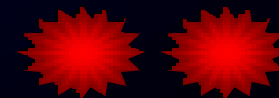
Phase I and Pharmacokinetic Study of Vorinostat, A Histone Deacetylase Inhibitor, in Combination with Carboplatin and Paclitaxel for Advanced Solid Malignancies

Suresh S. Ramalingam,^{1,3} Robert A. Parise,³ Ramesh K. Ramanathan,^{1,3} Theodore F. Lagattuta,³ Lori A. Musguire,¹ Ronald G. Stoller,¹ Douglas M. Potter,^{4,5} Athanassios E. Argiris,^{1,3} James A. Zwiebel,⁶ Merrill J. Egorin,^{1,2,3} and Chandra P. Belani^{1,3}

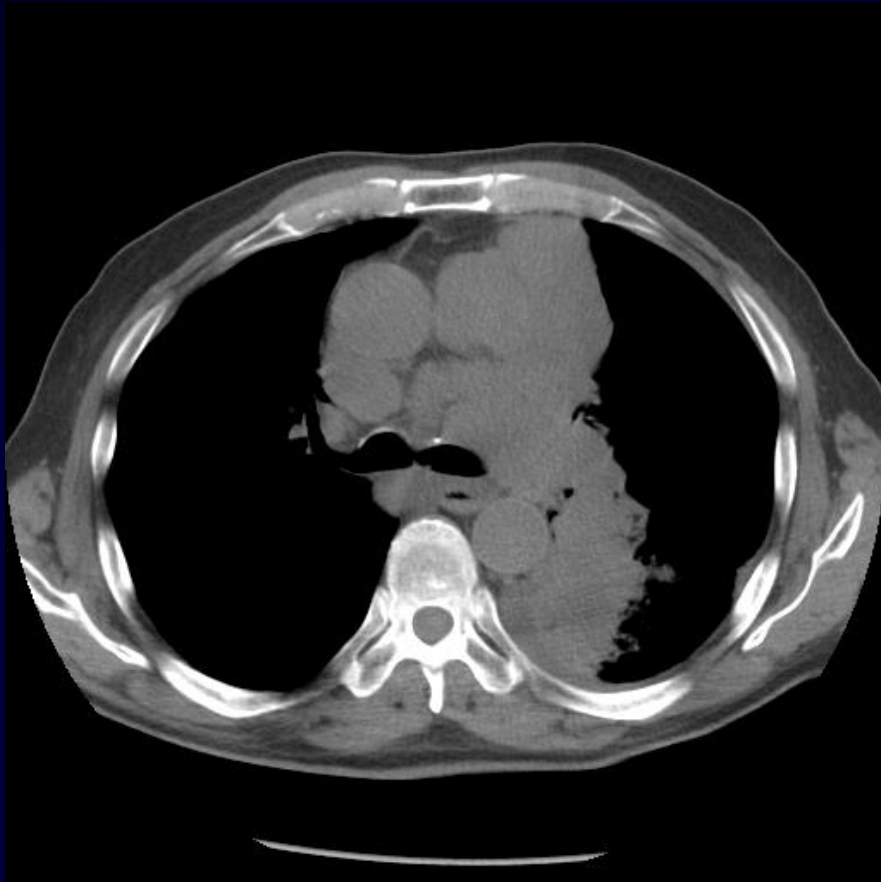
Table 1. Dose escalation scheme

Schedule	Dose level	Vorinostat, days 1-14 (mg)	Paclitaxel, day 1 (mg/m ²)	Carboplatin, day 1 (AUC mg/mL × min)	No. patients
A	1	200 qd	175	6	4
	2	300 qd	175	6	3
	3	400 qd	175	6	3
	4	400 qd	200	6	12
B	5	300 bd (days 1-7)	200	6	6

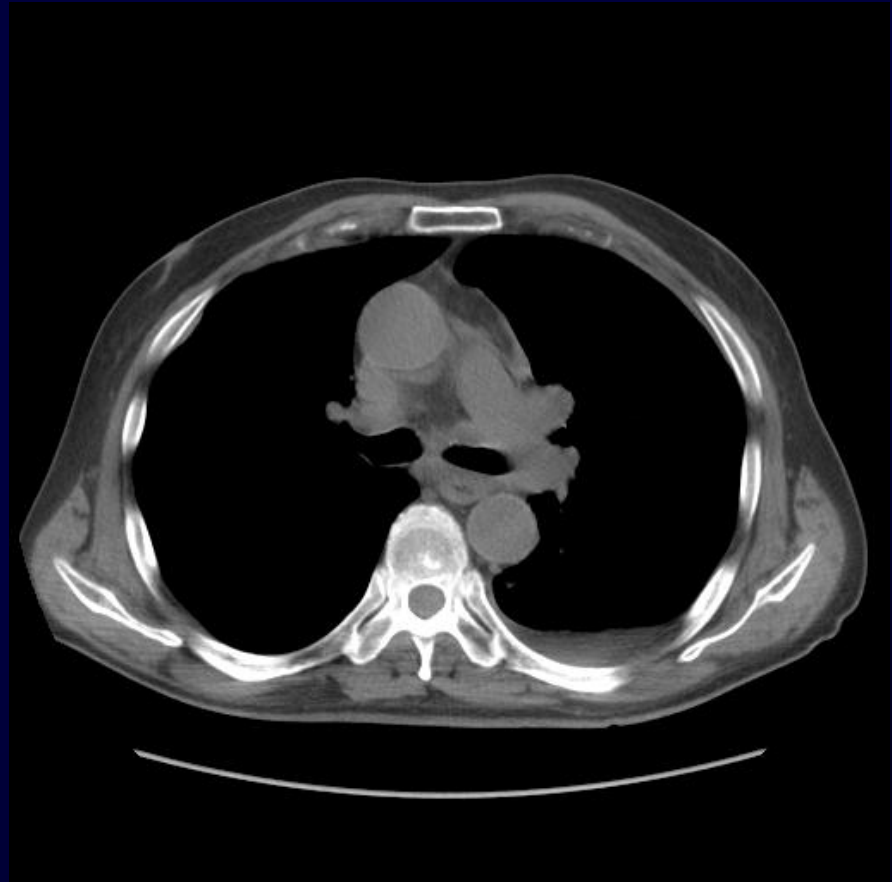
Promising anti-cancer activity in advanced NSCLC
10/19 objective responses; 4 patients with SD.



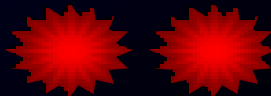
Objective Response In A Patient With Advanced NSCLC



Baseline



After 2 Cycles



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Rand Phase II Study

N=94 Patients
Stratification Factors:
Gender
Brain metastasis

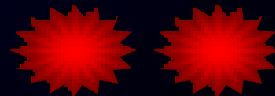
- Maximum of 6 cycles
- No cross over
- No maintenance therapy

2

Carboplatin
(AUC=6 mg/ml X min) (d 3)
Paclitaxel 200 mg/m² (d 3)
Vorinostat 400 mg QD(d1-14)

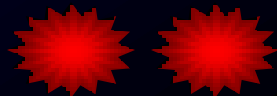
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Carboplatin
(AUC = 6 mg/ml X min) (d 3)
Paclitaxel 200 mg/m² (d 3)
Placebo QD (d 1-14)



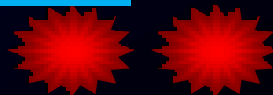
Efficacy

	Vorinostat	Placebo	Hazard Ratio	'p'
Response rate (RECIST)	34%	12.5%		0.021
Median PFS	6.0 m	4.1 m	0.79	0.33
Median survival	13 m	9.7 m	0.67	0.17
1-year survival rate	53%	35%		



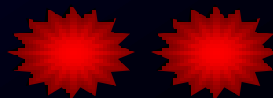
Non-Hematological Toxicity

Toxicity	Vorinostat (%) Gr 3/4/5	Placebo (%) Gr 3/4/5
Nausea	16/5/0	6/0/0
Vomiting	16/3/0	9/0/0
Diarrhea	8/0/0	9/0/0
Anorexia	13/2/0	9/0/0
Fatigue	30/3/0	21/3/0
Constipation	5/0/0	9/3/3
Neuropathy	16/0/0	16/3/0
Infection	0/3/0	0/0/3
Dehydration	3/10/0	-
Sodium, Serum-low	0/17/2	0/9/0
Treatment-related deaths	3%	-



Carboplatin, Paclitaxel + Vorinostat: Phase II/III Study

- Closed early due to futility
- Study utilized a slightly different treatment scheme
 - Patients were not pre-treated with vorinostat before chemo from cycle 2 onwards
 - Bevacizumab eligibility impacted study entry



Current Plans

Evaluation of a shorter schedule of vorinostat (5 days out of 21 days)

Safety assessment with doses up to 800 mg QD

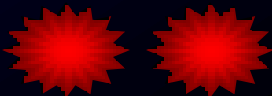
Rand phase II Study



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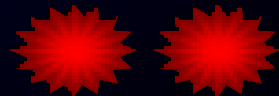
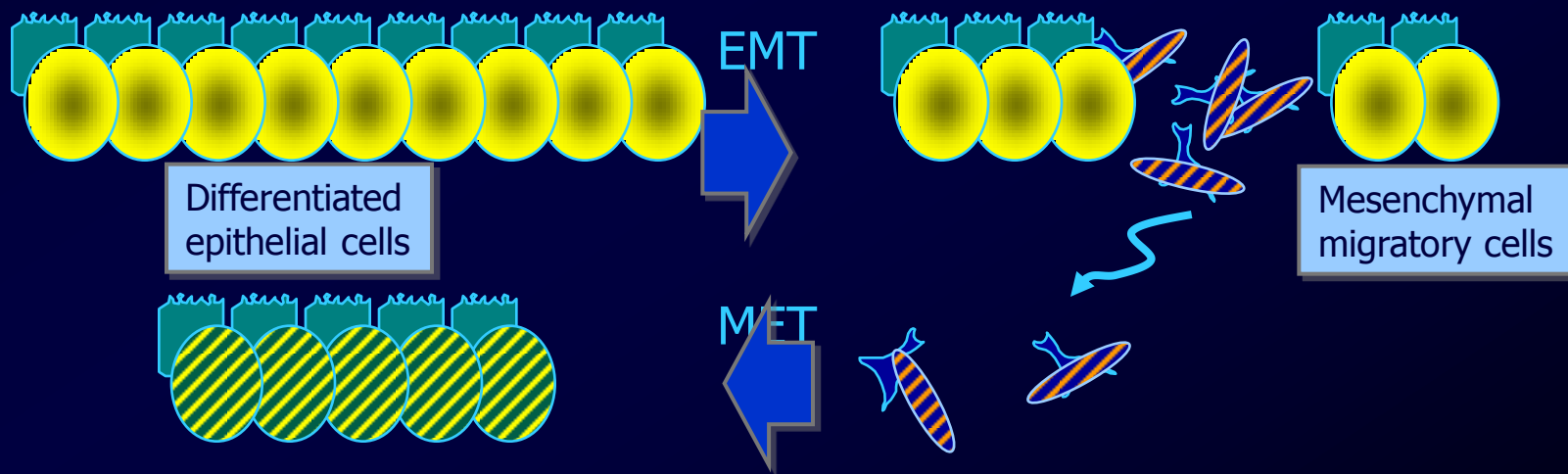
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NCI 8703, PI- Belani, California Cancer Consortium



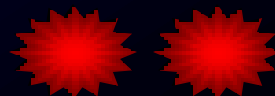
EGFRi Response a Factor of EMT

- Cancer cell invasiveness linked to Epithelial-Mesenchymal Transition (EMT)
- Loss of E-cadherin (CDH1) expression a hallmark of EMT
- EGFRi sensitivity and resistance correlates with epithelial to mesenchymal transition (EMT) markers
 - Shown first in NSCLC by U Colorado group (Witta and colleagues)

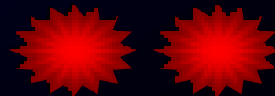
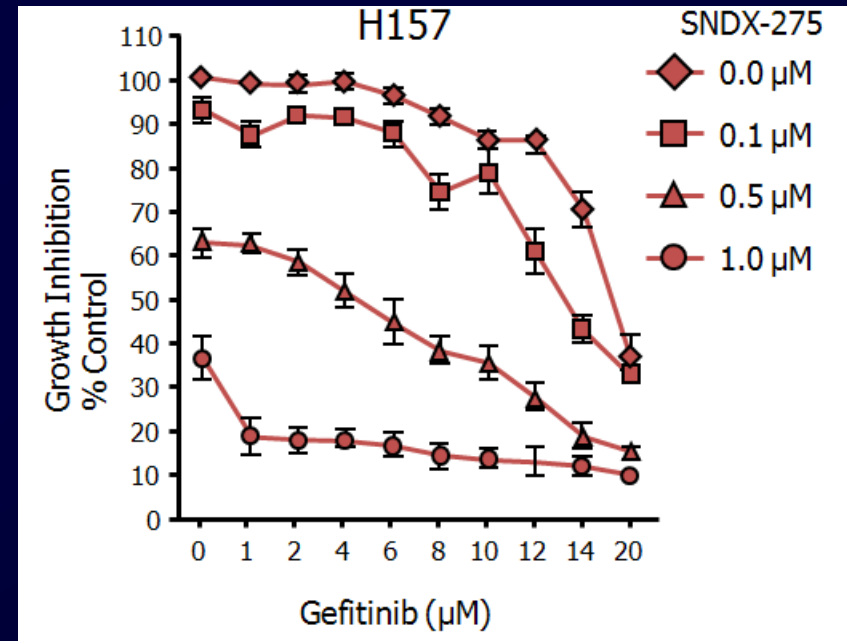
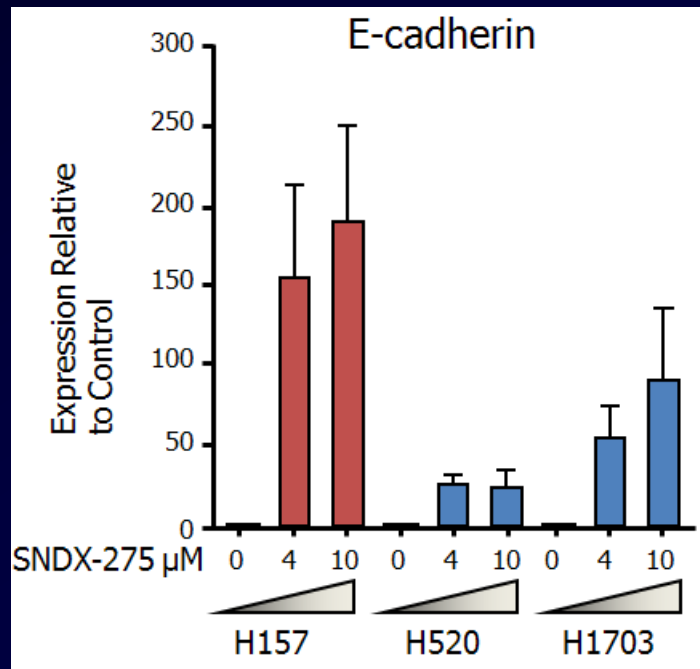


Entinostat

- Inhibitor of HDAC 1, 2 & 3
- Oral administration
- 10 mg on alternate weeks is the dosing under further development
- Common toxicities: Asthenia, diarrhea, platelets
- Activity seen across a variety of solid tumors

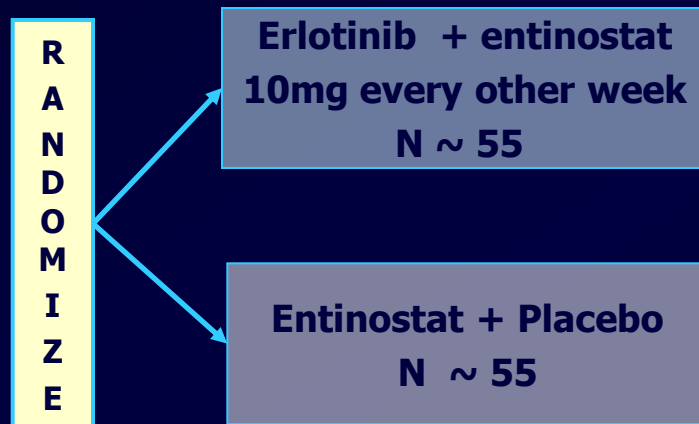


Entinostat Enhances Activity of EGFR TKI

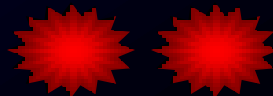


Ongoing Study: Erlotinib +/- Entinostat in NSCLC

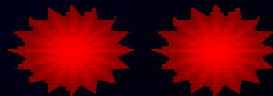
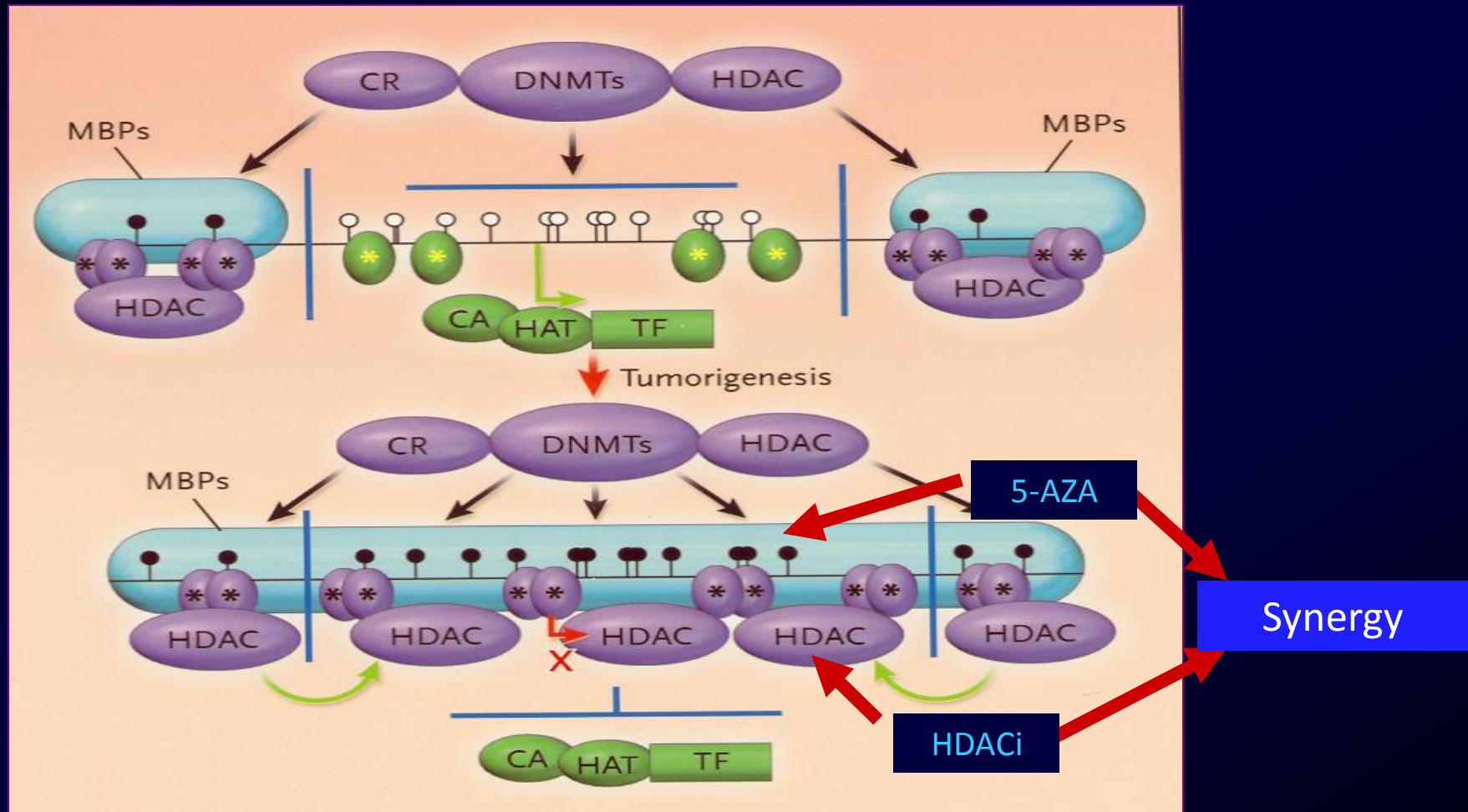
Patients with Advanced NSCLC eligible for
–Erlotinib Therapy in 2nd/3rd Line (ENCORE 401)



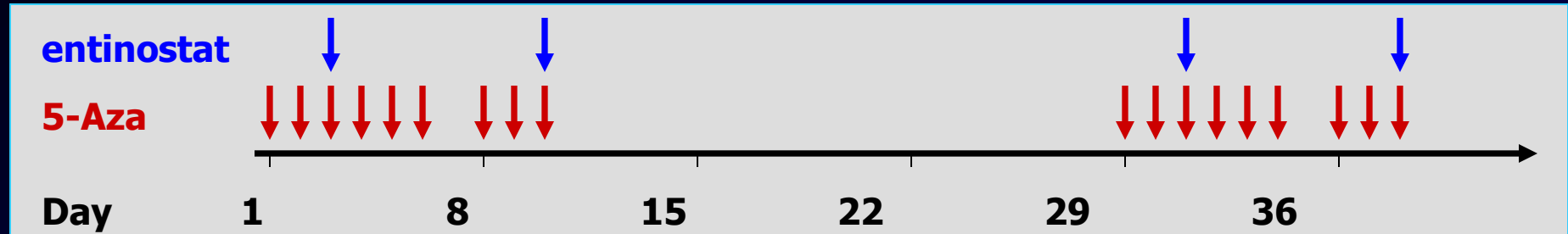
- Phase 2, randomized, blinded, placebo-controlled
- Efficacy Tarceva+entinostat vs. Tarceva in EGFRi-naïve patients
- Endpoint: 4 Month PFS Rate
- 30 US Oncology sites
- Patient accrual ongoing



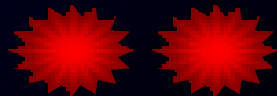
Combinatorial activities of HDACi and demethylating agents



Trial schema

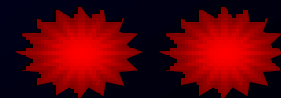


- Metastatic NSCLC; any number of prior Rx
 - 5AC dosing = 40 mg/m² SQ daily on days 1-6 and 8-10
 - Entinostat dosing = 7 mg PO (fixed dose) days 3 and 10
- Simon two-stage single arm phase II clinical trial
- Endpoints
 - Response rate, TTP, toxicity
 - Pharmacokinetic parameters
 - Pharmacodynamic correlates
 - Sputum, blood and tumor

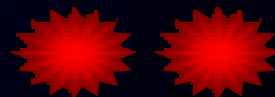
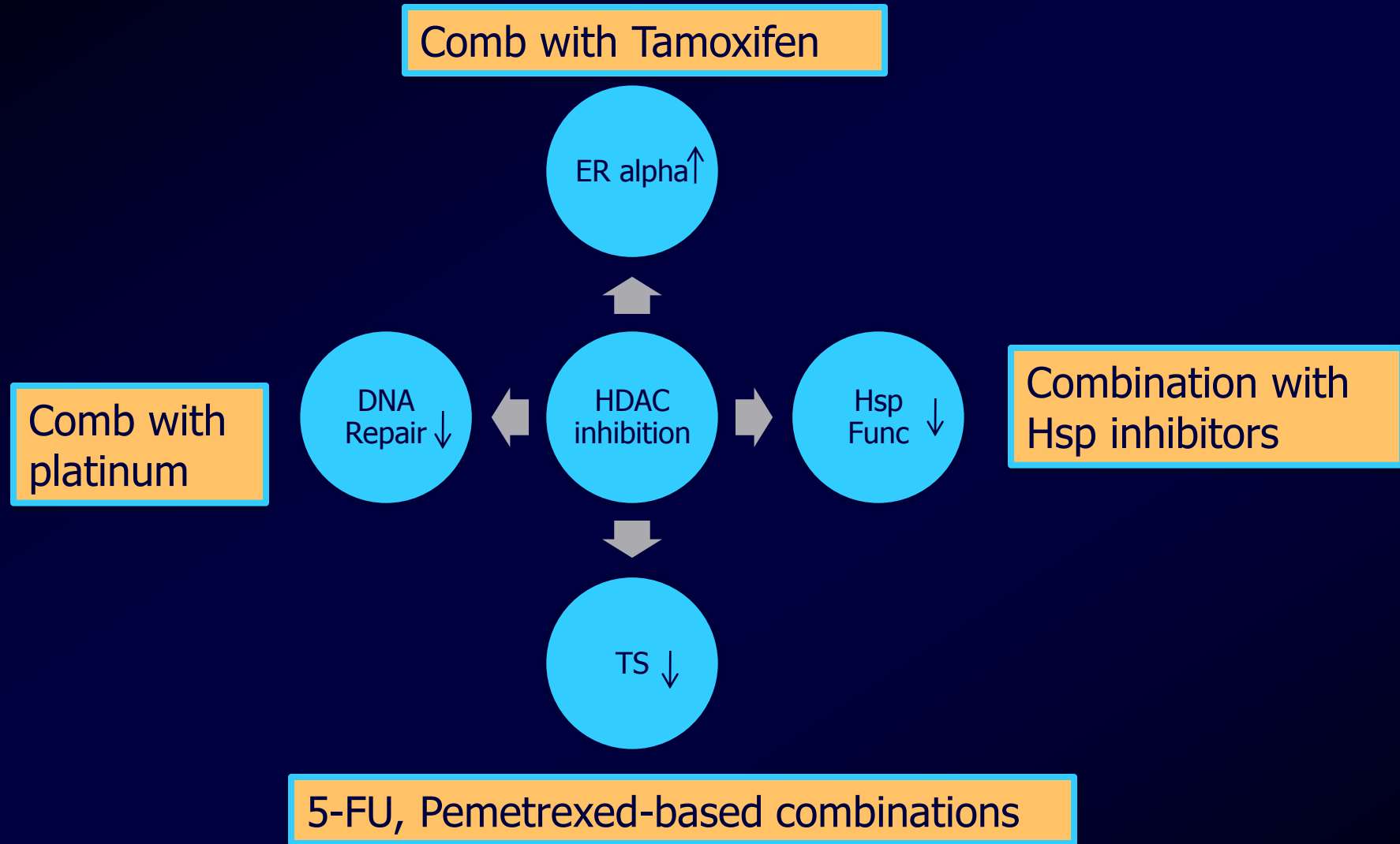


Interim response data (N=28 evaluable)

- 1 complete response
 - on treatment for 14 months
- 1 partial response
 - on treatment for 8 months
- 8 stable disease
 - one on treatment for 18 months
 - four treated for 4 months
 - One d/c due to scheduling after 3 months
- 17 progressive disease
- 8 not evaluable (finished less than 1 cycle)
- 3 being actively treated



Potential Applications of HDAC Inhibitors



Conclusions

- HDAC inhibition is a novel strategy for the treatment of cancer
- Combination strategies are most likely to be beneficial in NSCLC
- Though early results have been mixed, compelling preclinical evidence exists for continued evaluation of HDAC inhibitors in NSCLC

