(Following a somewhat self-indulgent and highly self- deprecating examination of my career as a CTEP investigator)

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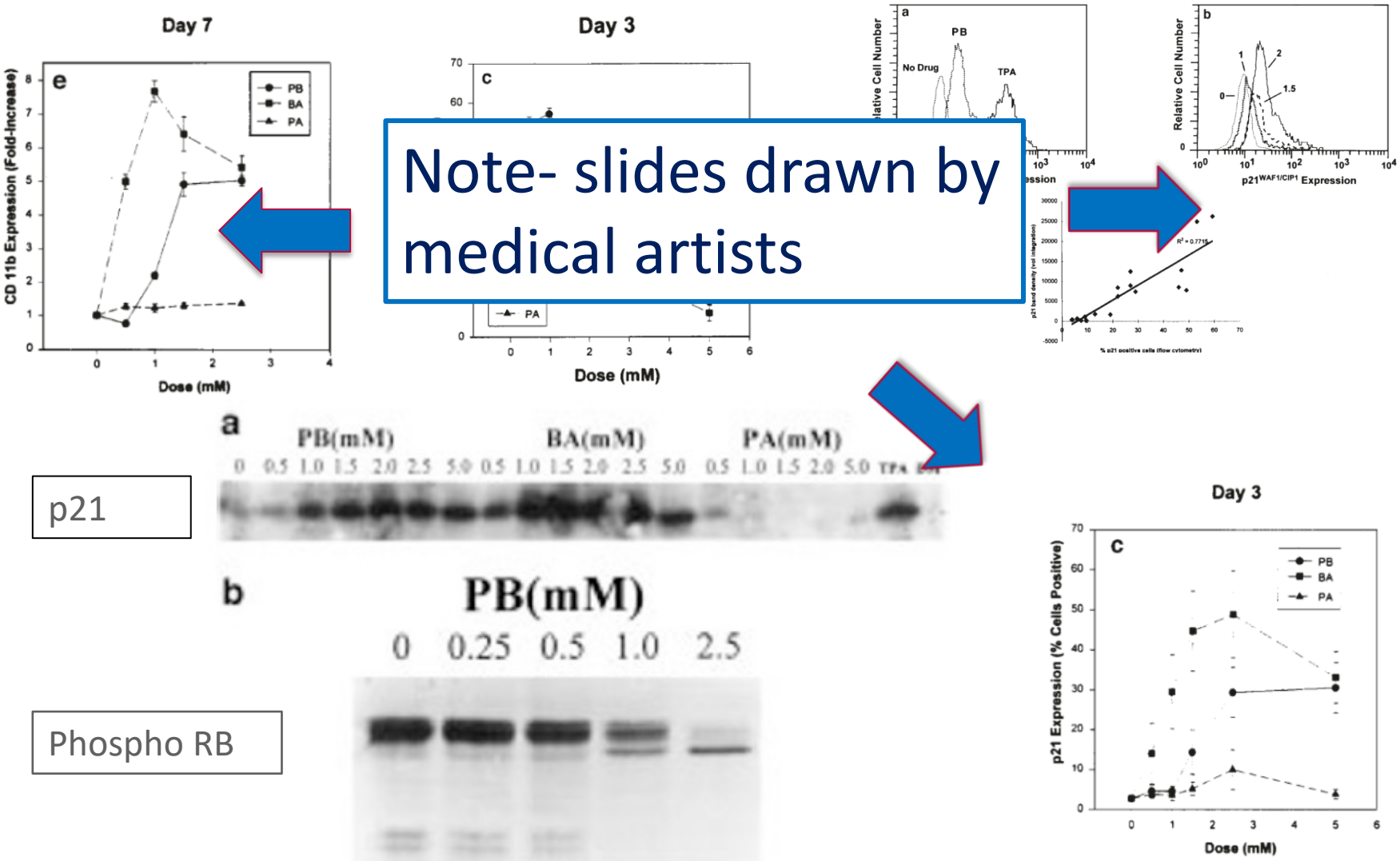
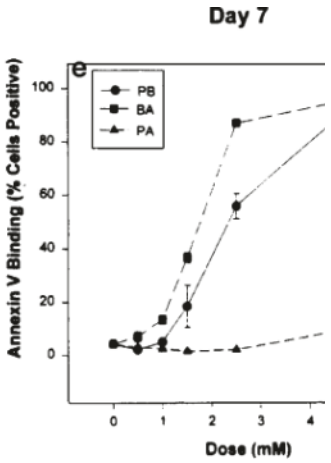
NIH NATIONAL CANCER INSTITUTE

August 25, 2023

Once upon a time ~ 1993





butyrate
a[1]

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Table 6 Percentage clonality

Schedule	Abnormality studied	FISH/metaphase cytogenetics (F/C)[a]	Percent clonal cells Week 0	Week 6	Week 12
7/14					
	−Y	F	38	83	off protocol
	del (5)	C	11	100	off protocol
	−7	F	65	78	off protocol
	−7	F	32	39	54
	−7	F	23	56	off protocol
	+8	F	31	16	28
	i14	C	50	62.5	0
21/28					
	+2	C	0	55	35
	+8	C	12.5	0	0
	+8	C	100	100	80
	−7	C	100	100	nd[b]

[a] F refers to samples in which clonality was monitored using FISH. C refers to samples in which clonality was monitored using metaphase cytogenetics.

[b] nd, not done.

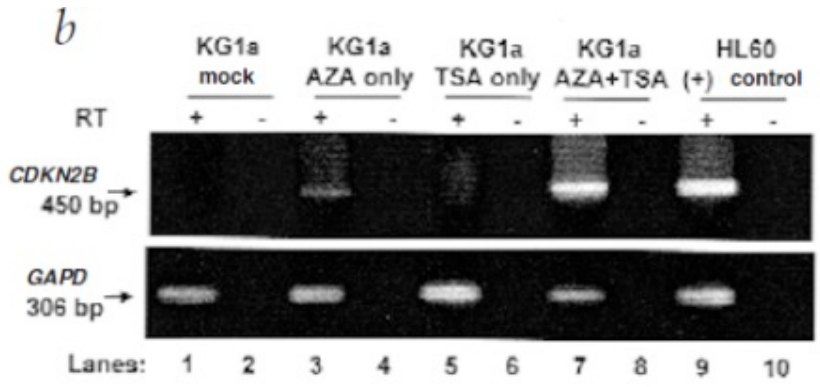
DiGiuseppe et al. Leukemia 1999. 13: 1243; Gore et al. Clin.Cancer Res. 2001. 7:2230; 2002. 8: 963-970.

Timeline

- 1994: R01: Clinical/PK/PD Sodium phenylbutyrate in Myeloid
  - CTEP study
- 1997: R21: Sodium phenylbutrate with all trans retinoic acid
  - CTEP study-aborted

Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer

Elizabeth E. Cameron[1,3], Kurtis E. Bachman[1,4], Sanna Myöhänen[1], James G. Herman[1] & Stephen B. Baylin[1,2,3,4]



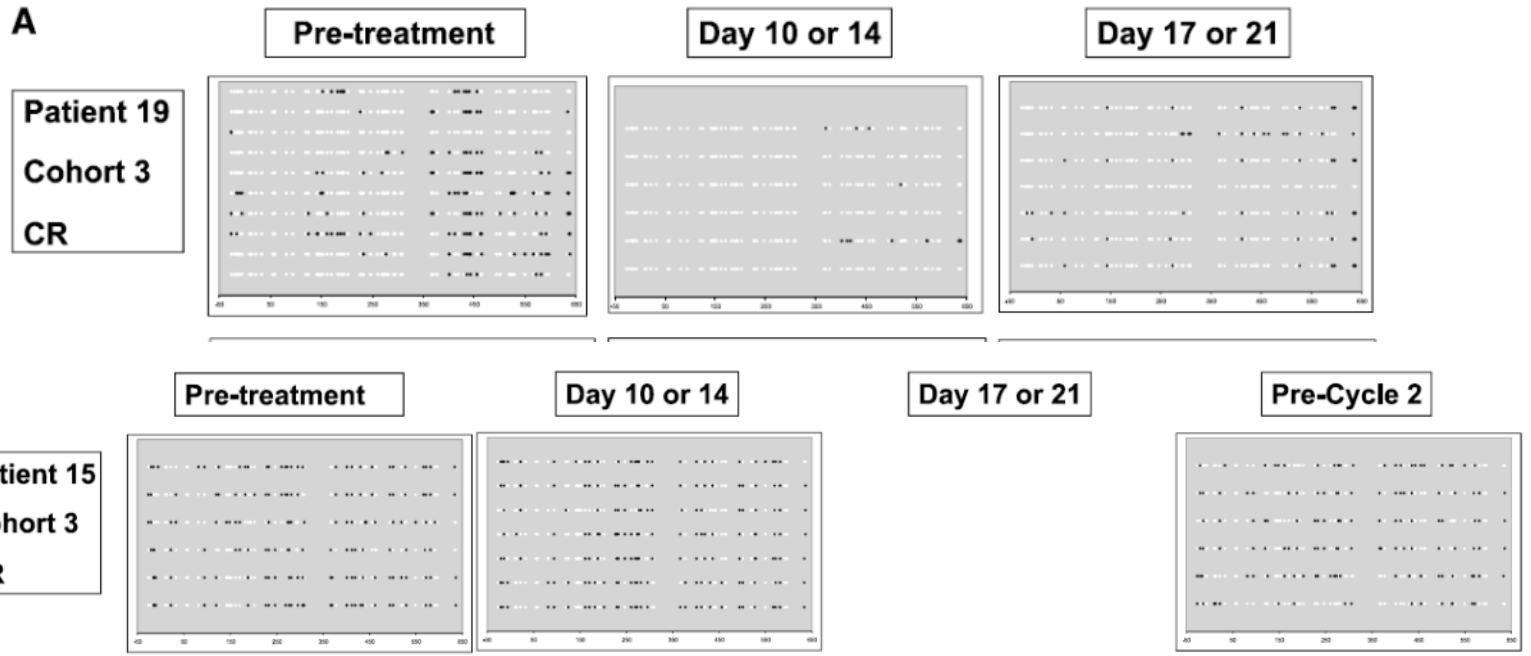
Timeline 2

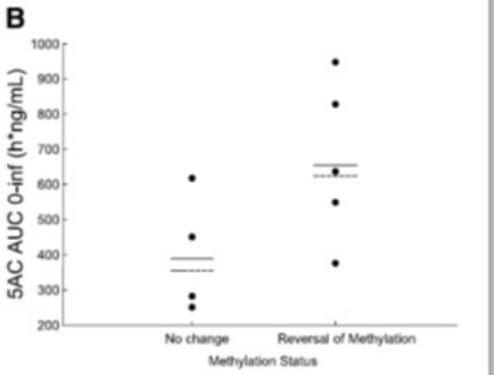
- ~1999 R01 phenylbutyrate plus azacitidine
  - CTEP Phase 1 trial

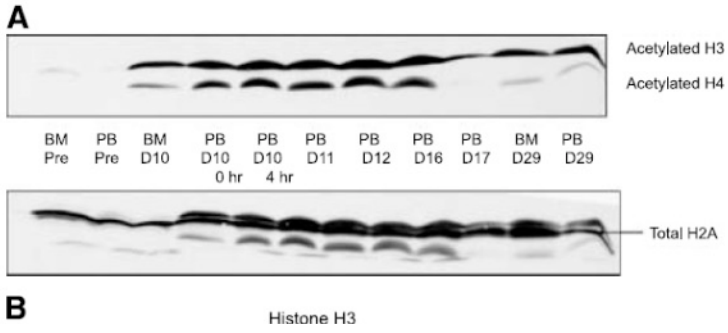
Combined DNA Methyltransferase and Histone Deacetylase Inhibition in the Treatment of Myeloid Neoplasms

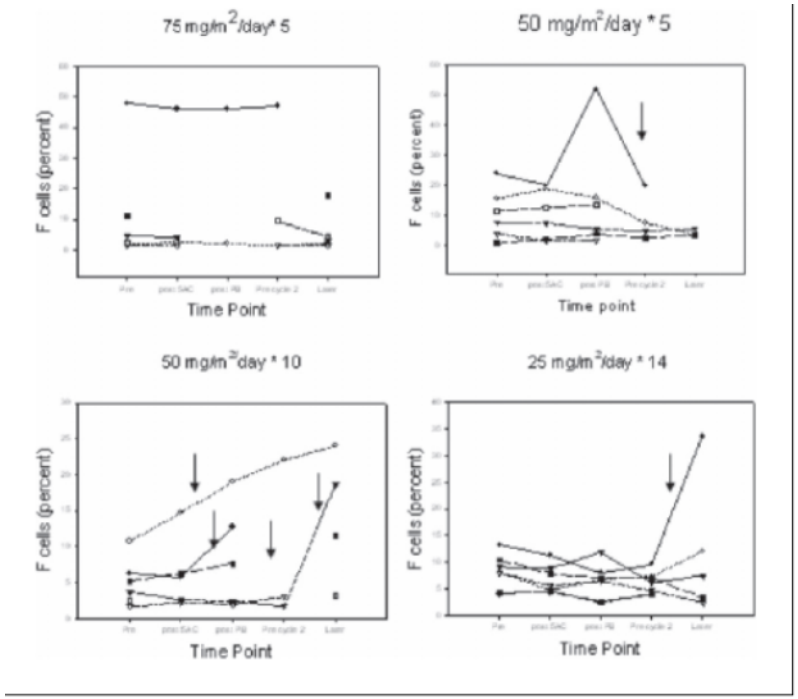
Steven D. Gore,[1] Stephen Baylin,[1] Elizabeth Sugar,[1] Hetty Carraway,[1] Carole B. Miller,[1] Michael Carducci,[1] Michael Grever,[2] Oliver Galm,[3] Tianna Dauses,[1] Judith E. Karp,[1] Michelle A. Rudek,[1] Ming Zhao,[1] B. Douglas Smith,[1] Jasper Manning,[1] Anchalee Jiemjit,[1] George Dover,[1] Abbie Mays,[1] James Zwiebel,[4] Anthony Murgo,[4] Li-Jun Weng,[1] and James G. Herman[1]

Cancer Res 2006; 66: (12). June 15, 2006









- ~2003 MS275 plus azacitidine Phase 1
  - R21
  - CTEP trial (never published)
- R01 MS275 plus azacitidine
  - ECOG RPh2

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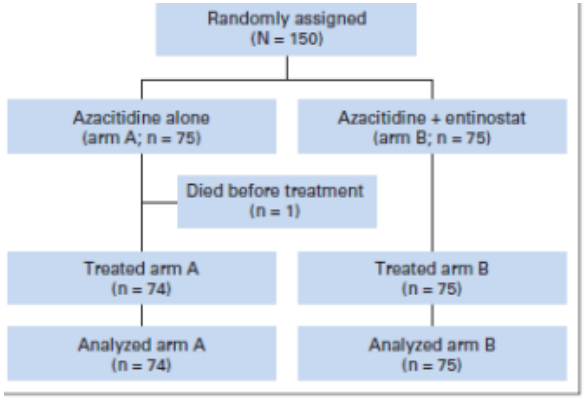
ORIGINAL REPORT

Prolonged Administration of Azacitidine With or Without Entinostat for Myelodysplastic Syndrome and Acute Myeloid Leukemia With Myelodysplasia-Related Changes: Results of the US Leukemia Intergroup Trial E1905

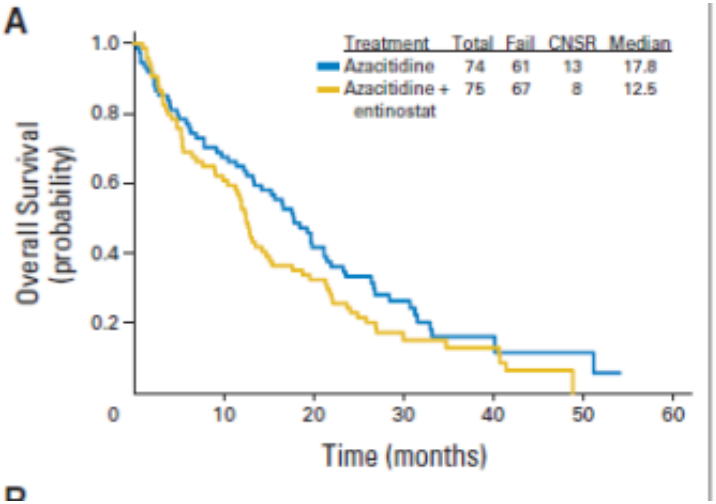
Thomas Prebet, Zhuoxin Sun, Maria E. Figueroa, Rhett Ketterling, Ari Melnick, Peter L. Greenberg, James Herman, Mark Juckett, Mitchell R. Smith, Lisa Malick, Elisabeth Paietta, Magdalena Czader, Mark Litzow, Janice Gabrilove, Harry P. Erba, Steven D. Gore, and Martin S. Tallman

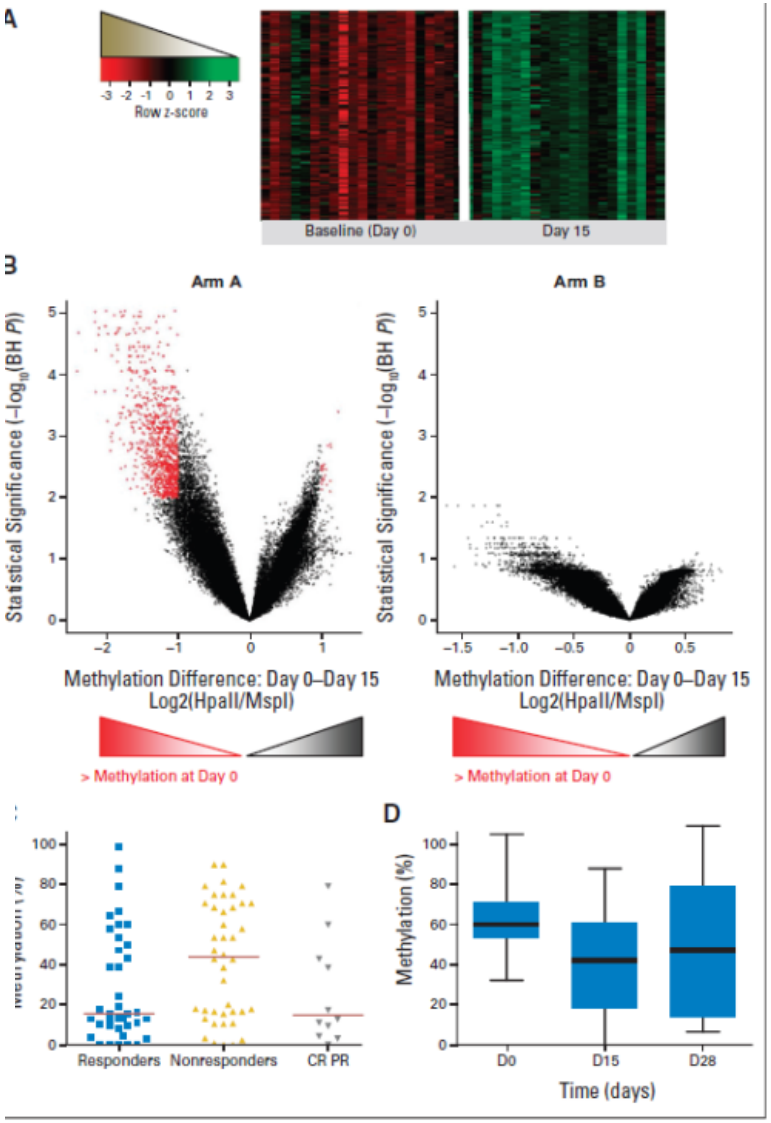
Thomas Prebet, James Herman, Lisa Malick, and Steven D. Gore, Sidney Kimmel Comprehensive Cancer Center at



R Ph 2: ECOG with US Leukemia Intergroup (R01 CA125563501)

	Arm A AZA alone	Arm B AZA+ Entinostat
Complete Remission	Trilineage Response: 31%	Trilineage Response: 27%
Partial Remission		
Trilineage HI		
HI not trilineage	12%	19%
No response	57%	56%





Br J Haematol. 2016 February ; 172(3): 384–391. doi:10.1111/bjh.13832.

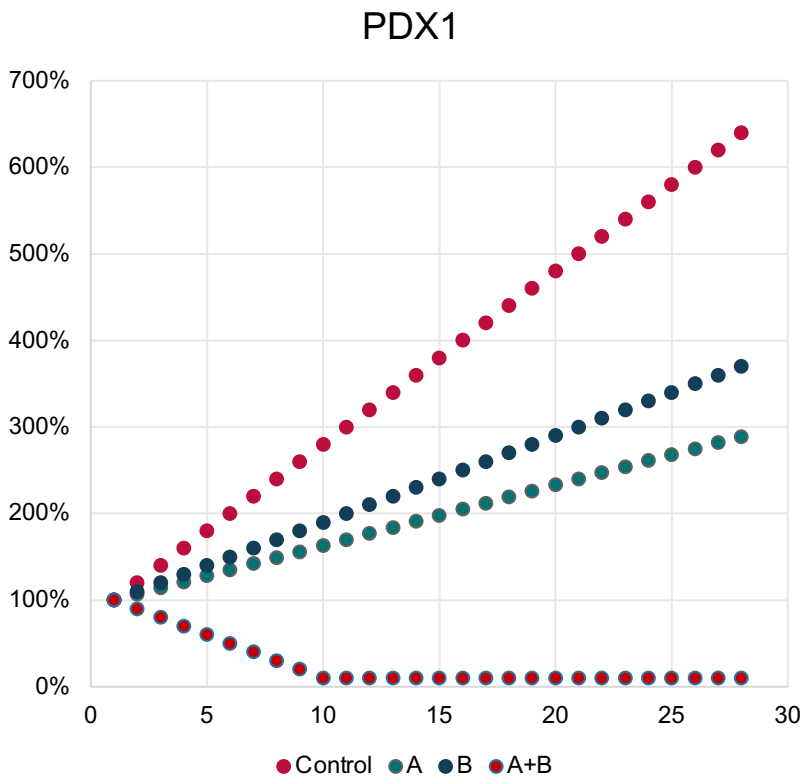
Azacitidine with or without Entinostat for the treatment of therapy-related myeloid neoplasm: further results of the E1905 North American Leukemia Intergroup study

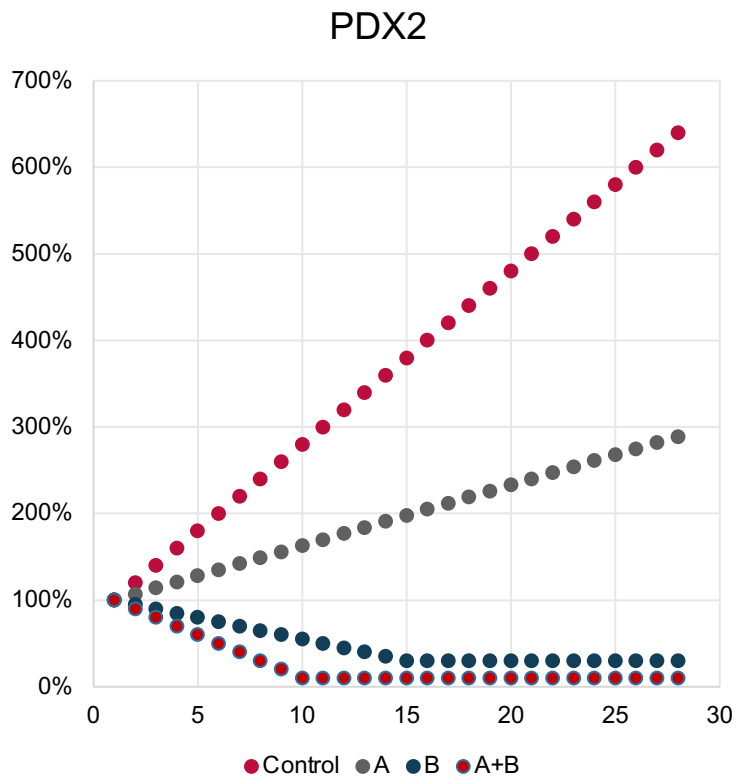
Thomas Prebet[1], **Zhuoxin Sun**[2], **Rhett P. Ketterling**[3], **Amer Zeidan**[1], **Peter Greenberg**[4], **James Herman**[5], **Mark Juckett**[6], **Mitchell R. Smith**[7], **Lisa Malick**[5], **Elisabeth Paietta**[8], **Magdalena Czader**[9], **Maria Figueroa**[10], **Janice Gabrilove**[11], **Harry P. Erba**[12], **Martin S. Tallman**[13], **Mark Litzow**[14], **Steven D. Gore**[1], and **on behalf of the Eastern Cooperative Oncology Group and North American Leukemia intergroup**

Why do we require preclinical evidence to prioritize clinical trial concepts?

- Insufficient number of patients and insufficient resources to fund every clinical trial proposal
- 'No resources to conduct preclinical studies' is not a justification to test novel therapies on patients without supporting evidence
- Unmet medical need is not a substitute for strong rationale and strong supporting data
- *Every patient enrolled on a study deserves our best effort to ensure that the study is scientifically supported and soundly designed,* ***so that their experience is likely to have meaning***
- Clinical studies are much more costly – in both dollars and human terms – that preclinical studies
- No models are perfect and no evidence is absolutely predictive

Broadly, what level of preclinical in vivo evidence is considered appropriate to support a concept for **non-IO** agents or agent combinations?





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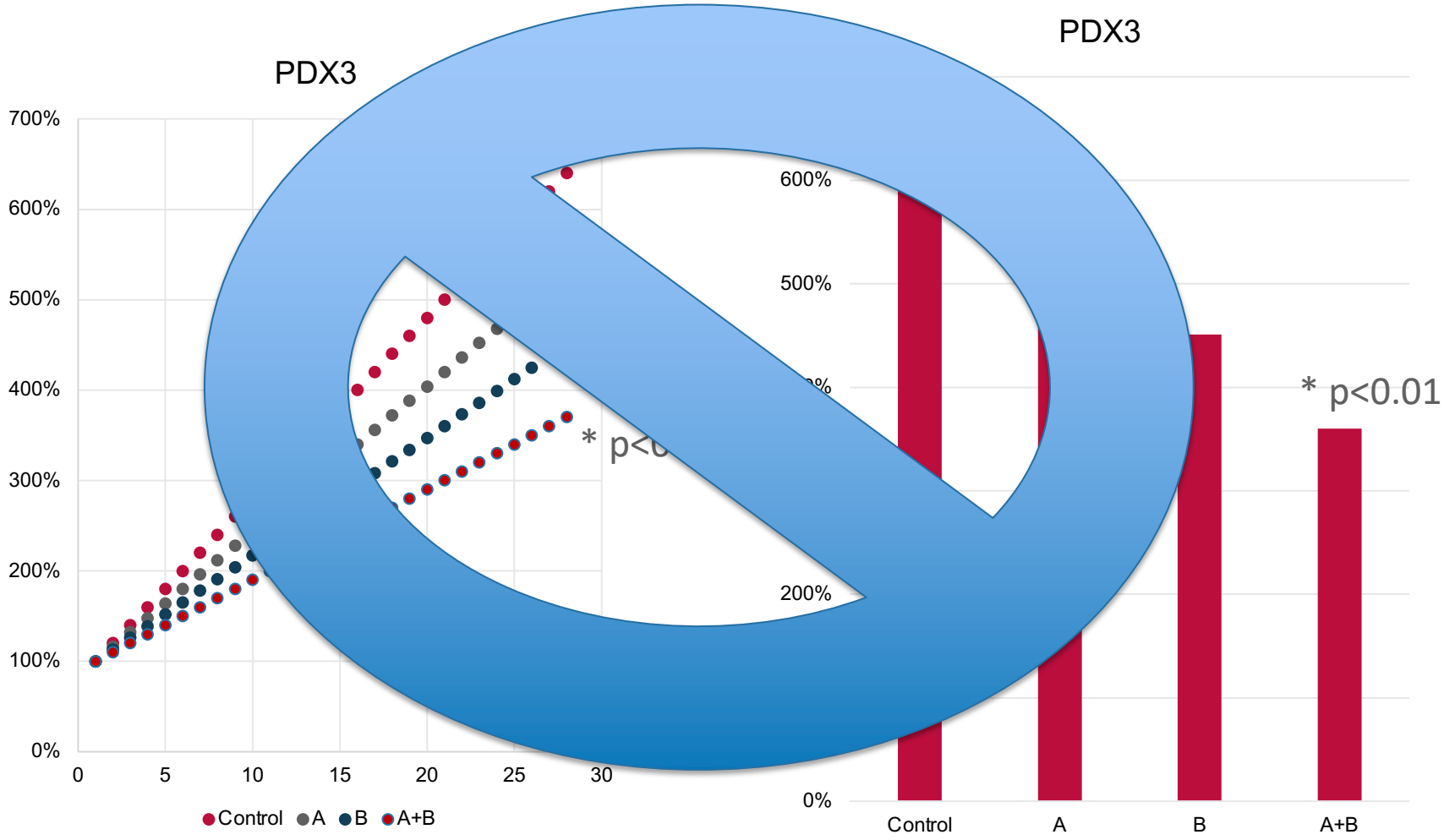

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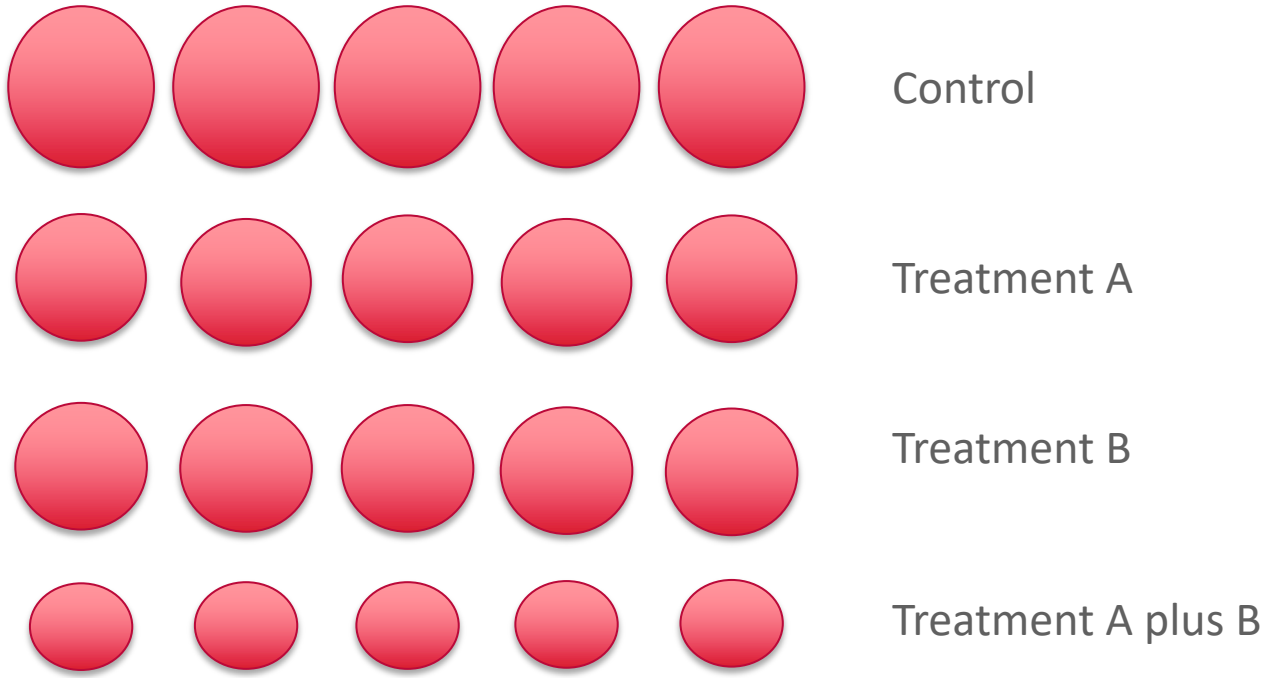

Broadly, what level of preclinical (or clinical) evidence is considered appropriate to support a concept for non-IO agents or agent combinations?

- For non-IO studies a histology-specific and molecularly relevant ***in vivo*** model should demonstrate anti-tumor activity
  - ***Effect size*** >>>> "statistical significance"
  - Strength in descending order: Tumor regression vs prolonged growth inhibition vs slowing rate of growth
  - K-M and growth curves **much better than one point in time**
  - **Duration** of experiment – the longer the better
  - More models better than fewer models; negative models important to establish potential MoA and biomarkers of response
  - Animals per cohort –the more the better, no magic number
  - Adequate controls, especially for combination experiments
  - For combinations, must show at least additivity

Broadly, what level of preclinical in vivo evidence is considered appropriate to support a concept for **IO agents**?

- The lack of predictive models for IO agents and combinations is a major challenge
- Every humanized host has its drawbacks- no consensus yet on which models should be used to test IO therapy combinations
- Impact of agent on PD1/PDL-1 axis or TME -**surrogates of unknown significance**
- In general we have not required pre-clinical *in viv*o evidence for IO studies
  - LOI's evaluated based on lack of duplication of other efforts or potential for biomarker development

If *in vivo* experiments are required, are there guidelines on the number of models that need to be tested to demonstrate either monotherapy or combinatorial efficacy?

- No official guidelines for number of animals, but for combination experiments would like to have at least 8 per group
- The greatest weaknesses
  - **irrelevant models**
  - **inadequate controls**, not the number of animals per cohort
- If a combination is hypothesized to work within a given molecular context, there should be models presented **with and without** that context

Considerations for in vitro evidence

- In vitro cytotoxicity data can be used to select appropriate in vivo models but are **insufficient** to justify a clinical trial
- useful for proof-of-mechanism studies
- should use drug concentrations that are **pharmacologically achievable** in patients – both concentration and duration of exposure
- In vitro assays should use genetically and histologically relevant models

Special Cases

- All agents under investigation are known to have clinical activity in the tumor under investigation
- Strong in vitro evidence of combinatorial effect
  - In vivo models still preferred

Why partner with CTEP?

- Access to priority drugs in tumors which are not pharma-priority
- Novel-novel combinations
- Community of outstanding co-investigators
  - ETCTN
  - D-FCI
- Career Development Opportunities
- NCLN assays
  - Whole Exome Sequencing
  - (bulk) RNA Seq
  - PD multiplex assays
    - Cell death
    - DNA damage and repair
  - U24 PK labs
  - (Scintillating medical monitors)

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