Looking ahead to 2014-2015: promising targeted drugs in selected STS histologies

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Mount Sinai *The Tisch Cancer Institute*

Conflicts of interest

- Consulting
  - ABIM
  - Sarcoma Alliance for Research through Collaboration (SARC)
  - Eisai / Morphotek
  - Lilly / Imclone
  - GlaxoSmithKline
  - Bayer
  - Champions Biotechnology
  - Foundation Medicine
- Research support
  - Morphotek/Eisai, Tracon, Bayer, SARC
- Off-label use
  - Everything except doxorubicin, DTIC, ifosfamide, pazopanib (STS) [trabedctedin], or imatinib, sunitinib, regorafenib (GIST)

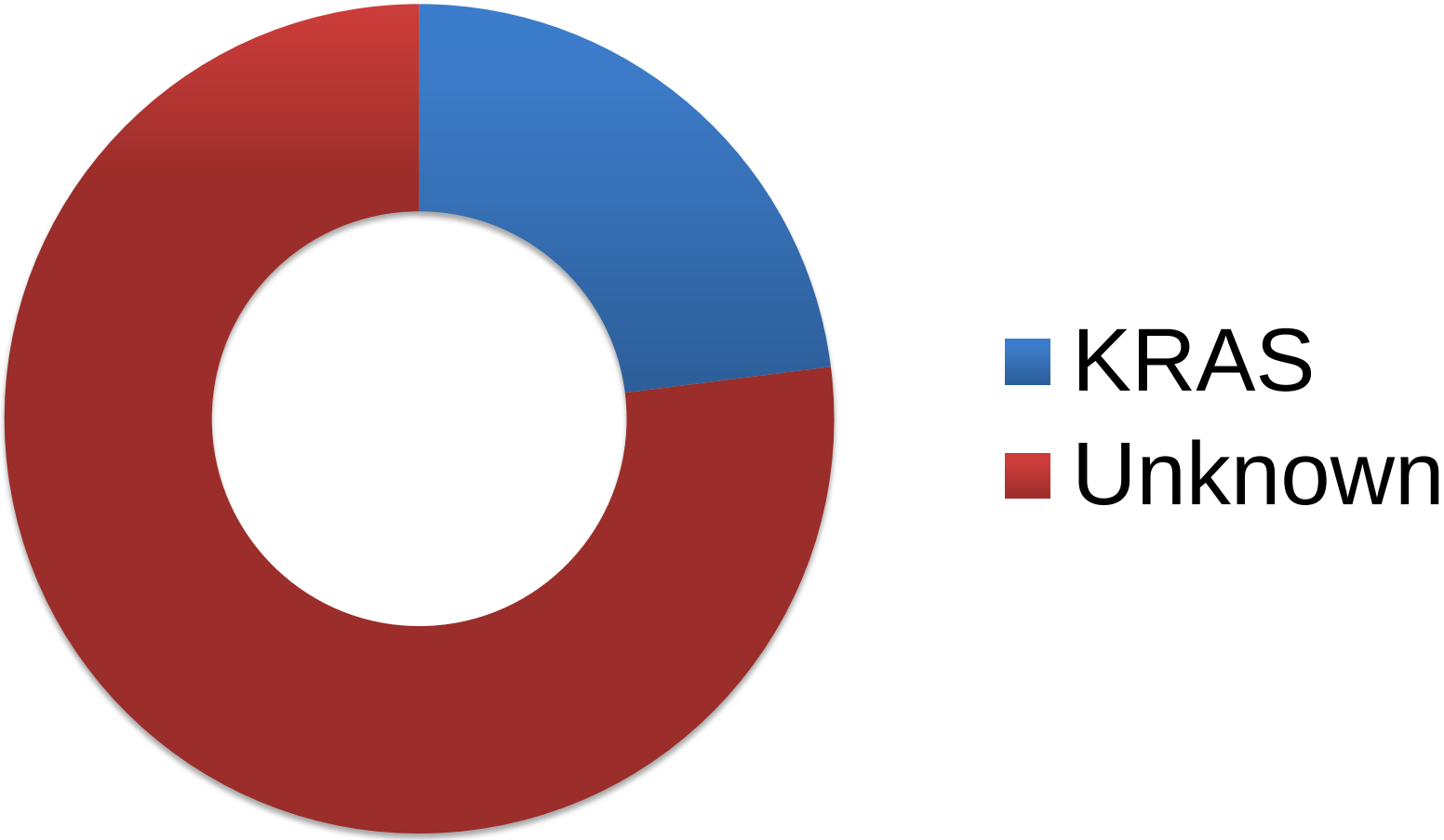
Outline

- Everything I learned was wrong…

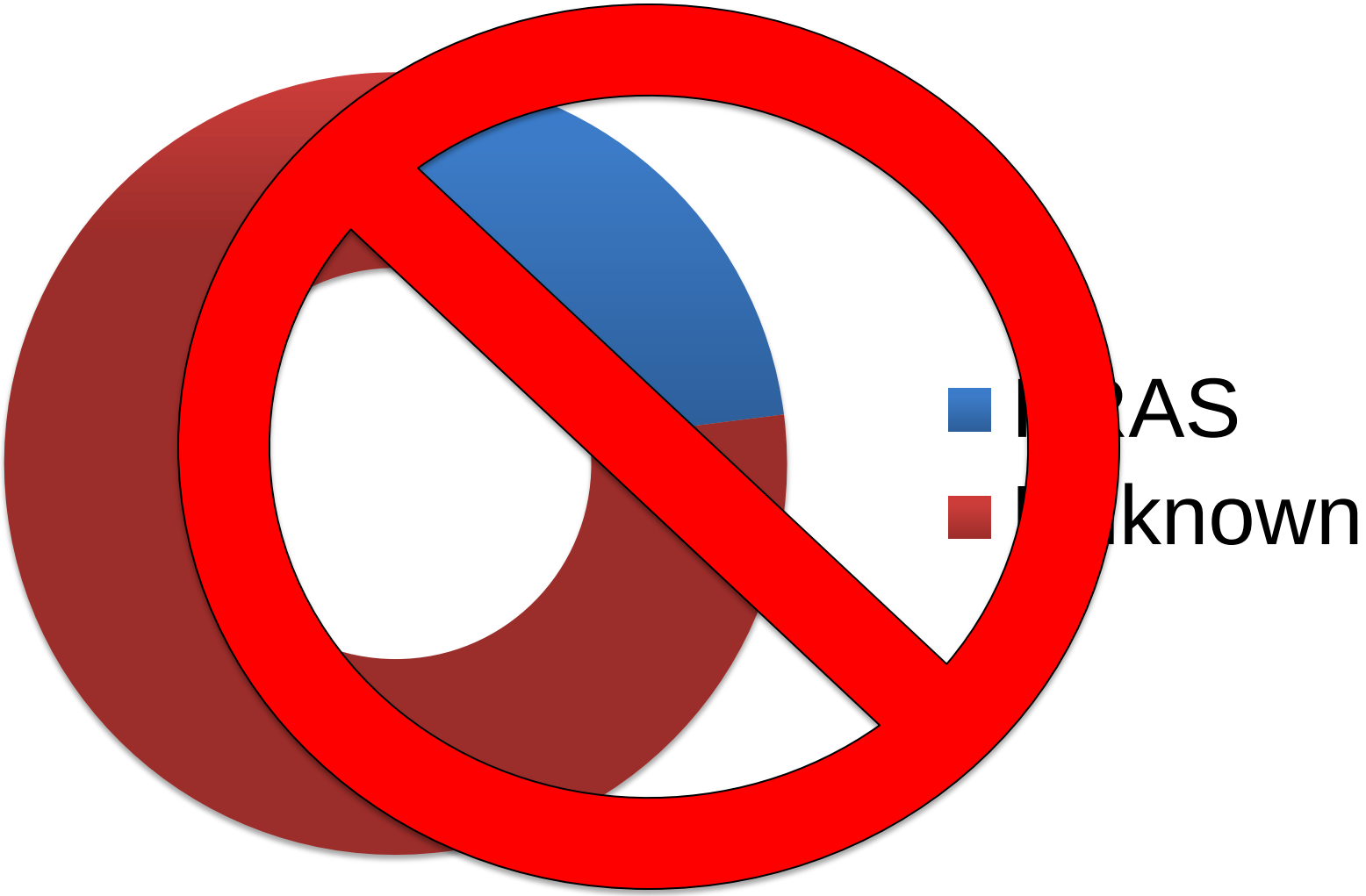
…or I misunderestimated sarcoma biology

- How do we choose the target
- How do we choose the targeted agent
- Using better the drugs we have
- New & different, but how do we get there?

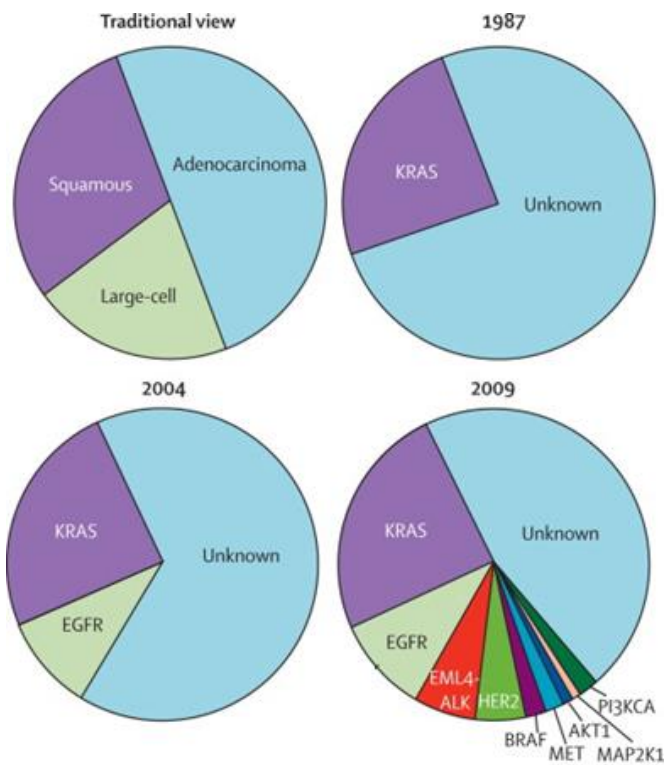
What I learned: lung cancer

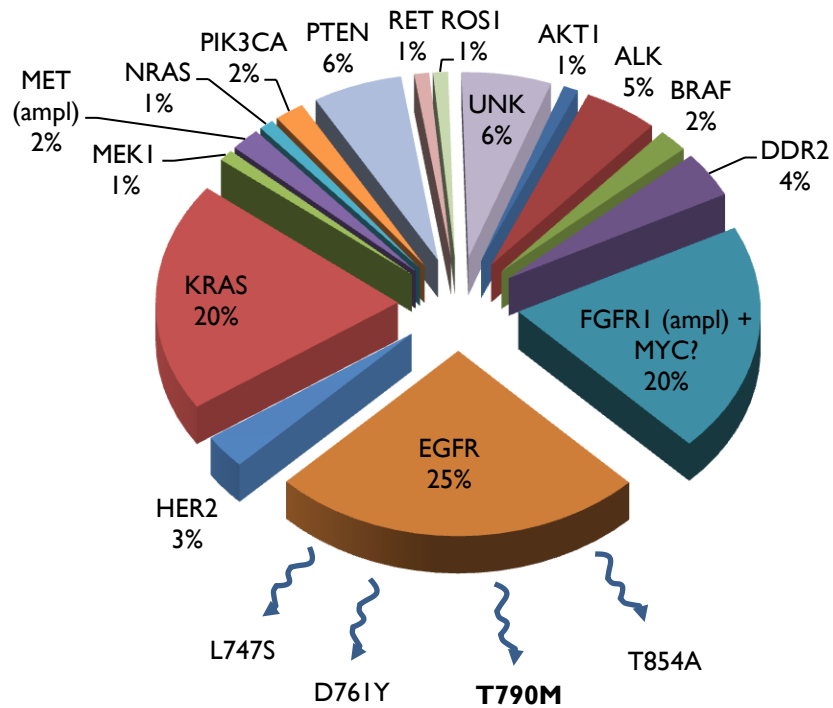


What I learned



NSCLC: more than squamous and adeno





Pao W & Girard N. Lancet Oncol 2011; 12: 175
Mycancergenome.org (12/2013)
Gainor JF & Shaw AT. JCO 2013; 31: 3987

What's more

- It is still early days to determine if a mutation indicates a specific tumor will be …
  - Sensitive
  - Resistant or
  - (No correlation)

…to a given treatment

Finding targets and targeted therapetics in sarcomas

Ever-growing list of sarcoma gene alterations

Endometrial stromal sarcoma, low grade	*EPC1-PHF1*	GOF	Fusion gene
Endometrial stromal sarcoma, low grade	*JAZF1-PHF1*	GOF	Fusion gene
Endometrial stromal sarcoma, low grade	*JAZF1-SUZ12*	GOF	Fusion gene
Endometrial stromal sarcoma, low grade	*MEAF6-PHF1*	GOF	Fusion gene
Epithelioid hemangioendothelioma	*WWTR1–CAMTA1*	GOF	Fusion gene
Epithelioid hemangioendothelioma	*YAP1-TFE3*	GOF	Fusion gene
Epithelioid sarcoma	*SMARCB1*	LOF	Deletion; mutation?
Ewing sarcoma	*EWSR1-E1AF*	GOF	Fusion gene
Ewing sarcoma	*EWSR1-ERG*	GOF	Fusion gene
Ewing sarcoma	*EWSR1-FEV*	GOF	Fusion gene
Ewing sarcoma	*EWSR1-FLI1*	GOF	Fusion gene
Ewing sarcoma	*FUS-ERG*	GOF	Fusion gene
Ewing sarcoma-like	*BCOR-CCNB3*	GOF	Fusion gene
Ewing sarcoma-like	*CIC-DUX4*	GOF	Fusion gene
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3*	GOF	Fusion gene
Extraskeletal myxoid chondrosarcoma	*TAF15-NR4A3*	GOF	Fusion gene
Extraskeletal myxoid chondrosarcoma	*TCF12-NR4A3*	GOF	Fusion gene
Extraskeletal myxoid chondrosarcoma	*TFG-NR4A3*	GOF	Fusion gene
Fibromyxoid sarcoma, low-grade (Evans tumor)	*FUS-CREB3L1*	GOF	Fusion gene
Fibromyxoid sarcoma, low-grade (Evans tumor)	*FUS-CREB3L2*	GOF	Fusion gene
Fibrosarcoma, infantile	*ETV6-NTRK3*	GOF	Fusion gene

Part 2: what can you actually treat?

- Actionable

– GIST	*KIT, PDGFRA* mut	KIT, PDGFRA activation
– IMT	t(2p23;mult)	ALK activation
– PVNS	t(1;2)	CSF1 expression
– DFSP	t(17;22)	PDGFB expression

- Not (**yet**) **directly** actionable

– Ewing sarcomas	t(11;22)
– Synovial sarcomas	t(X;18)
– Myxoid-round cell	t(12;16)
– Alveolar rhabdomyosarc	t(1;13); t(2;13)
– Chondro	IDH1, 2 mut

– *TP53* mutation, loss; *NF1* loss; *CDKN2A* loss….

Surprisingly(?) few mutations seen
(46 mutations in 21 genes in 207 tumors)

Subtype	*PIK3CA*	*TP53*	*NF1*	Other kinases or tumor suppressors
Myxoid-round cell liposarcoma	19% (4 /21)			
Pleomorphic liposarcoma		17% (4/24)	8% (2/24)	
Myxofibrosarcoma			10% (4/38)	
All samples				No more than one case each

Barretina J et al. Nature Genet 2010; 42: 715

Rhabdo: Mutation frequency by translocation status

Gene	Mutations in fusion (+) cases n=53	Mutations in fusion (-) cases n=94	Frequency in fusion (-) cases
NRAS		11	12%
FGFR4		9	10%
PIK3CA	1	7	7%
BCOR	1	7	7%
FBXW7		7	7%
KRAS		6	6%
TP53		5	5%
NF1		5	5%
HRAS		4	4%

Shern JF et al. Cancer Disc 2014; doi: 10.1158/2159-8290.CD-13-0639

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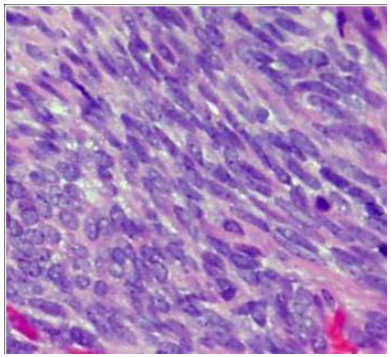
Tumor genomic testing

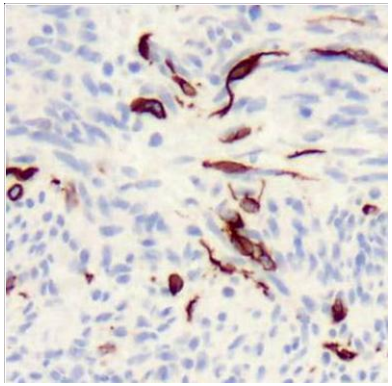
FAC QUOD VOS VOLO
LIFE SCIENCES

Lucy van Pelt
Sarcoma NOS
Sample date 1/15/2014

TUMORSCAN® REPORT

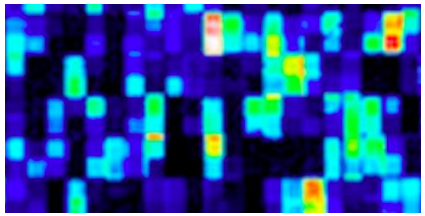
TOPO1: IHC POSITIVE 2+ 95%
MGMT: present, weak staining
PGP IHC: negative 2+ 100%
EGFR: not detected
ER IHC: negative 0+ 100%
HER2/neu FISH: not amplified
KIT: present, 2+ staining
TS: IHC positive 50%
KIT seq: wild type
BRAF seq: wild type
TP53 mutation: present
UGT1A: GG allele
CDKN2A: mutated





FINAL REPORT

The problem



NGS

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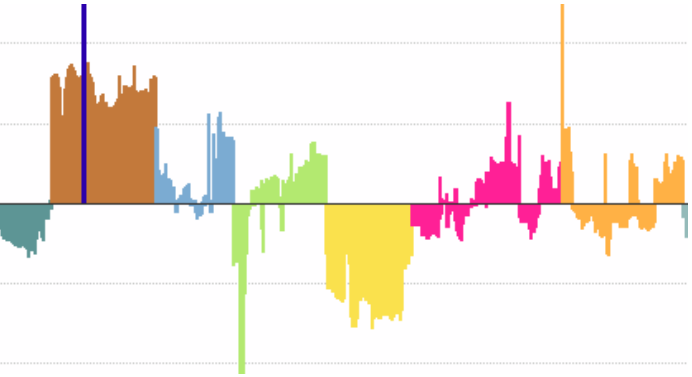

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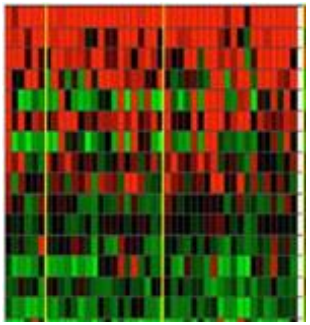


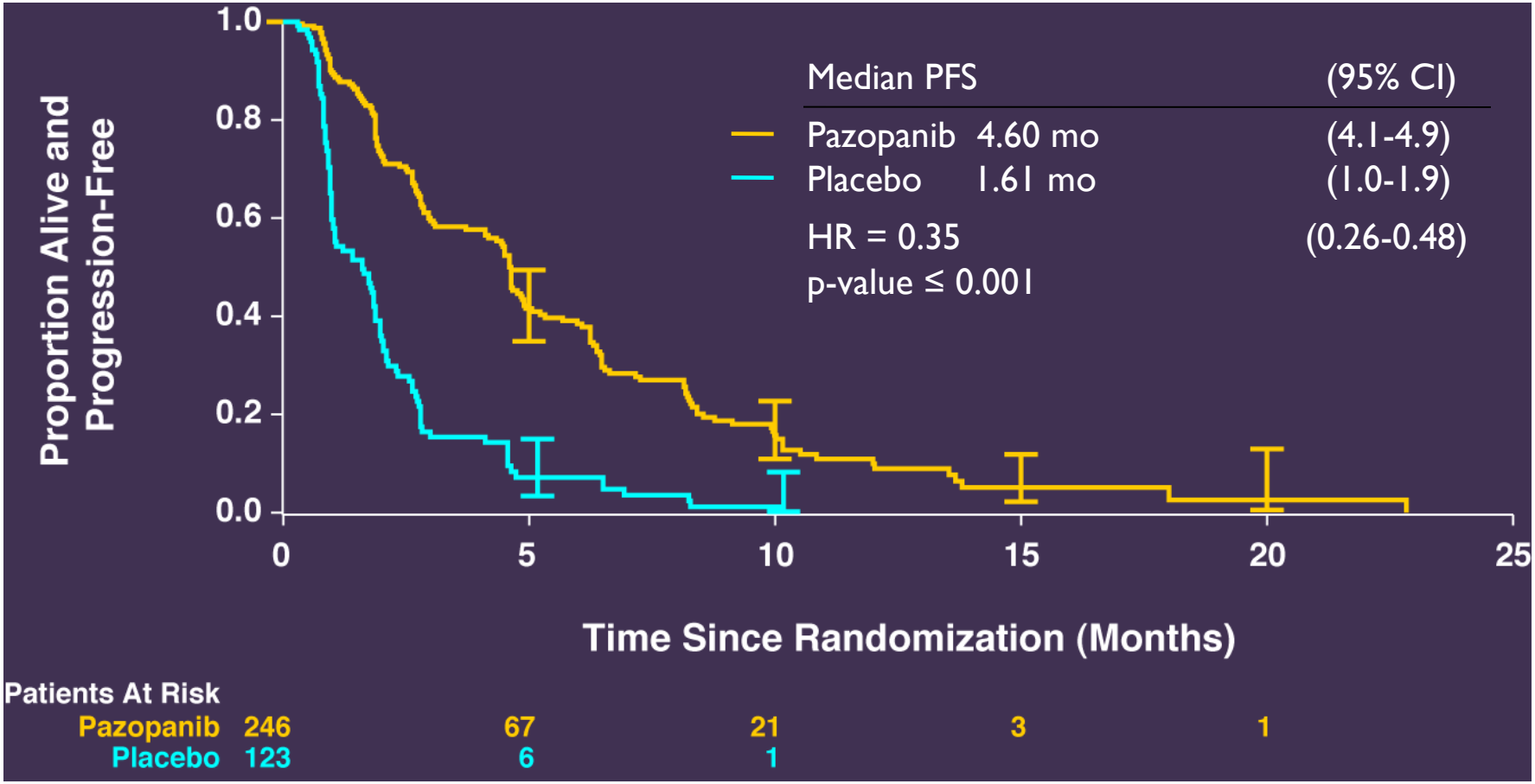
Expression

Sarcomas: activity beyond cytotoxics

KIT, PDGFR	GIST
ER, PR, AR	Endometrial stromal sarcoma
IGF1R	Ewing sarcoma, SFT
EGFR family	Chordoma
VEGF(R)	SFT, angiosarcoma
mTORC1	PEComa
ALK	IMT
Autocrine (PDGF, CSF1)	DFSP, PVNS
CDK4, MDM2 ??	WD-DD Liposarcoma, intimal sarcoma
Still frustrating	Leiomyosarcoma, UPS

Angiogenesis

Pazopanib significantly improved PFS in metastatic soft tissue sarcoma pts progressing after standard chemotherapy



Van der Graaf WTA et al. Lancet Oncol 2012; 379: 1879

A 4% overall response rate with pazopanib in metastatic STS

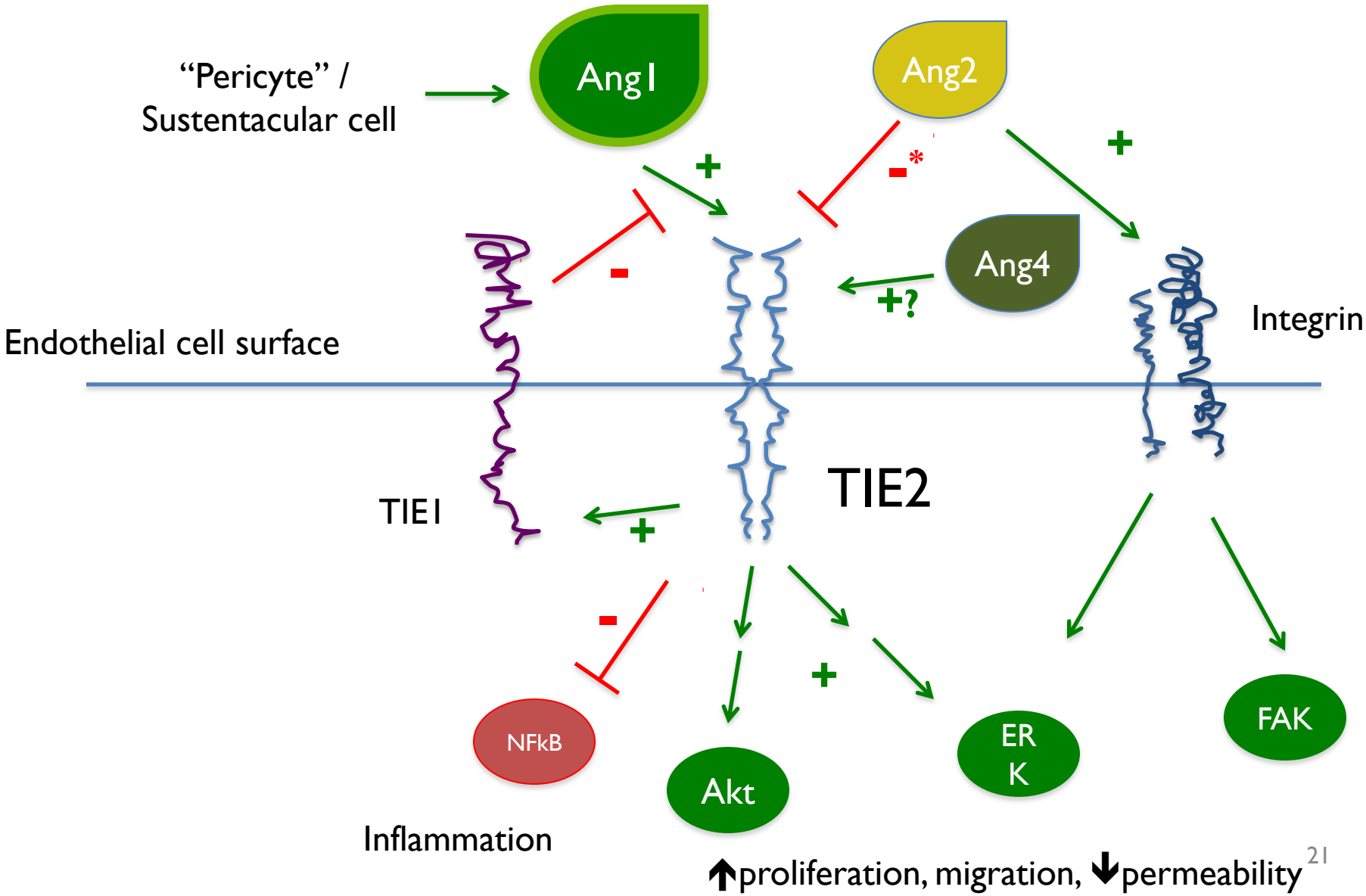
	% of Patients	
	Placebo (N=123)	Pazopanib (N=246)
Best response		
Complete response	0	0
Partial response	0	**4**
Stable disease	27	54
Progressive disease	62	27
Not evaluable	11	14
Tumor shrinking		
Any reduction from baseline	12	50

Van der Graaf WTA et al. Lancet Oncol 2012; 379: 1879

What is next in antiangiogenesis?

- MET inhibitors?
  - Cabozantinib, crizotinib
- TIE2 inhibitors?
  - Not so active in other cancers
- New mAbs
  - Endosialin (Morphotek)
  - Endoglin (Tracon)
- FGFR inhibitors
  - Brivanib phase II study (-) in sarcoma…but is it an FGFR inh?
- Eph/Ephrin interactions
  - Targeted by some small molecule oral kinase inhibitors (SMOKIs)
- Can you target tumor vasculature with immunotherapy?

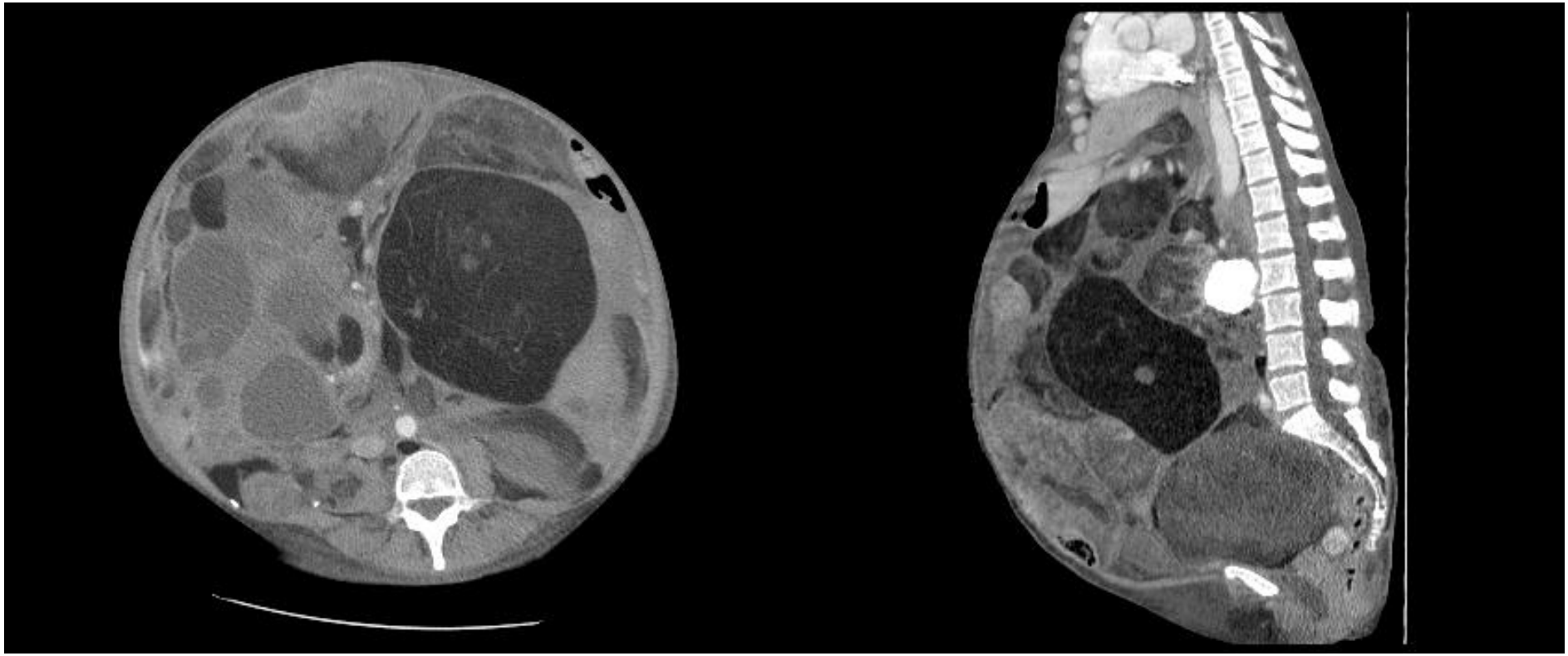
Even one molecule is complicated: TIE2 signaling



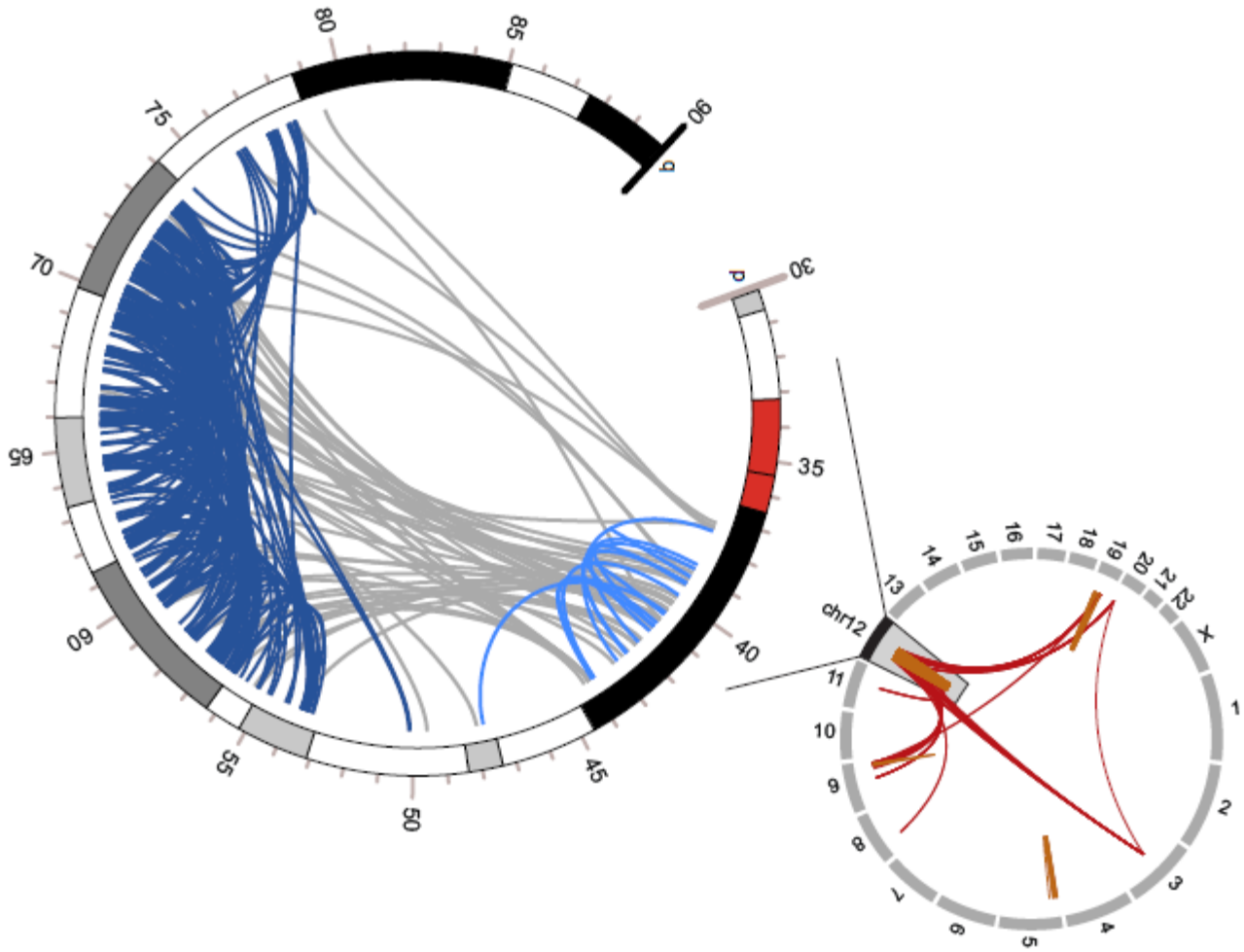
Liposarcoma

A good example of trying to target specific genetic features of a solid tumor

What we are up against:
well differentiated / dedifferentiated liposarcoma

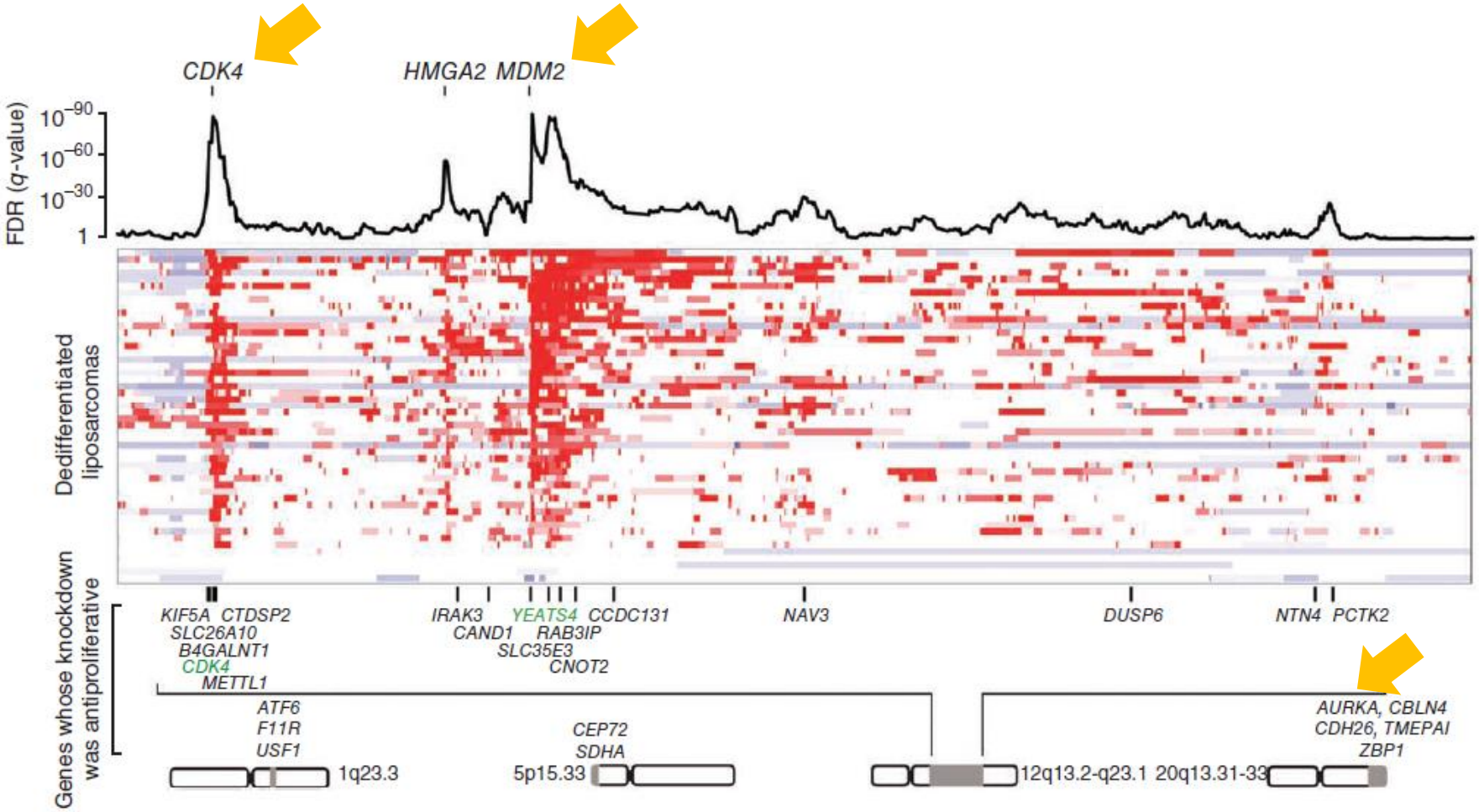


Translocations in WD/DD LS



Taylor BS et al. Nat Rev Cancer. 2011; 11:541

WD DD LS: 12q amplicon

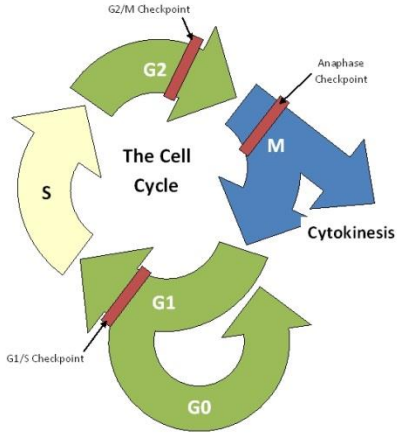


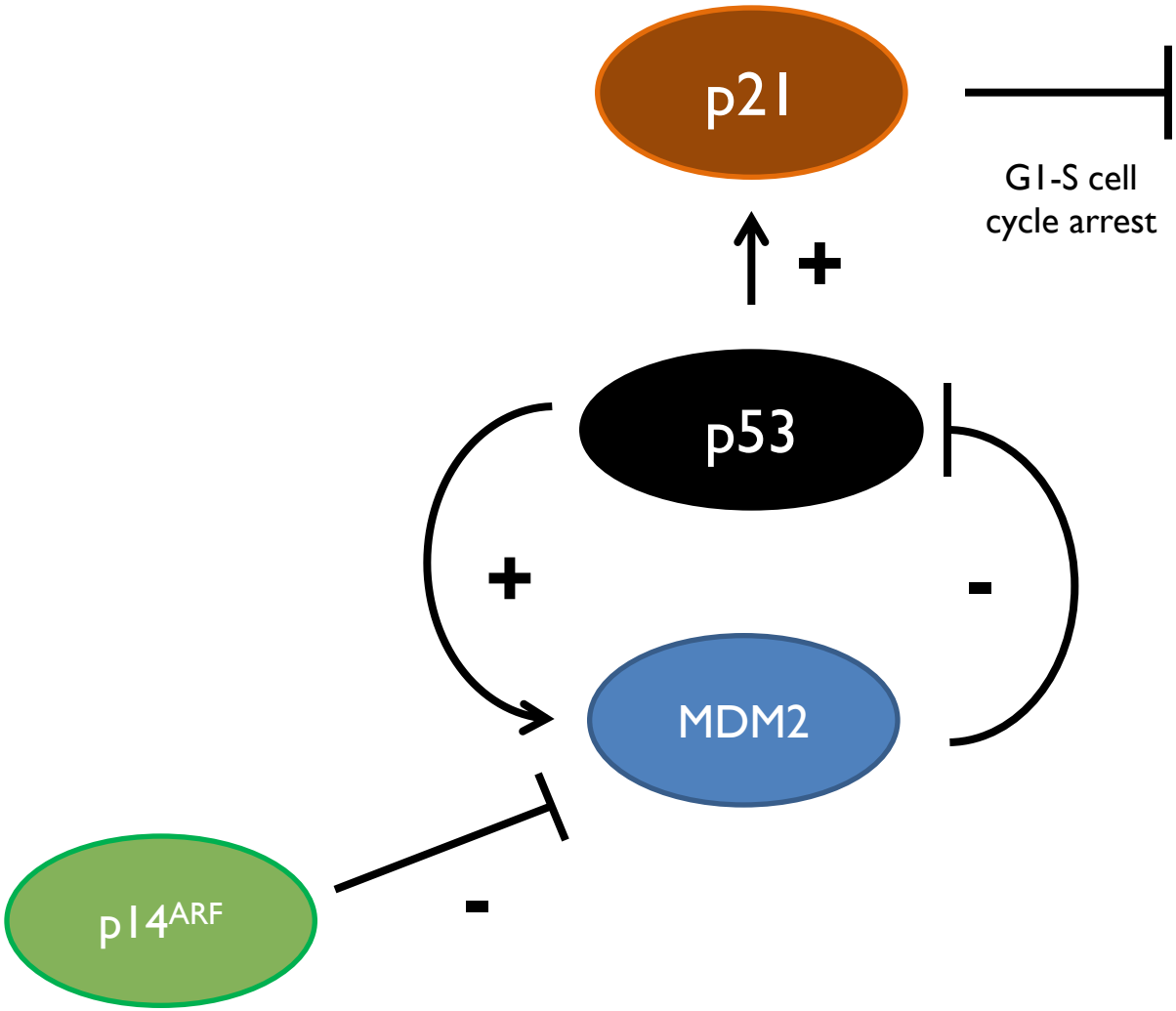
Barretina J et al. Nat Genet 2010; 42: 715

WD DD LS: where does this lead?

- HDM2 inhibitors
- CDK4 inhibitors
- Aurora kinase inhibitors
- Differentiation therapy?
  - PPAR gamma ligands: inactive alone
  - HDAC inhibitors
  - DNAMT inhibitors
  - Combinations

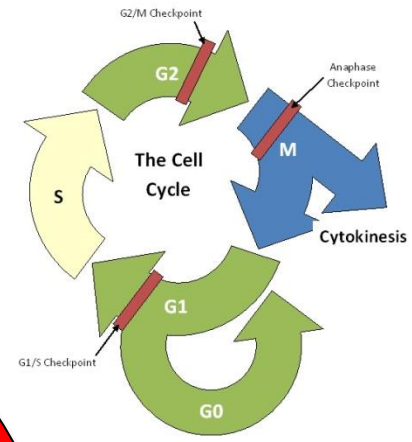
p53/MDM2

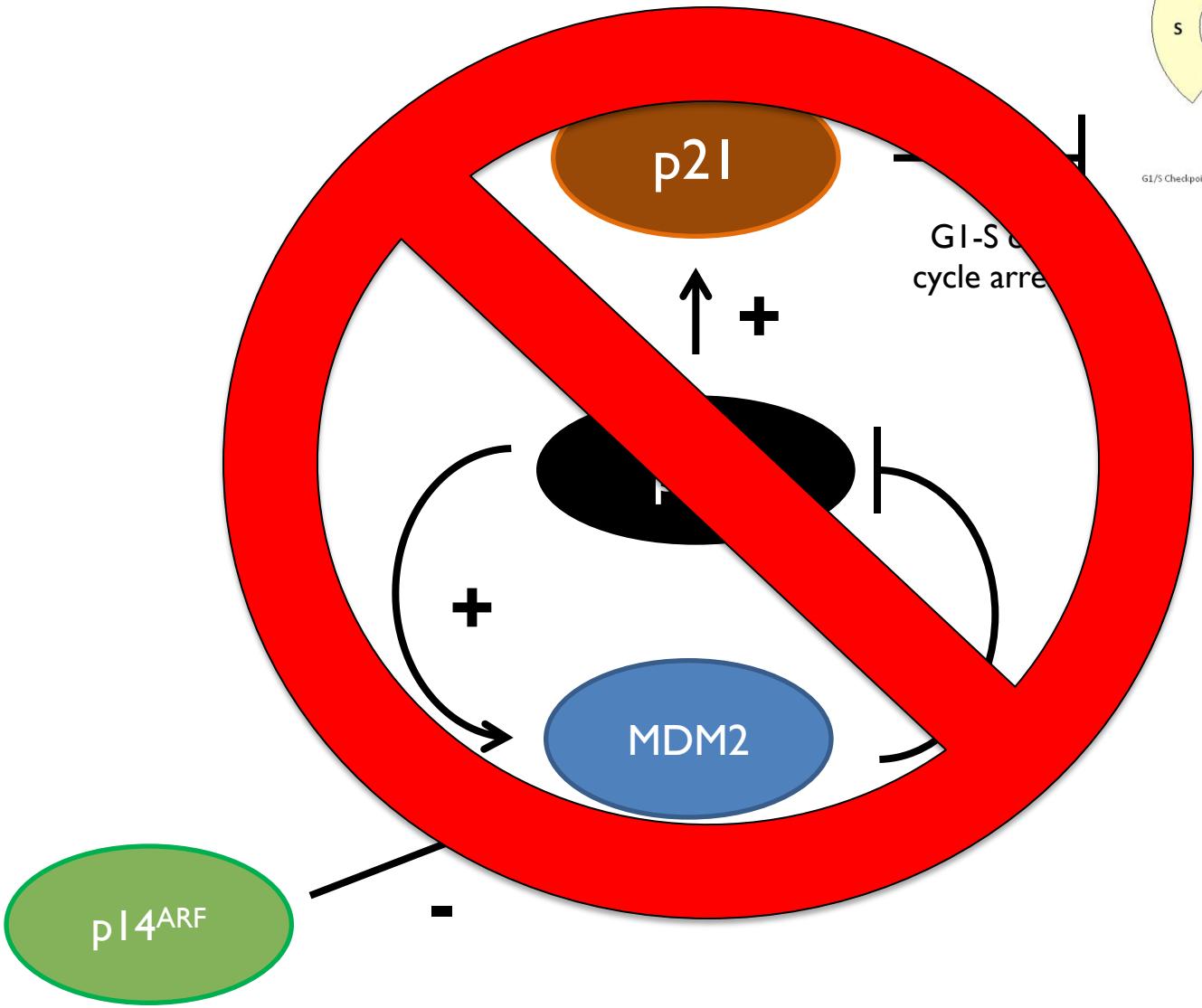

G2/M Checkpoint
G2
Anaphase Checkpoint
M
The Cell Cycle
S
Cytokinesis
G1
G1/S Checkpoint
G0


p21
G1-S cell cycle arrest
+
p53
+
-
MDM2
p14ARF
-

It's child's play!

p53/MDM2



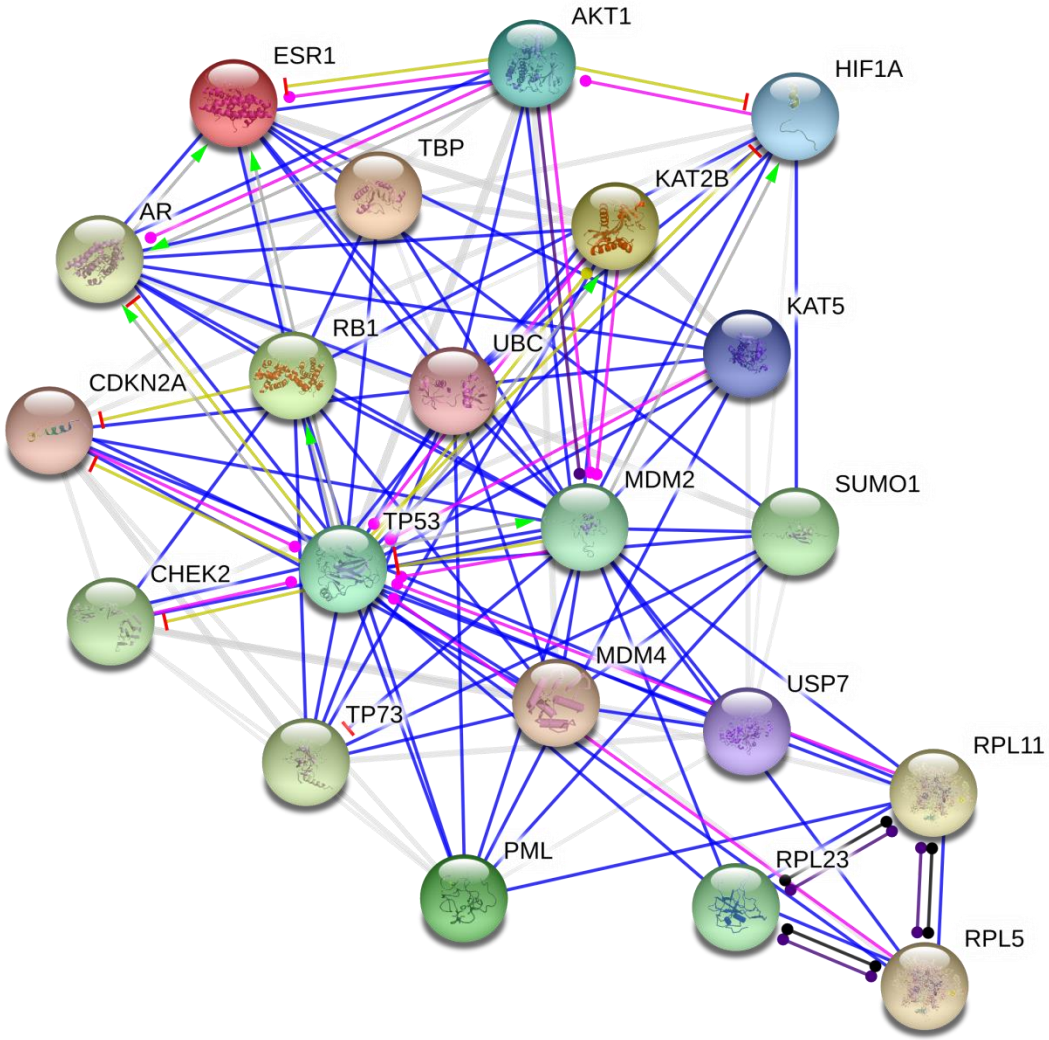


p63

p73

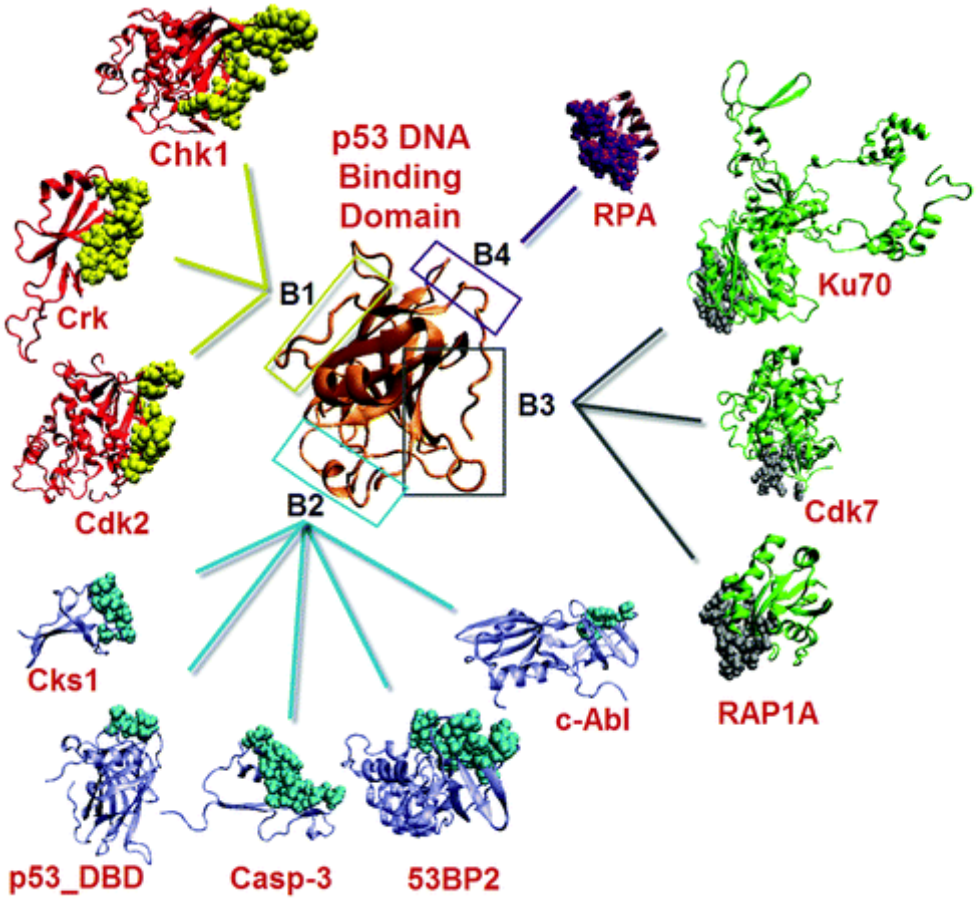
MDM4

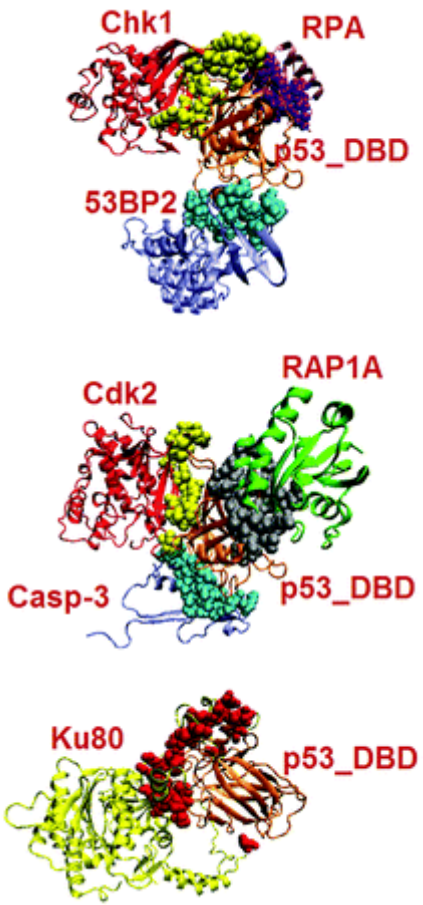
Maybe not so easy?



String 9.0; http://string-db.org

p53 only interacts with MDM2?





Tuncbag N et al. Mol BioSyst 2009; 5: 1770

HDM2 inhibitors

Nutlin-3a

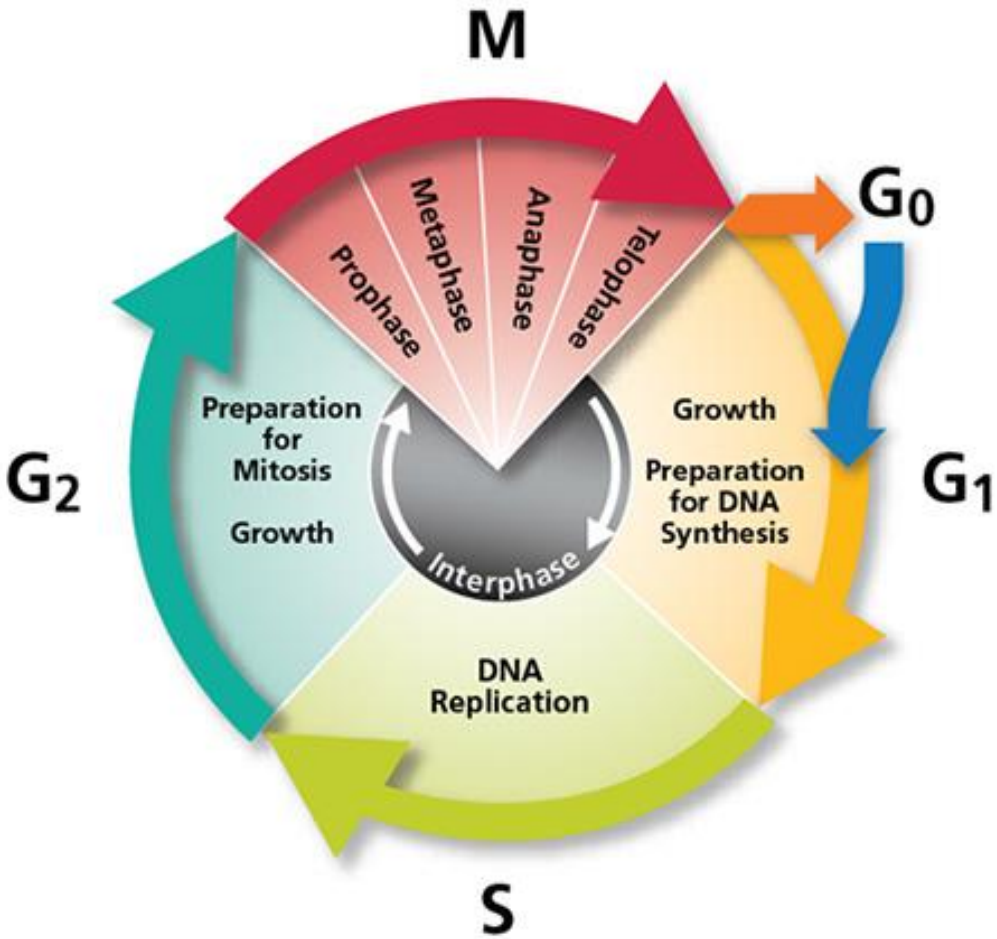
- Binds p53 interacting site on HDM2
  Inactive as single agent in *TP53* mutant tumors
- May act through E2Fs in concert with
  cytotoxic agents in *TP53*-mutant tumors
- Oral administration, adequate PK in phase I
- Toxic at pharmacologically relevant doses
  - Nausea, vomiting
  - Hematological toxicity
- 2nd generation agents under study now

Neoadjuvant therapy with RG7112

- n=20 pts, Rx 1440 mg/m^2 daily x 10, q 28 days
- 3 cycles of therapy, then surgery: 1 PR, 14 SD
- 13/14 eval with HDM2 ampl; 2/19 *TP53* mut
- Toxicity
  - Nausea/vomiting: G3-4 in 2
  - Neutropenia: G3-4 in 3
  - Thromocytopenia: G3-4 in 5 (prolonged, late)
    - Related to AUC and Cmax
- Feasible…but combinable? Stem cell toxin?
- One of several examples in sarcoma where preclinical promise has not borne fruit to date

Ray-Coquard IL et al. J Clin Oncol 29: 2011 (abstr 10007b)

The cell cycle—it's simple!



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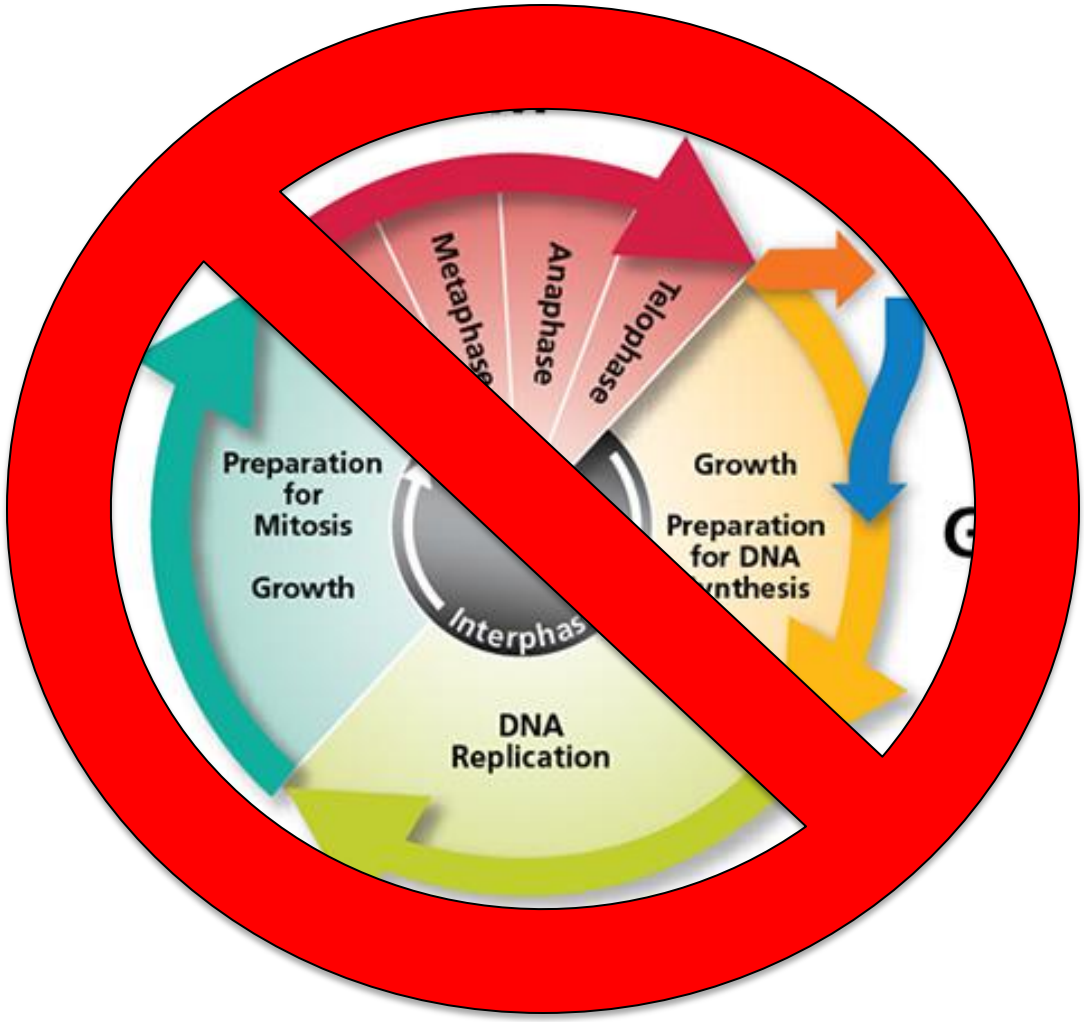


Wholesale cyclin substitutions complicate cell cycle blockade

Satyanarayana A and Kaldis P. Oncogene 2009; 28: 2925

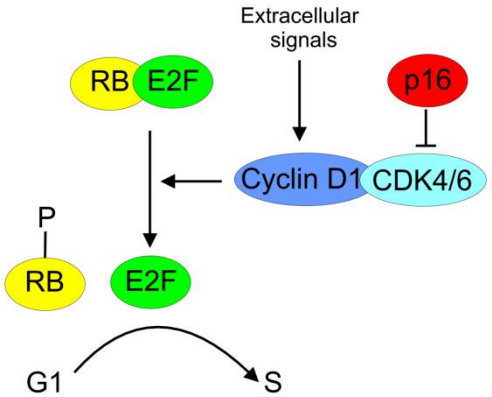
CDK inhibitors

- *CDK4* is part of the 12q amplicon
- CDK inhibitors often block >1 molecule
  - PD0332991 Pfizer: CDK4/6
  - LEE011 Novartis CDK4/6
  - P276-00 CDK1/6
  - Terameprocol CDK1/survivin
  - AG-024322 CDK1/2/4
  - Dinaciclib (SCH727965) CDK1/2/5/9
  - BMS-387032 (SNS-032) CDK2/7/9
- PD0332991 phase II in liposarcoma: minor activity
  - 1 of 29 patients with RECIST PR; others with some evidence of tumor shrinking

Dickson MA et al. JCO 2013; 31: 2024

Criteria for successful CDK4 inhibition

- Rb must be intact for CDK4 inhibitors to function
- Up-regulation of other genes may engender resistance to CDK4 inhibitors, e.g. p16
- Conversely, loss of p16 may predict for sensitivity to CDK4 inhibitors (J. Fletcher—WD DD liposarcoma)
- Rb intact, p16 low ovarian cancer lines were more sensitive to a CDK4/6 inhibitor than those without either feature



Dean JL et al. Oncogene. 2010; 29:4018
Katsumi J et al. BBRC 2011; 413:62
Konecny GE et al. CCR 2011; 17: 1591

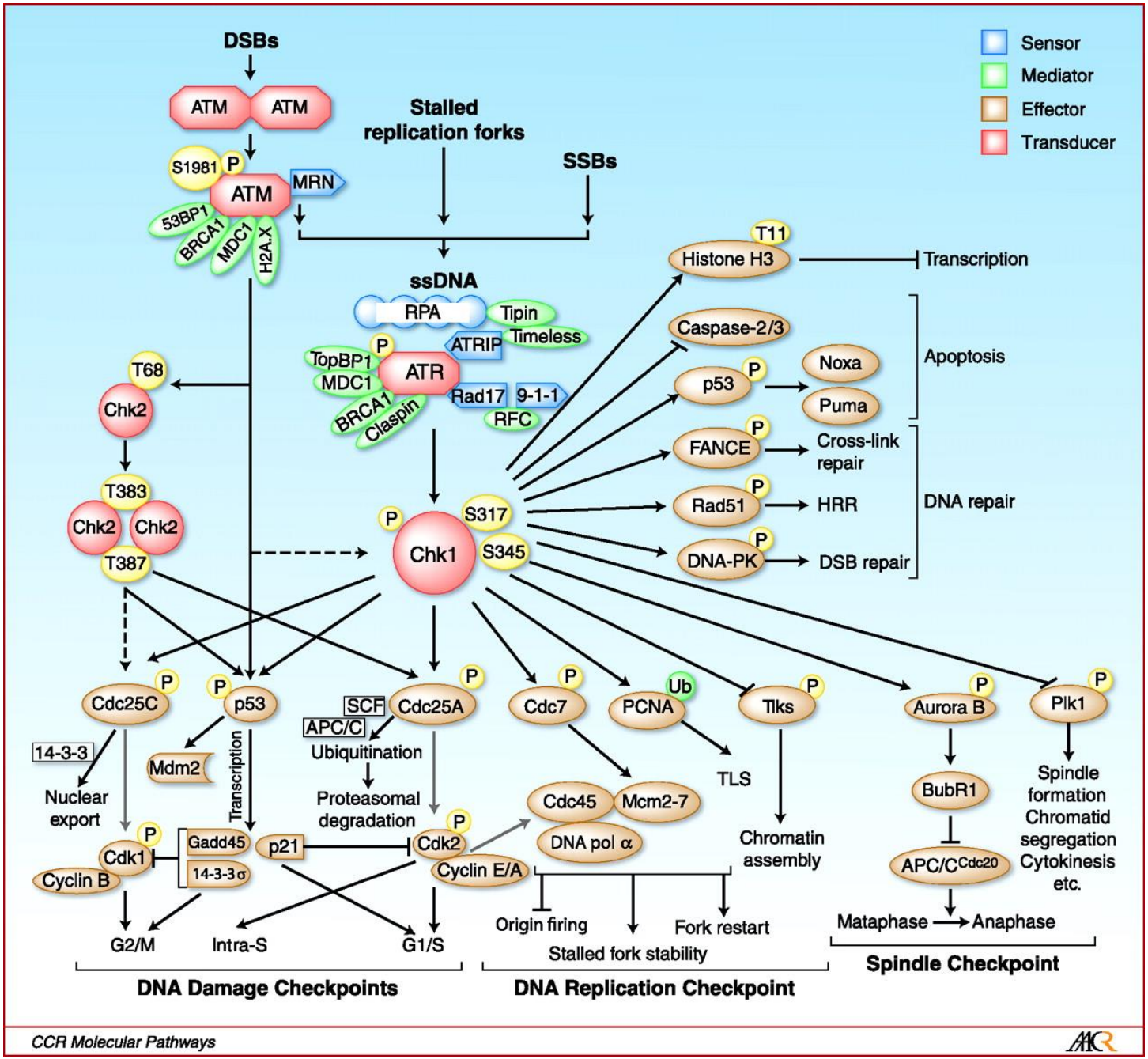
CDK4 inhibitor PD0332991 is active in ER+ HER2- breast cancer

- Letrozole ± PD0332991 (3/1) in ER+ HER2- BrCA
- n=165
- RR 31% vs 26%
- Median PFS 26.2 mo vs 7.5 mo
- HR 0.37 ($p<0.001$)
- Overall survival data pending

Finn RS et al. SABCM 2012; Abstract #S1-6

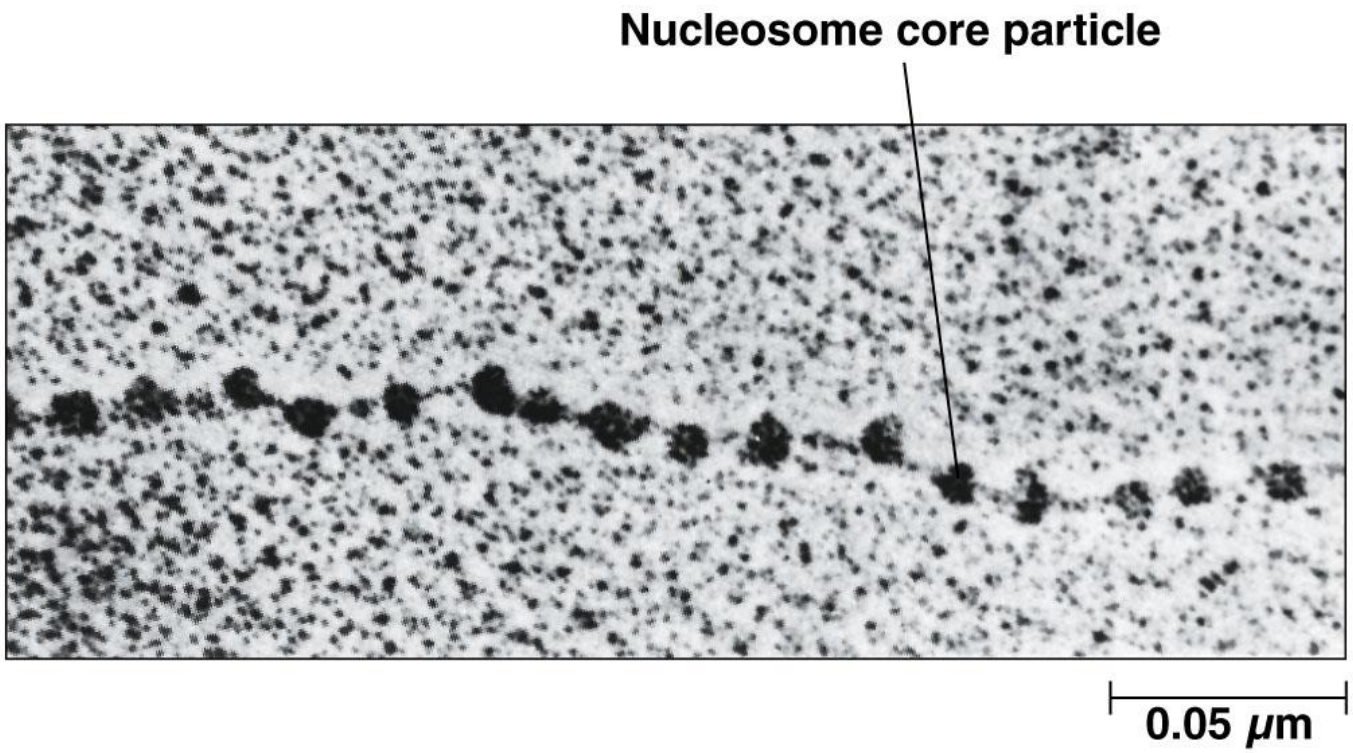
Novel mechanisms to induce apoptosis

- bcl2 antisense Rx
- PARP inhibitors with or without cytotoxic agents
- Survivin, IAP inhibitors
  - Specificity an issue
- CHK1, 2 inhibitors
  - Very few under study, after some interest
- Aforementioned CDK inhibitors
  - Caution, you need some of those molecules
- Interesting other agents
  - Newer generation ecteinascidin (PM01183)
  - Newer generations of proteasome inhibitors?



Dai Y et al. CCR 2010; 16: 376

Another new frontier: these are not your mother's histones



Wilkins MHF, Zubay G, Wilson HR. J Mol Biol 1959; 1: 179
Olins AL & Olins DE. Science 1974; 183: 330
Kornberg RD. Science 1974; 184: 868

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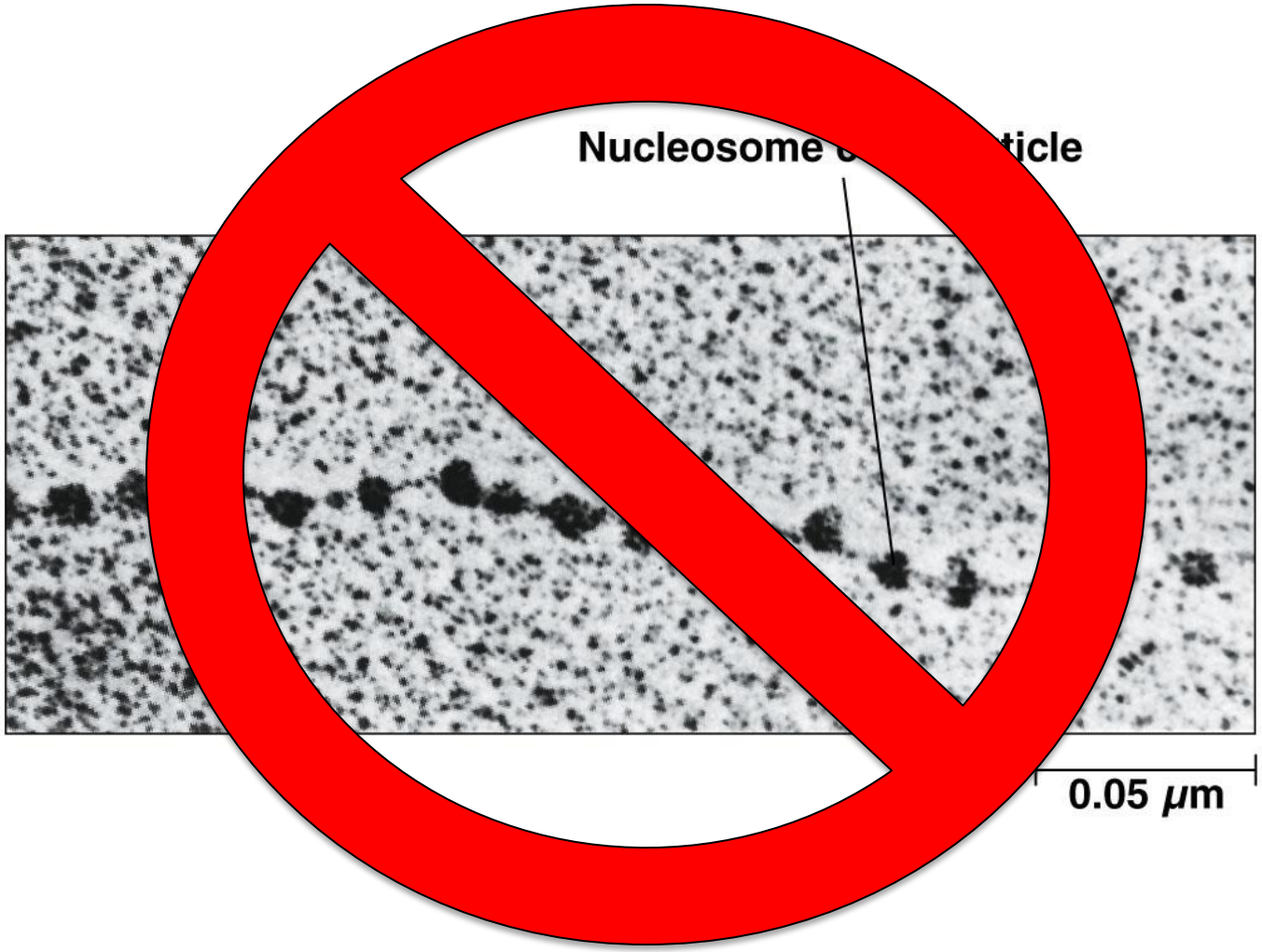
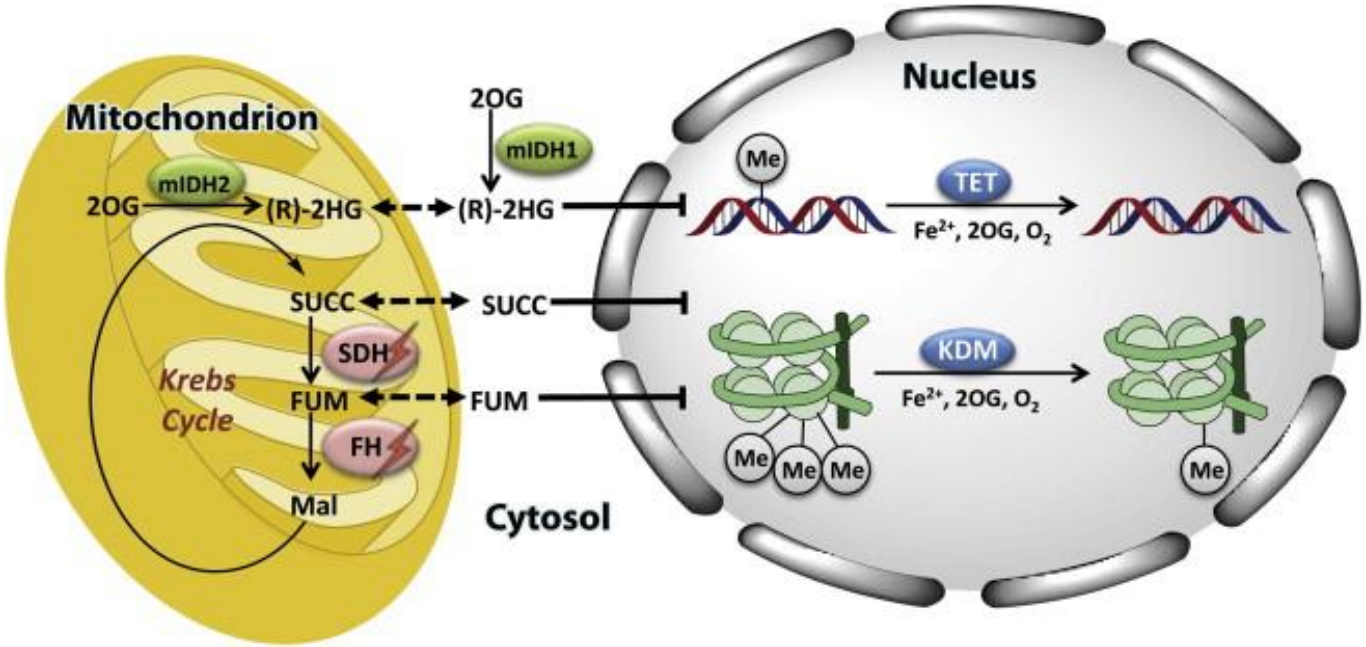


Wilkins MHF, Zubay G, Wilson HR. J Mol Biol 1959; 1: 179
Olins AL & Olins DE. Science 1974; 183: 330
Kornberg RD. Science 1974; 184: 868

Striking changes in DNA & histone methylation that will influence future cancer therapy

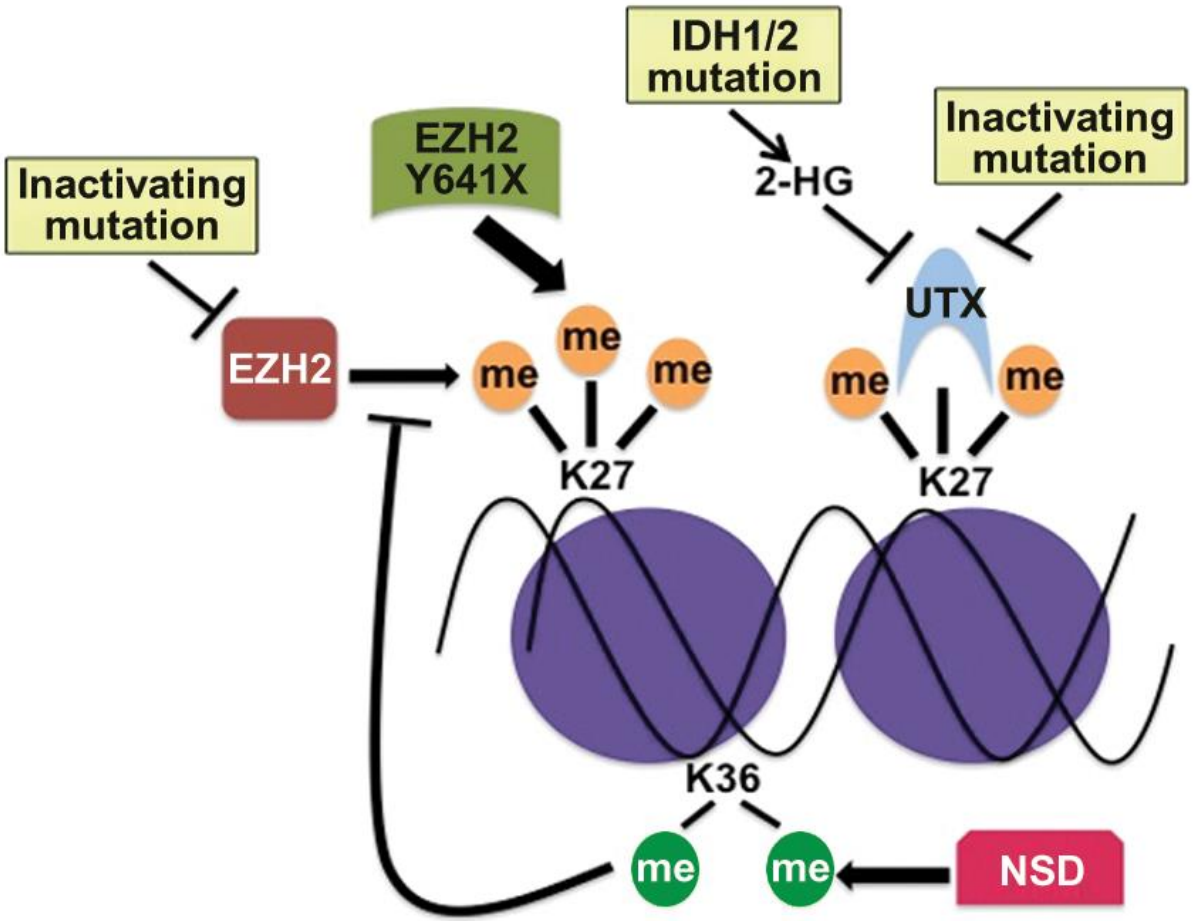
IDH mutations

SDH mutations



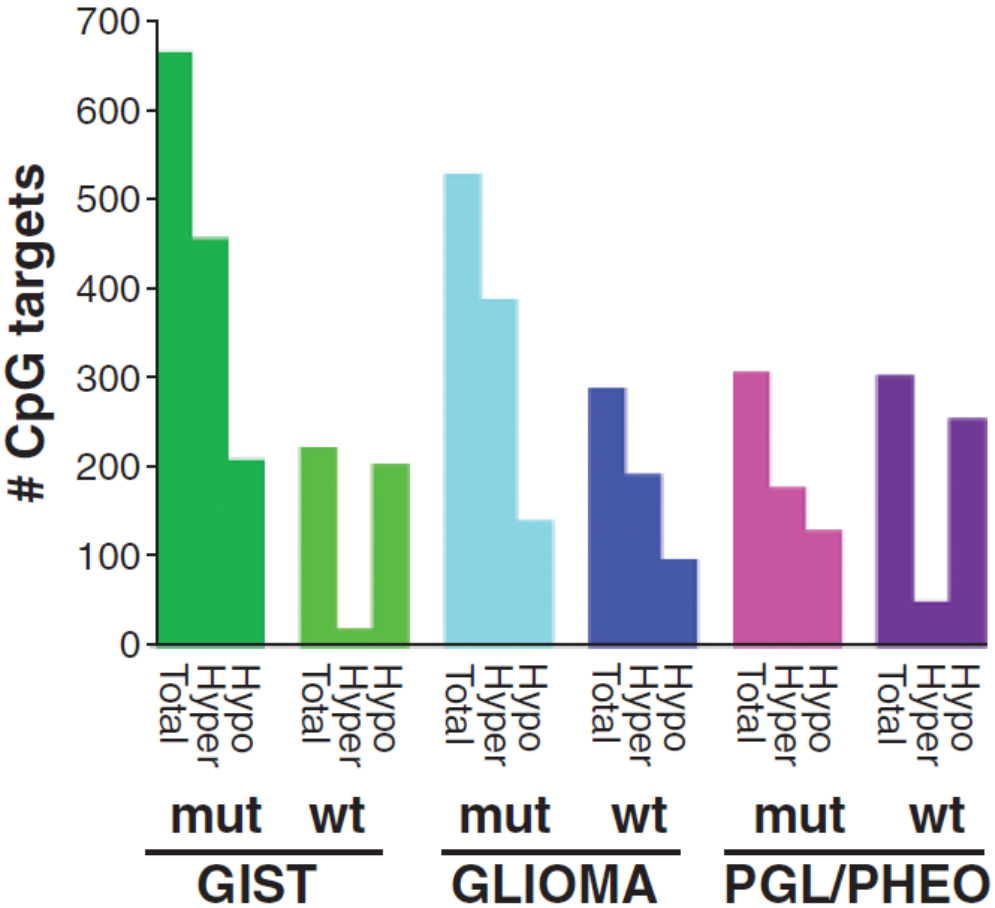
Lu C et al., Turcan S et al., Koivunen P et al. Nature 2012; 483: 474, 479, 484
Letouze E et al. Cancer Cell 2013; 23: 739
Yang M and Pollard PJ. Cancer Cell 2013; 23: 709

Metabolic alterations ↔ epigenome



WT GIST vs. other SDH or IDH altered tumors

Differentially methylated targets in SDH or IDH mutant tumors

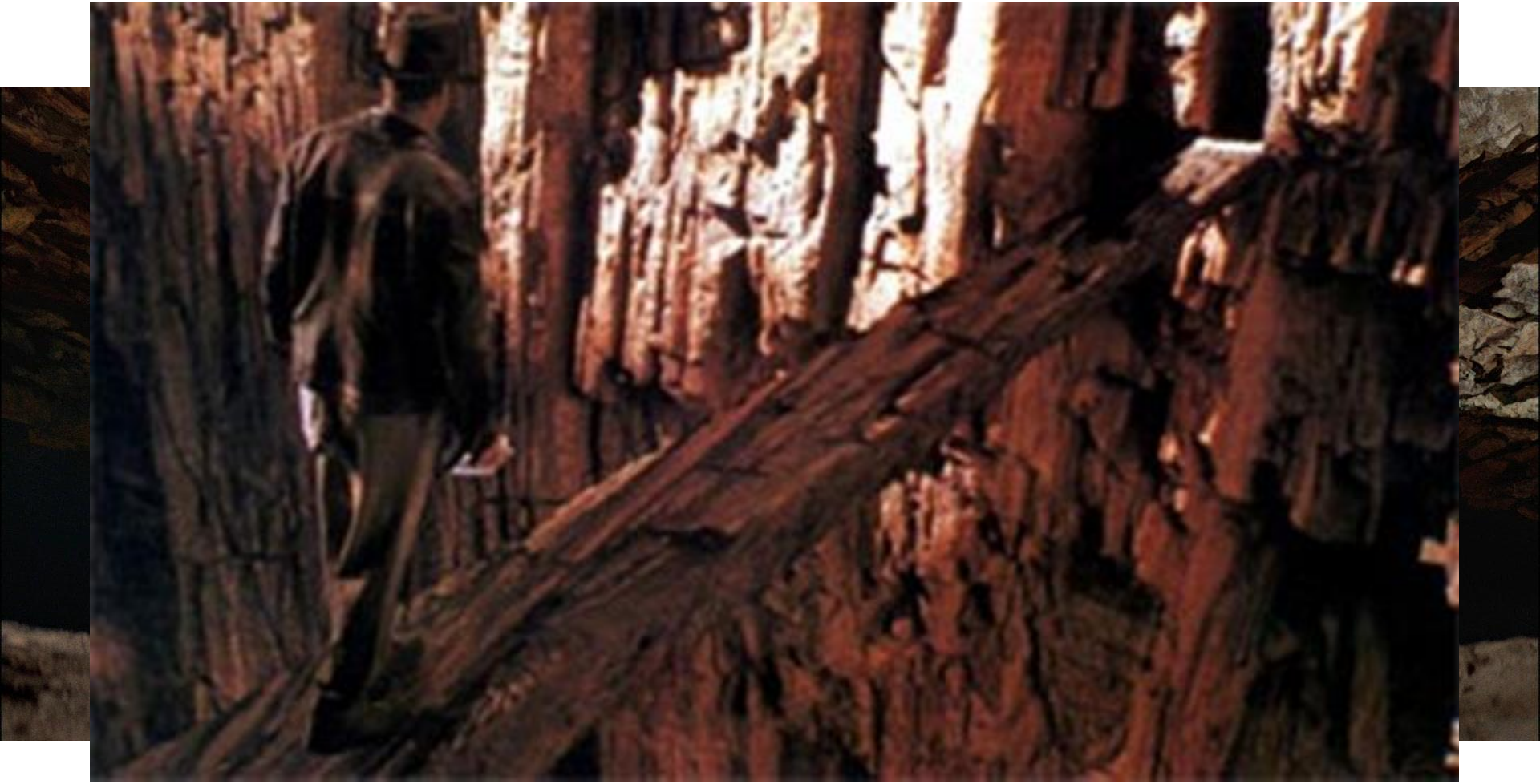


Killian JK et al. Cancer Discov 2013; 3: 648

Obvious next steps

- *IDH1/2* mutants ➔ IDH inhibitors: chondrosarcoma
- *SDH* mutation: GIST – similar agents?
- (DNA)MT inhibitors (decitabine, 5-aza, newer drugs?)
- HDAC inhibitors: Not very successful so far
  - LBH-589 = panobinostat phase II, 20 mg TIW
    - n=53
    - Thrombocytopenia, fatigue, anemia
    - Only responders: sex cord stromal tumors! (GCT *FOXL2* mut)
    - Phase I with imatinib: 0 RECIST PR / 17 pts
  - Choy et al. Doxorubicin + abexinostat phase I
    - Mostly heme toxicity as limiting factor (WBC, PLT)
    - 1 PR, 11 SD of 17 pts for all dose levels

Cassier P et al. Br J Cancer. 2013; 109: 909
Choy E et al. Proc AACR 2013; 73: Abstr LB-167



The great unknown: immunotherapy

Immunology: it's easy! Two signals

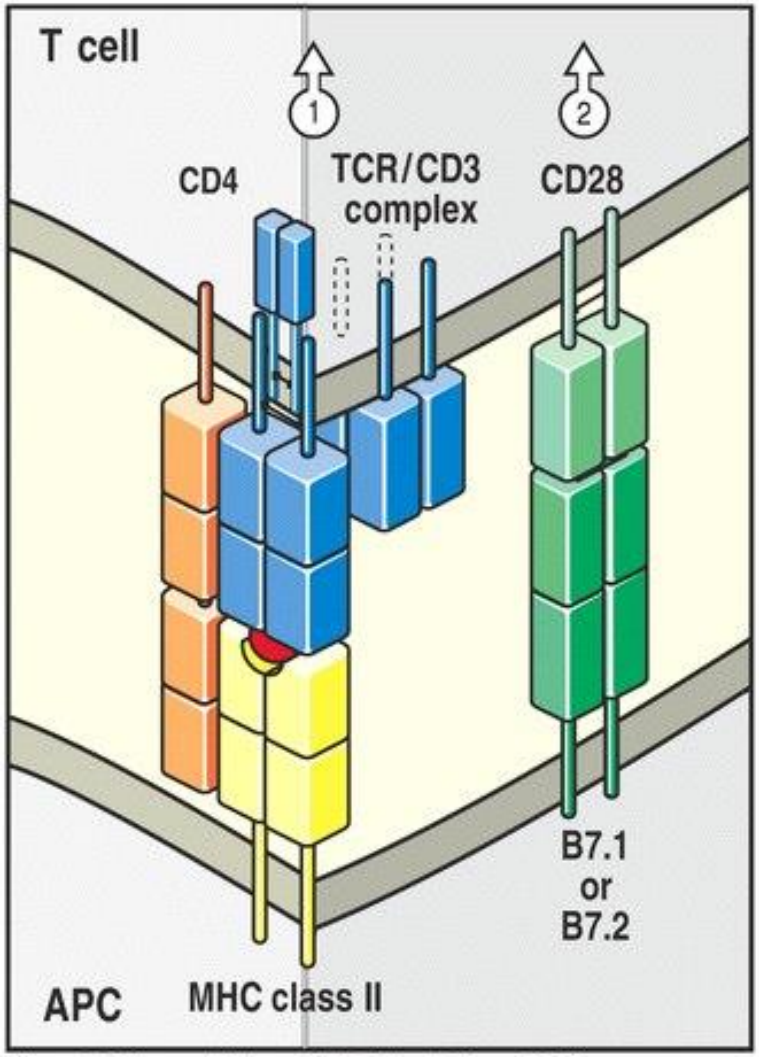


Figure 8-11 Immunobiology, 6/e. (© Garland Science 2005)

Immunology: it's easy! Two signals

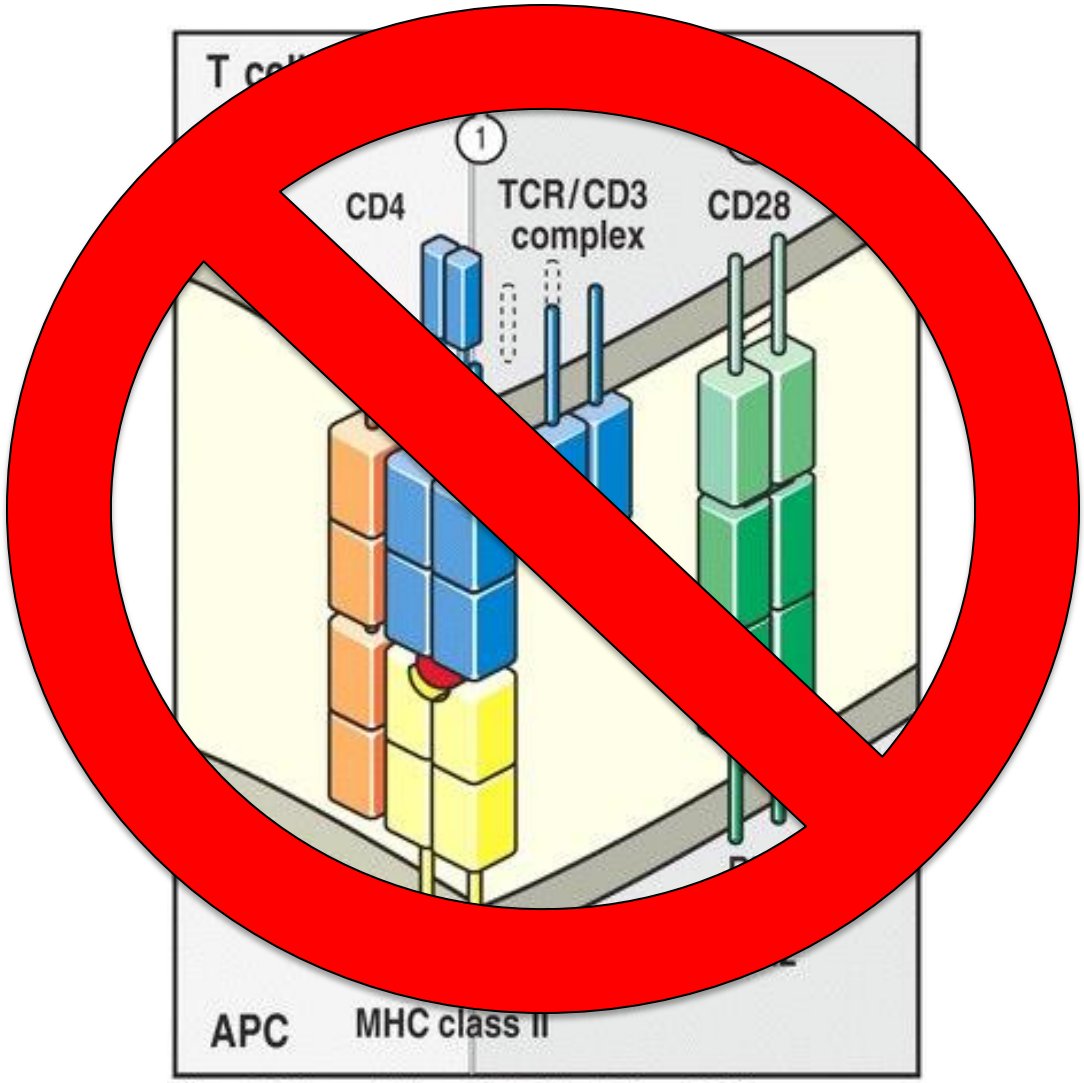
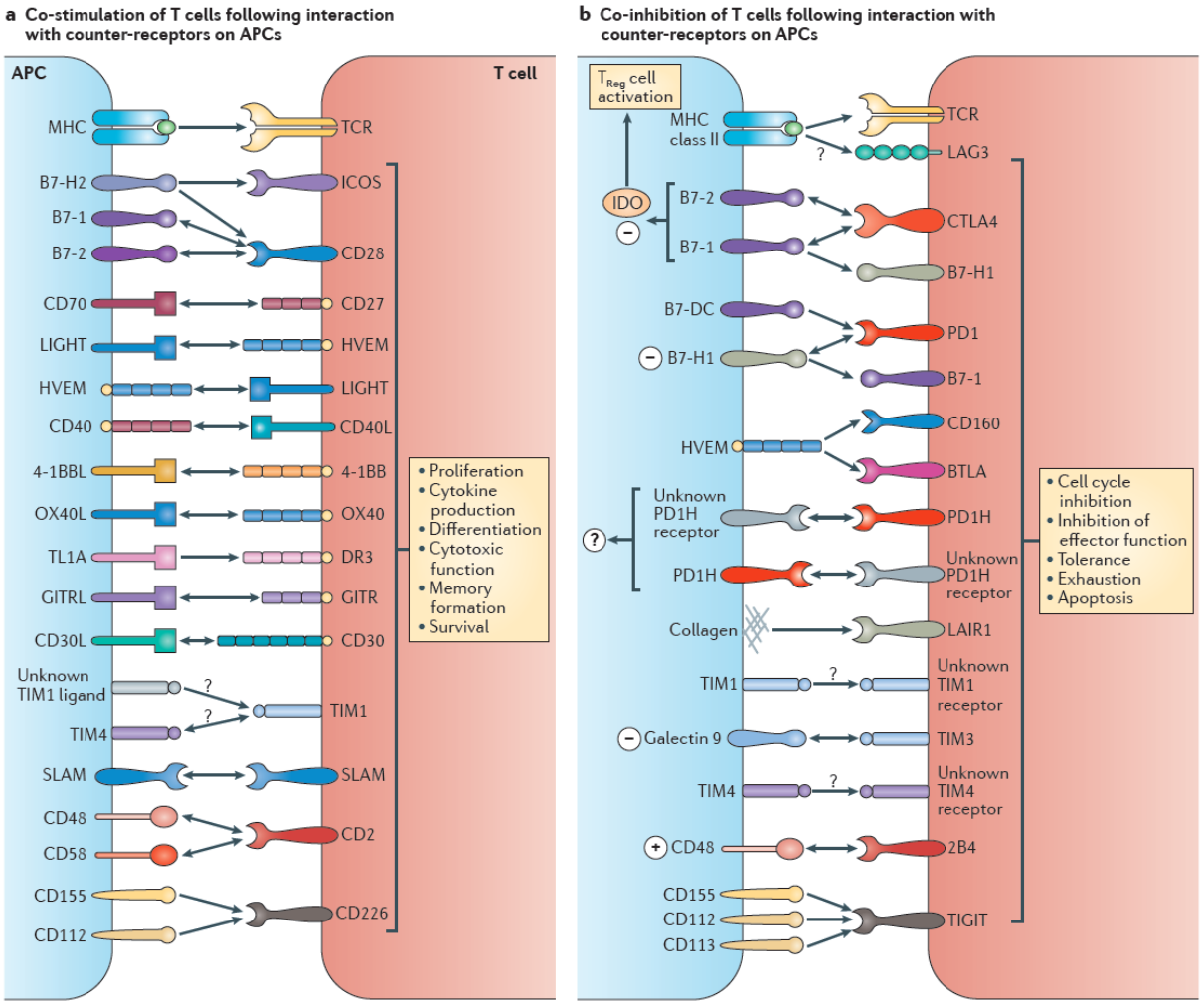


Figure 8-11 Immunobiology, 6/e. (© Garland Science 2005)

Immunology: it's easy! Two signals



Newer agents with some preclinical support

- Immunotherapy: a blank slate for sarcomas
  - Nearly no data regarding clinical immunotherapy in any soft tissue sarcoma subtype
  - Ipilimumab inactive in a cohort of 6 synovial sarcoma patients
  - Vaccines appear largely inert by themselves
  - Most promise: synovial sarcoma, myxoid-round cell liposarcoma
    - ex vivo T cell expansion
    - CART therapy

Sarcoma 2013;2013:168145

C-T (cancer-germ line) antigens in sarcomas

TABLE I – IMMUNOPHENOTYPING OF 25 SYNOVIAL SARCOMAS FOR NY-ESO-1 (MAb ES121), MAGE-A1 (MAb MA454) AND CT7 (MAb CT7-33): COMPARISON OF ANTIGENIC PHENOTYPE, MORPHOLOGY AND SYT-SSX TRANSLOCATION TYPE

Number	SYT-SSX fusion transcript	Clinical stage of sample	Histologic type	MAb ES121	MAb MA454	MAb CT7-33
1	1	P	BSS	+	–	–
2	2	P	MSS	++++	Focal	–
3	1	P	BSS	+	–	–
4	1	R	MSS	–	–	–
5	2	R	MSS	++++	–	–
6	1	P	BSS	++	–	+
7	2	R	MSS	++++	–	–
8	1	M	BSS	++++	–	Focal
9	1	M	BSS	–	–	–
10	2	R	MSS	+++	–	–
11	2	M	MSS	Focal	–	–
12	1	P	MSS	+++	–	–
13	1	P	BSS	++++	+	–
14	1	P	MSS	+++	–	–
15	2	P	MSS	+++	–	–
16	1	P	BSS	++	–	–
17	1	P	BSS	–	–	–
18	1	M	MSS	+++	+	–
19	1	P	BSS	+++	+	–
20	1	P	BSS	++++	–	–
21	1	R	BSS	–	–	–
22	1	P	BSS	–	–	–
23	1	P	MSS	++++	–	–
24	1	P	MSS	++++	–	–
25	1	R	BSS	+	–	–

Grading: Focal approx. <5%; +, 5% to <25%; ++, 25% to <50%; +++, 50% to <75%; ++++, >75%. P, primary; M, metastasis; R, recurrence; BSS, biphasic synovial sarcoma; MSS, monophasic synovial sarcoma.

Lee SY et al Proc Natl Acad Sci U S A. 2003; 100:2651
Jungbluth AA et al. Int J Cancer. 2001; 94: 252

Cancer – germ line antigens

- Many, not all, on X chromosome
- MAGE, BAGE, GAGE, LAGE,…
- PRAME
- CT7
- NY-ESO-1
- SSX genes (!)

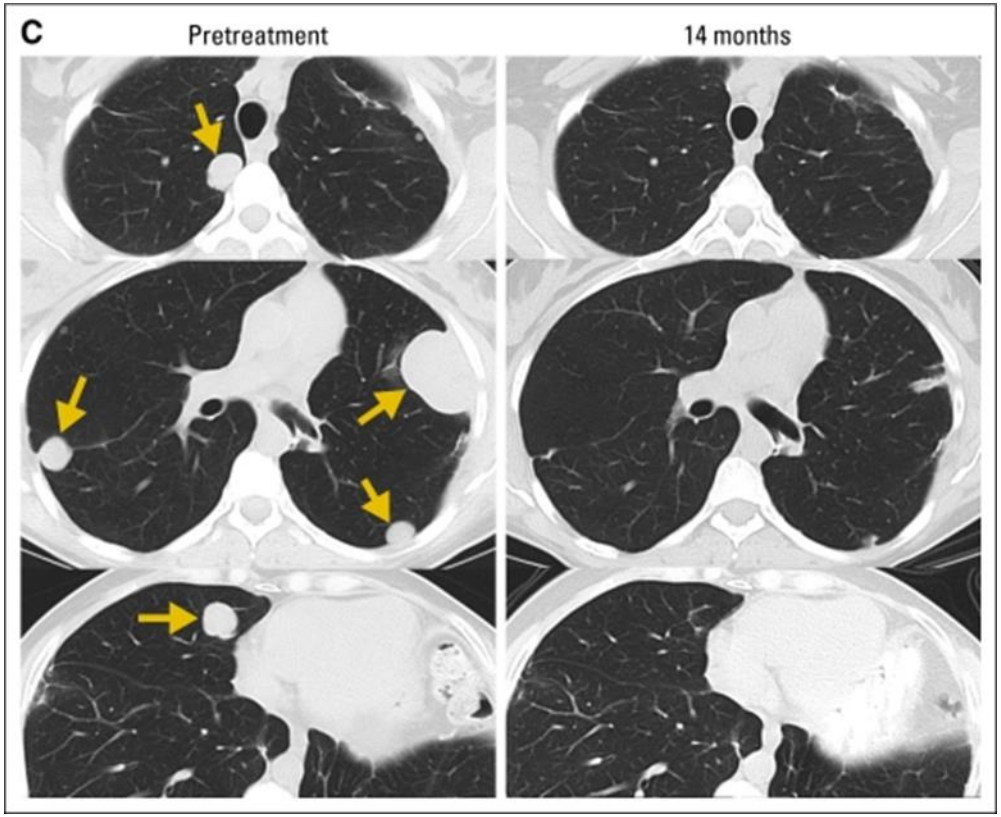
Table 1 | **Characteristics of CT-X antigens**

CT antigen gene family	CT identifier	Number of genes in family	Chromosome location	Expression during germline maturation	Function
MAGEA	CT1	12	Xq28	Spermatogonia	Translational co-repressor
MAGEB	CT3	4	Xp21–p22	Migrating PGCs	Unknown
GAGE1	CT4	8	Xp11.4–p11.2	ND	Unknown
SSX	CT5	5	Xp11.23–p11.22	ND	Transcriptional repressor
NY-ESO-1	CT6	3	Xq28	Spermatogonia	Unknown
MAGEC1	CT7	2	Xq26, Xq27.2	ND	Unknown
MAGEC2	CT10	1	Xq27	ND	Unknown
CTp11/SPANX	CT11	4	Xq27.1	Spermatids	Unknown

Table 2 | **Characteristics of non-X CT antigens**

CT antigen gene family	CT identifier	Number of genes in family	Chromosome location	Expression during germline maturation	Function
BAGE	CT2	5	13	Spermatogonia	Unknown
SCP1	CT8	1	1p13–p12	Spermatocyte	Structural component of synaptonemal complexes
BRDT	CT9	1	1p22.1	ND	Possible transcriptional regulatory protein
HAGE	CT13	1	6q12–q13	ND	ATP-dependent RNA helicase
ADAM2	CT15	1	8p11.2	Spermatocyte, spermatids	Sperm–egg membrane binding
LIP1	CT17	1	21q11.2	ND	Membrane-associated phospholipase
TSP50	CT20	1	3p14–p12	Spermatocyte	Protease

Treatment of synovial sarcoma with *ex vivo* expanded NYESO1 T cells

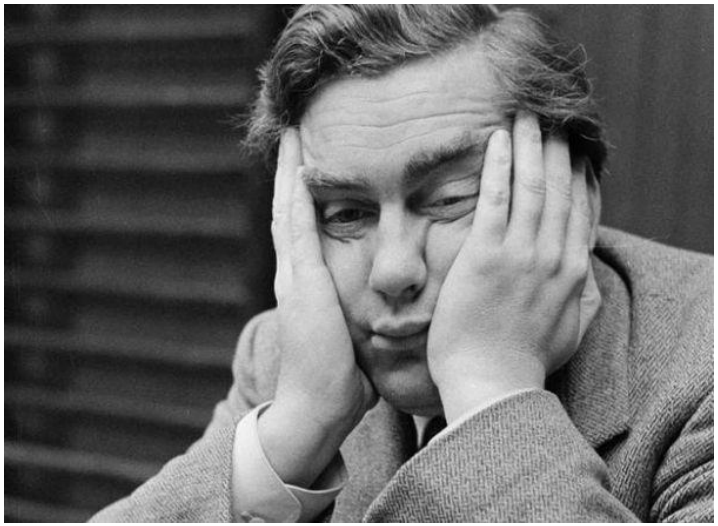


Robbins PF et al. J Clin Oncol. 2011; 29:917

Next steps for immunotherapy

- PD1 mAbs
  - RFP from CTEP for BMS mAb → add ipi
  - Likely other trials of single agents
  - PD1L mAbs?, other costimulators?
  - Addition of vaccines
- CART therapy or *ex vivo* trained T cells
  - NCI: NY-ESO-1 CART in context of HLA-A2
  - HLA-A1 specific trial
  - Mesothelin (+) sarcomas – HLA independent study
  - Other studies pending…

Use what we have better



Variations on existing agents

- Anthracyclines
  - Epirubicin vs Doxorubicin? (Frustaci JCO 2003)
  - Albumin bound doxorubicin = aldoxorubicin
    - Randomized trial: aldoxorubicin 350 mg/m2 vs doxorubicin 75 mg/m2 q3 wk
    - n=123 (2:1)
    - PFS 5.7 vs. 2.8 mo, 6 mo PFS 47% vs 24%, RR 23% vs 0%
  - PLD/Doxil®/Caelyx®
- Microtubule active compounds
  - Eribulin, oral vinorelbine
  - Liposomal Docetaxel
- Novel alkylating agents
  - TH302
  - Palifosfamide failed
  - Novel minor groove binding agent: lurbinectedin = PM01183

Combinations

Too numerous to explore

Kinase inhibitor + kinase inhibitor

Kinase inhibitor + cytotoxic

Cytotoxic + cytotoxic

Immunotherapy? Combinations with above?

Sequencing of drugs?

Finally: a simple methodological issue

"How do we get there" in studying new agents or combinations

The good old days? Streptozotocin phase II

TABLE 2. Experience with Streptozotocin in 51 Patients

Tumor type	Total patients	Evaluable for response	Nonresponders				Responders	
			O-O	*O-A*	*O-B*	*II*	*I-A*	*I-B*
Kidney, adenocarcinoma	5	4	4					
Kidney, Wilms'	1	1		1				
Pancreas adenocarcinoma	5	5	3		2			
Pancreas, islet cell carcinoma	4	4	2				1	1
Ileum, carcinoid	4	4	2	1				1
Colon, adenocarcinoma	3	3	2			1		
Hepatoma	2	1	1					
Gallbladder, adenocarcinoma	1	1					1	
Salivary, adenoid cystic	2	2	2					
Oral, squamous	2	2	1				1	
Ovary, adenocarcinoma	5	4	4					
Breast, adenocarcinoma	1	1	1					
Testis, embryonal	1	0						
Testis, choriocarcinoma	1	0						
Lung, adenocarcinoma	1	1	1					
Lung, squamous	3	3	2				1	
Unknown primary carcinoma	2	0						
Melanoma	3	0						
Leiomyosarcoma	1	1				1		
Synovial sarcoma	1	1						1
Kaposi's sarcoma	1	0						
Liposarcoma	1	1	1					
Anaplastic sarcoma	1	0						
Acute granulocytic leukemia	2	0						

TABLE 1. Categories of Response

Category	Definition
O	No clinically useful effect on course of disease:
O-O	Disease progresses; no objective or subjective improvement.
O-A	Subjective improvement without objective changes.
O-B	Objective improvement for one month or more without subjective improvement.
O-C	Objective and subjective improvement of less than one month's duration.
I	Objective and subjective improvement of at least one month's duration:
I-A	Objective improvement of 25-50% for one month or more, with subjective improvement.
I-B	Objective improvement greater than 50% in all lesions for one month or more, with subjective improvement.
I-C	Complete objective and subjective remission for one month or more; regression of all manifestations of disease.
II	Interruption of progression of disease for one month or more, without objective improvement.

Stolinsky DC et al. Cancer 1977; 30:61

He that is without sin among you, let him first cast a stone… (John 8:7) –

Bortezomib phase II sarcoma trial

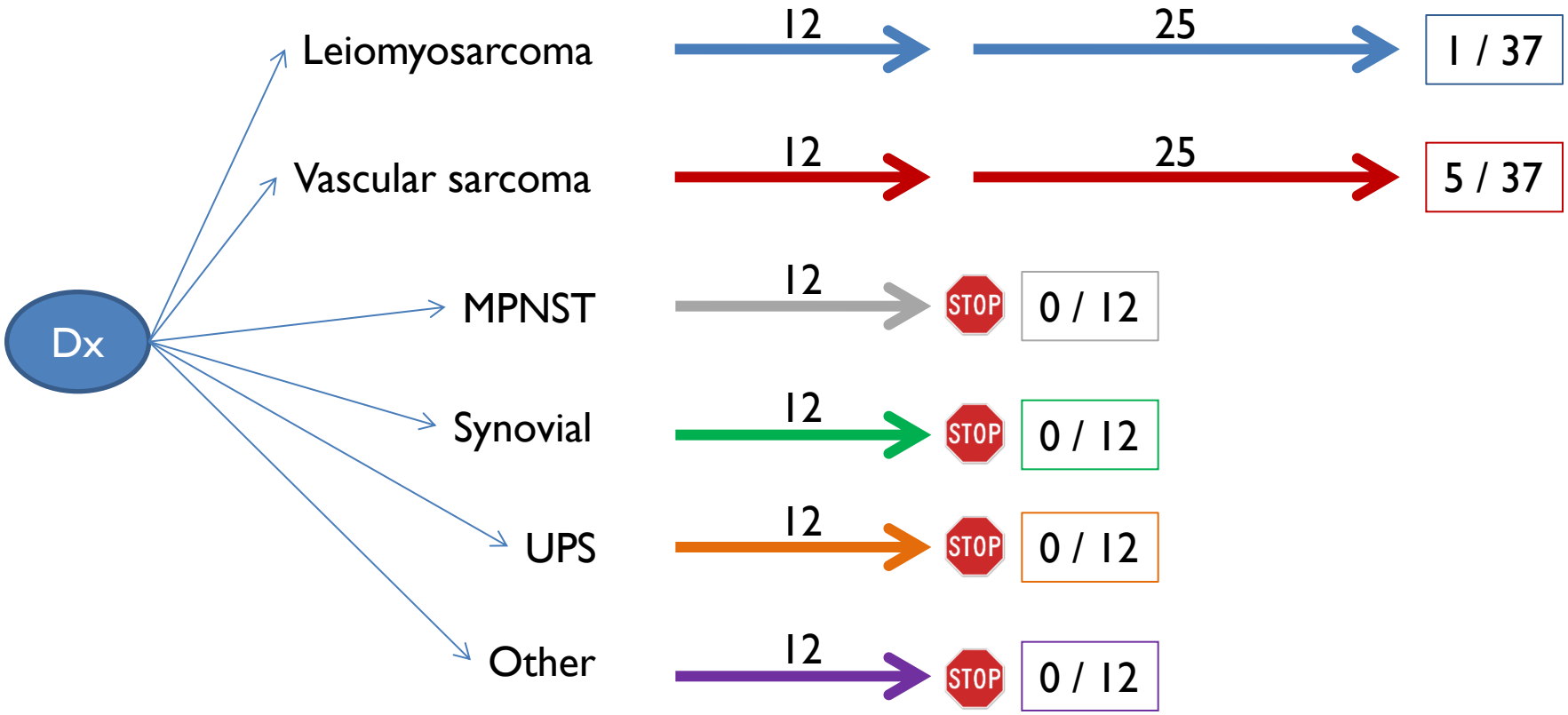
TABLE 1
Patient Characteristics

Characteristics	No. (range)
Histology	
MFH/high-grade sarcoma NOS	6[b]
Leiomyosarcoma	4
Liposarcoma	
Well differentiated/dedifferentiated	2
Pleomorphic	2
Synovial sarcoma	2
Alveolar soft part sarcoma	2
Ewing sarcoma	2
Follicular dendritic cell sarcoma	1
Extraskeletal osteogenic sarcoma	1
Gastrointestinal stromal tumor	1
Epithelioid sarcoma	1

Maki RG et al. Cancer 2005; 103:1431

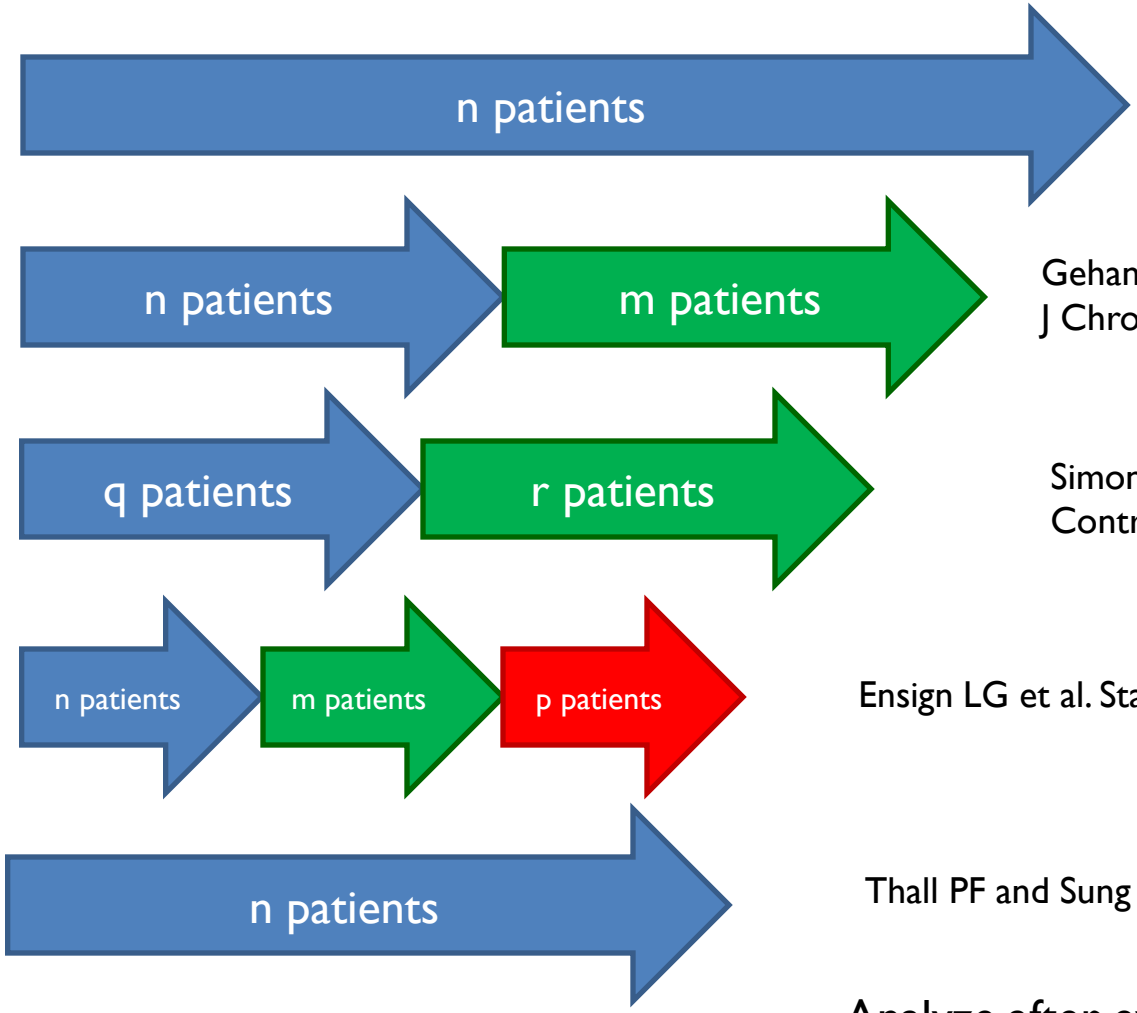
An easy way to find a signal: two-stage study, "high bar" for response

Sorafenib phase II (not quite I-SPY 2…)



Maki RG et al. JCO 2009; 27:3133

You, too, can do a Bayesian trial !



Gehan EA et al.
J Chronic Dis 1961; 13: 346

Simon R. 1989;
Control Clin Trials 10: 1

Ensign LG et al. Stats Med 1994;13: 1727

Thall PF and Sung HG 1998; 17: 1563

Analyze after every patient:
continuous monitoring

Please: subtype specific data!

Just like our pediatric colleagues

And by that destiny to perform an act
Whereof what's past is prologue, what to come
In yours and my discharge.

Antonio, The Tempest, 2, 1

For more Shakespeare quotes, email bobmakimd@gmail.com