FDA Oncology Drug Approval

Endpoints, Effectiveness, and Approval

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Not an official FDA policy

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Overview for oncology drug approval

- Evidence for efficacy and safety
- Good Evidence = Approval
- Endpoints for trial design
- Endpoints for FDA approval
- Trial design issues for efficacy
- Trial results analysis
- "Targeted" therapy approval and problems

Interplay of disease state, existing Rx options, endpoint options, strength of evidence

FDA - Oncology Drugs

- Not – Drug imports from Canada

- Not – Vioxx, Celebrex, Plan B

- No stock market tips

FDA Oncology Drug Approval

- FDA – U.S. Food and Drug Administration
  - In the Dept of HHS – Executive Branch
- Created by Congress because of prior unsafe drugs being marketed
- FDA charged by Congress to evaluate all prescription drugs seeking marketing in the U.S.
- Federal Laws, Regs govern these activities

Requirements for Drug Approval

U.S. Statutes –Congress

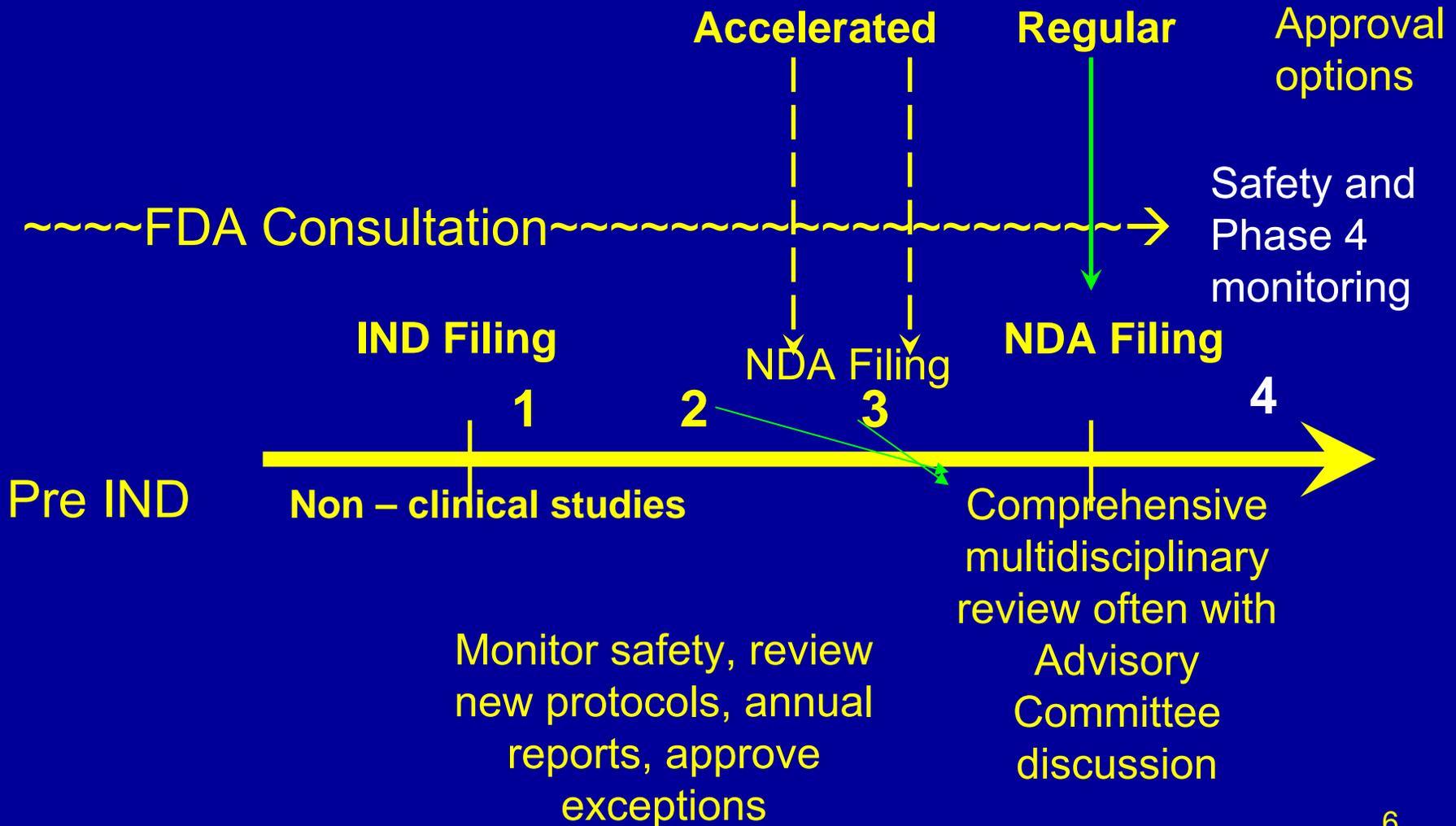|	
Labeling	1906 Pure Food & Drug Act
Safety	1938 Food, Drug, and Cosmetic Act (FDC)
Efficacy	1962 FDC Amendments

Harris-Kefauver

FDAMA Amdnts. 1997

Code of Federal Regulations (CFRs) provides interpretation of laws

Regulatory Perspective on Drug Development and Approval

Accelerated

Regular

Approval options

~~~~FDA Consultation~~~~~~~~~~~~~~~~~~~~~~~→

Safety and Phase 4 monitoring

IND Filing

NDA Filing

NDA Filing

1   **2**   **3**   **4**

Pre IND

Non – clinical studies

Comprehensive multidisciplinary review often with Advisory Committee discussion

Monitor safety, review new protocols, annual reports, approve exceptions

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Drug Development Focal Points - FDA Meetings

Phase	Format	Intent (FDA concerns)
Pre-IND / IND	T-con, FTF, none	Ph 1 design – FDA safety - population and dosing
EOP1	Tcon, FTF	Ph 2 design – FDA safety - population and dosing
EOP2	FTF	Ph 3 design – FDA safety, study design & analysis
Pre-NDA	FTF (face to face)	Results; format & content of reports; time frame of submission; priority?

FDA - Oncology Drugs

- Office of Oncology Drug Products – OODP
- Three divisions

  DDOP- Chemotherapy drugs for Cancer

  DBOP- Biologic oncology therapies BLAs

  DMIHP- Medical Imaging and hematology

Drug Approval Tracks

- FDA Modernization Act 1997 (FDAMA):
  - For unmet medical need - 312 subpart E
  - Fast track – process for meeting with FDA
  - Priority review – 6 month NDA review time frame for products addressing unmet medical need
  - Endorsed possibility of accepting <u>one</u> high quality study

- Special Protocol Assessment – clinical protocols for phase 3 studies forming primary basis for demonstrating efficacy for NDA; 45 day clock

FDA Oncology Drug Approval

- How do you achieve approval ?
- Provide substantial evidence of
    Efficacy and Safety

- What is substantial evidence for Effectiveness
  - "A & WC investigations" CFR 314.126
  - required by 1962 amend. to FFDCA
  Source = Controlled clinical trials

Basis for New Drug Approval

- Demonstration of efficacy with acceptable safety in adequate and well-controlled studies   CFR 314 - NDA Regulations

- Ability to generate product labeling that
  - Defines an appropriate patient population for treatment with the drug
  - Provides adequate information to enable safe and effective use – prescribing of the drug

- Analogous rules for Biologics - BLA

FDA Oncology Drug Approval

- Clinical trials:
  - When we do not know which therapy is better
  - Patients are fully informed of the uncertainty about which therapy is better and give consent
  - We can compare one treatment with another in a controlled way
  - Today's "standard" therapy was last year's investigational treatment

FDA Oncology Drug Approval

- Controlled clinical trials:
  - Can be verified, repeated if necessary
  - Can allow us to be convinced a new therapy is effective – or it is not.
  - Allow us to compare how well tolerated -
  (how safe) a new therapy is versus a standard

- Efficacy with Safety => Approval

Some trial considerations

- Usual situation for many FDA drug approvals
  - Multiple studies
  - Studies are large 1,000 – 5,000 patients
  - Placebo control group
  - Double Blinded or a blinded independent assessment
  - Highly significant p values (0.001)
- Oncology drug data submitted for approval
  - One study, 100 – 800 patients
  - No blinding, no placebo control
  - Heterogeneous patient group
  - Statistical evidence ~ 0.03 – 0.05
  - *Concern – how confident can we be that results are real

FDA Oncology Drug Approval

- Suppose YOU are the FDA –

- What benefits should a new drug have to allow its marketing approval in the U.S.?

- How "safe" should the drug be?

FDA Oncology Drug Approval

- What benefits should a new drug have for marketing approval in the U.S.?

- LIVE LONGER ---------------------Effective
- LIVE BETTER – QUALITY ------Effective

FDA Oncology Drug Approval

- What benefits should a new drug have for marketing approval in the U.S.?

- LIVE LONGER ----------------------Effective
- LIVE BETTER – QUALITY ------Effective
- SAFER THAN ALTERNATIVES with efficacy
- Benefits outweigh Risks   (312.84)
  - B / R assessment - in disease context
- COST ?   Less expensive? / Reimbursement ?
  – Not purview of FDA

FDA Oncology Drug Approval

- Judgment of Benefits versus Risks
- But - NEVER Have ALL the Data
- Some benefits or adverse effects occur:
  - Rarely
  - After long time interval

- How long to study and wait before Approval
- Too slow or too fast to approve?

What Drugs Are Safe

None of them

What Drugs Might Help Someone?

All of them

Can we tell in advance who might be helped and who might be hurt by a drug?

NO

But we hope to be able to soon

Two Types of Drug Approval:
Regular or Accelerated

Endpoints Supporting Regular Approval

<u>Regular</u> Approval ⇔ Demonstrate Clinical Benefit

- Longer life
- Better life (relief of tumor-related Sx) - PRO
  - Requires a valid measure of how a patient feels or functions
- Favorable effect on established surrogate

Accelerated Approval (AA)

Only applies in the setting of a new drug for a serious or life-threatening illness:

- Improvement over available therapy

- Study may use a surrogate endpoint, <u>reasonably likely</u> to predict clinical benefit

- Requires <u>confirmation</u> of benefit

Fed Register 1992

Oncology Trial Endpoints (1)

- CLINICAL BENEFIT ENDPOINTS

- LIVE LONGER – Measure Survival- OS
  Efficacy, reassures for safety, unbiased endpt
  but – subsequent therapy, long time required

- LIVE BETTER – Measure QOL – PRO
  Important: control group + blinding needed (bias)
  hard to measure, scale problems, missing data
  Drug Tox. symptoms versus tumor symptoms

- SAFETY (Benefit / Risk assessment)
  => COMPARISONS ARE NECESSARY
  – HOW? controlled clinical trials

Oncology Endpoints (2)

- DISEASE-FREE SURVIVAL (DFS)
  - Composite of survival and NED
  - Recurrence is associated with symptoms, new therapies, cognitive effects
  - Adjuvant treatment setting
    - Breast cancer
    - Colorectal cancer
      - 3 year DFS ($p \leq 0.03$) => 5 year OS
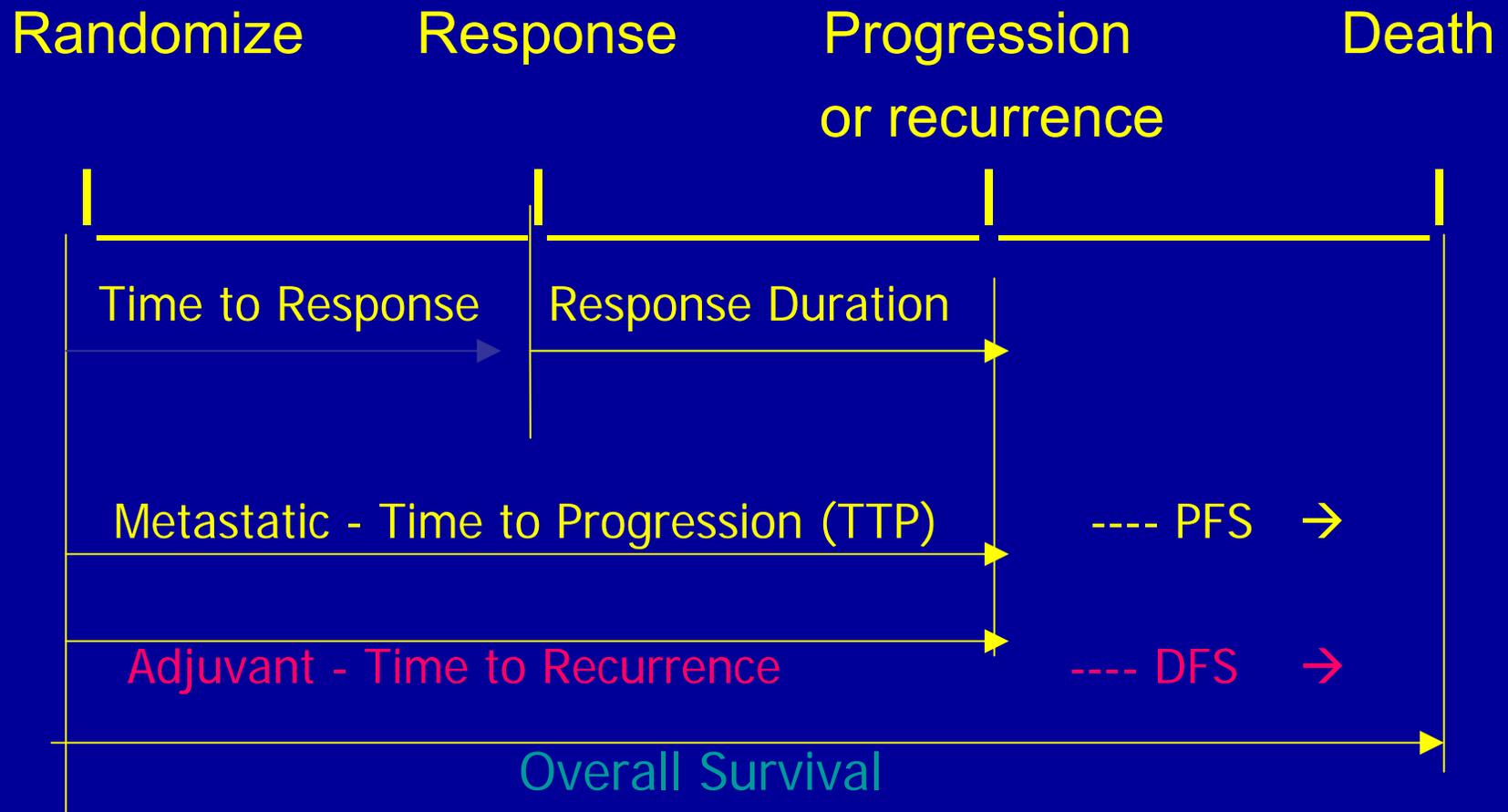   - New areas likely – lung, prostate, brain, etc

Endpoints - Regular Approval (3)

- Survival
- QOL – PRO
- BETTER SAFETY - with efficacy
- DFS – adjuvant and leukemia settings
- <u>Improvements</u> convey/are clinical benefits
- <u>Improvements</u> show effectiveness

 Demonstrate these endpoints

   = (Full) Regular Approval (RA)
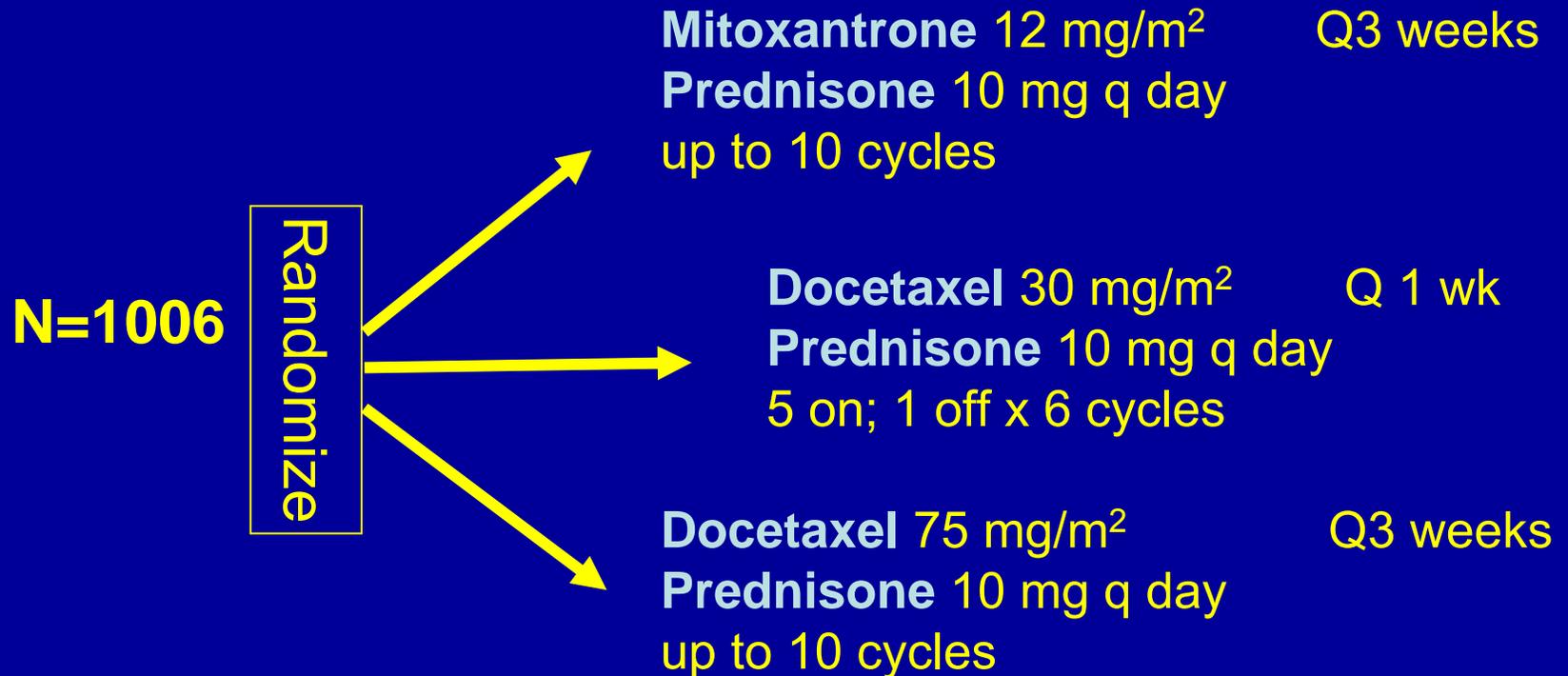
Tumor measurement endpoints

Randomize   Response   Progression   Death
                         or recurrence

Time to Response | Response Duration

Metastatic - Time to Progression (TTP)   ---- PFS →

Adjuvant - Time to Recurrence   ---- DFS →

Overall Survival

Tumor assessment endpoints (5)

- ## Response - Response rate (RR)
  ### = Drug activity (not the same as efficacy)
  anatomic imaging – measure tumor - RECIST criteria

  Complete responses (CR) – stronger evidence

- ## Time to progression (TTP)
  Progression – anatomic imaging - RECIST based

  Includes stable disease (natural history)

- ## Progression-free survival (PFS)
  – Composite of progression (TTP) and Death
  – Includes stable disease
  [ODAC (preliminary) – several months' difference ?]

Tumor assessment endpoints (6)

- Biomarkers – many different roles, utilities
  - Screening; diagnosis; predictive; prognostic
- Biomarkers: not reliable to date
  - Not highly predictive of outcome
  - CEA failure to correlate for colon
  - CA-125 ovarian ?
  - PSA failed to correlate with survival
        Tax 327 approval study example

Biomarker "surrogacy" from TAX 327 study

N=1006 | Randomize

Mitoxantrone 12 mg/m^2 Q3 weeks
Prednisone 10 mg q day
up to 10 cycles

Docetaxel 30 mg/m^2 Q 1 wk
Prednisone 10 mg q day
5 on; 1 off x 6 cycles

Docetaxel 75 mg/m^2 Q3 weeks
Prednisone 10 mg q day
up to 10 cycles

M Eisenberger, et al. Proc ASCO, 2004. Abs 4.

Docetaxel HRPC TAX 327 Trial- PSA endpoint

	Docetaxel 3-weekly	Docetaxel weekly	M+P
PSA response	45	48*	32
Pain response	35%	31%	22%
Meas. Dis response	12%	8%	7%
Med OS months	18.9	17.4	16.5
Logrank p **HR (95% C.I.)** **versus M+P**	**0.009** **HR=0.76** **(0.62, 0.94)**	**0.36 *** **HR=0.91** **(0.75, 1.11)**	

M Eisenberger, et al. Proc ASCO, 2004. Abs 4; D Petrylak, et al. Proc ASCO, 2004. abs 3.

Tumor assessment endpoints and approval (7)

- RR / TTP / PFS

  Hope – get results faster from studies

  Often used in phase 2 studies with single arm

  Hard to judge in single arm - no comparator

- Are these "surrogate" endpoints ?

  Problem - inconsistent relation to clinical benefit in phase 3 trials

- Valid surrogates: Blood pressure / Cholesterol
  - Strong and consistent relation with outcomes

Approval and tumor assessment endpoints (8)

Regular Approval – RA (OS, QOL, ↑ Safety)
  – If Clinical Benefit shown (live longer, better, safer) - or -
  – Benefit on Established surrogate - (DFS, Heme CR)

Accelerated Approval - AA (1992 – 314 subpart H)

- For Serious or Life Threatening illnesses
- Show meaningful therapeutic benefit over existing therapy or improved patient response over available therapy
- May be based on a <u>surrogate</u> <u>endpoint</u> which is <u>reasonably</u> <u>likely</u> to predict clinical benefit - <u>or</u>
- a clinical endpoint other than survival or irreversible morbidity

Approval and tumor assessment endpoints (9)

- AA uses tumor assessment endpoints

  <u>Magnitude</u> and <u>consistency</u> of effect important

  RR + TTP may achieve AA

  TTP <u>alone</u> unlikely to be sufficient

  RR + TTP with hormone Rx – breast cancer may => RA

  CRs with Duration – Hematologic cancers may => RA

  Endpoints and FDA Oncology Drug Approvals

  Johnson, Williams, Pazdur

  Journal of Clinical Oncology 2003; 21:1404-1411

- Disease - Endpoint – Drug - Approval

Tumor assessment endpoints: TTP (10)

- Advantages:
    - Smaller sample size, shorter follow-up
    - Results sooner than a survival endpoint
    - Not affected by subsequent Rx
    - Determined by the entire treated group,
      not just responders (= response duration)
    - May correlate with delay of new or more severe
       symptoms or complications of malignancy

Tumor assessment Endpoints: TTP (11)

- Limitations
  - Most oncology trials unblinded => assessments may be subject to <u>bias</u>
    - Physicians may choose when to assess a particular symptom or a tumor marker
    - Missing measurements of target / non-target lesions
    - Asymmetry of assessment timing
- Need <u>precise</u> <u>prospective</u> definition of TTP
- Consistent supportive evidence also
  - RR, PRO

What about Response - CR or PR (13)

- MBC with hormone Rx: RR + TTP may => RA

- <u>Durable</u> CRs - Hematologic malignancies
  - fewer infections, visits, transfusions – may => RA

- CR assessment must be prospectively defined

- Examples of CR based regular approvals:
  - Cladribine for hairy cell leukemia (CRs > 8mo)
  - Pentostatin for hairy cell leukemia CRs > 24 mo
  - Ifosfamide in combination for 3rd-line therapy of germ cell testicular tumors (CRs > 2 years)
  - IL-2 for renal cell carcinoma / melanoma – cures ?
  - AsO_3 and ATRA for APL – RA: small, single arm

Effectiveness: Oncology Trial Design (1)

How to show effectiveness –

1. Choose appropriate endpoint (with FDA)

- Disease, therapy, and regulatory context

2. Choose appropriate study design (with FDA)

– Phase 2 or phase 3 – many phase 2 results not confirmed in phase 3!

– Usually phase 3 with comparator arm of:

- Standard of care treatment or Placebo
- Prospective, randomized, blinded * comparison
  – Blinding or masking: allocation, investigator, patient, sponsor

Effectiveness: Oncology Trial Design (2)

2. Appropriate study design: How to compare?

- Type of comparison – Superiority vs. Non-inferiority
  - Superiority:
    - versus placebo or add-on design
    - "head to head" with an active control Rx (risky)
  - Non-inferiority – problems IN ONCOLOGY
    - Estimating effect of control treatment
    - Constancy assumption - historical control
    - Retention margin
    - Large sample sizes required

Effectiveness: Oncology Trial Design (3)

3. Appropriate Analysis Plan
- Pre-specified - why?
  - Control error rate (chance of false positive conclusion)
  - Not post-hoc, data-driven
- Estimate the difference to be detected
  - What can your new drug do?
- Size the study – what power do you want to have to demonstrate the <u>primary</u> endpoint
- ITT population for comparison of arms – Why ?

Effectiveness: Oncology Trial Design (4)

– ITT population for comparison of arms – <u>Reduces Bias</u>

- Cannot define the analysis population AFTER data examined

– ITT to see <u>differences</u> between arms

Effectiveness: Oncology Trial Design (5)

4. Statistical meaning

– Null hypothesis = assume no difference between groups

– Stat test – How likely is this difference a result of chance?

– If unlikely due to chance, maybe due to treatment?

– FDA concern - Error of a false positive conclusion (1/20)

- ? Acceptable error rate – pre-specified = Alpha
- two-sided 0.05 - generates our $P < 0.05$

– If there's no difference found? $\equiv$ Equivalence?

- No! –Only means you cannot reject null hypothesis

– Bayesian perspectives

4. Clinical meaning beyond statistical meaning

Oncology Approval Example - Prostate

- 2004 Docetaxel (Taxotere) approval for HRPC

- 2003 - Approved drugs for treatment of HRPC
  - Estramustine   1981

  - Mitoxantrone   1996 *

  - Zoledronic acid   2003 *

  * approvals based on QOL-PRO not on survival

TAX 327

N=1006   Randomize

→ **Mitoxantrone** 12 mg/m^2 Q3 weeks
Prednisone 10 mg q day
up to 10 cycles

→ **Docetaxel** 30 mg/m^2 Q 1 wk
Prednisone 10 mg q day
5 on; 1 off x 6 cycles

→ **Docetaxel** 75 mg/m^2 Q3 weeks
Prednisone 10 mg q day
up to 10 cycles

SWOG 9916

N=770   Randomize

→ **Mitoxantrone** 12 mg/m^2 Q 3 weeks
Prednisone 5 mg bid

→ **Docetaxel** 60 mg/m^2 d 2   Q 3 weeks
Estramustine 280 mg d1-5*
Dexamethasone 20 mg, tid d 1 & 2

*Warfarin and aspirin

M Eisenberger, et al. Proc ASCO, 2004. Abs 4; D Petrylak, et al. Proc ASCO, 2004. abs 3.

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Docetaxel HRPC Trials
Statistical Designs

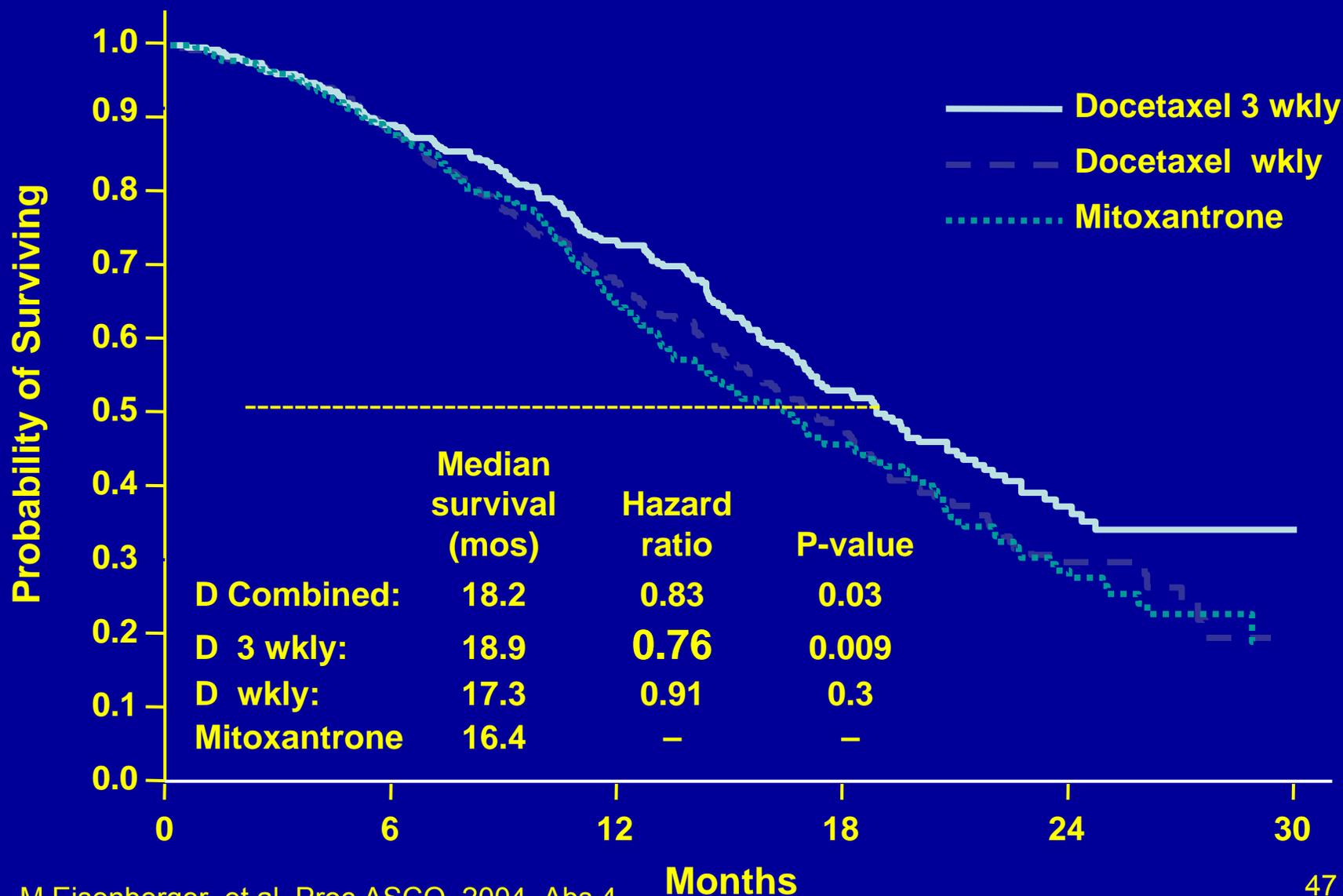## TAX 327

- Power: 90% to detect a 25% reduction in hazard of death (HR=0.75)

- Accrual - 1006 patients

- Two studies available –

- HRPC – hormone-refractory prostate cancer

SWOG 9916

- Power: 80% to detect a 33% reduction in hazard of death (HR=0.67)

- Accrual - 770 patients

not just one

Survival (overall survival) -TAX 327

	Median survival (mos)	Hazard ratio	P-value
D Combined:	18.2	0.83	0.03
D 3 wkly:	18.9	0.76	0.009
D wkly:	17.3	0.91	0.3
Mitoxantrone	16.4	–	–

Legend: Docetaxel 3 wkly; Docetaxel wkly; Mitoxantrone

M Eisenberger, et al. Proc ASCO, 2004. Abs 4.

"Statistically Significant" Results

- Response rates – proportions - Chi square test
- Survival curves – KM - time to event (OS, PFS)
  - Median survival – midpoint on KM curves
    - Why not 75% or 25% ?
    - Why not 1 year or 2 year survival (% alive at __)
  - P value - logrank test comparing the survival distributions (curves)
  - Hazard ratio – Cox model assumptions
  - Confidence intervals (not overlap 1)
- Clinically significant ?

Statistical / Clinical Significance ?

- Best case – have both

- Can you have stat sig. but not clinical - yes
  - Approval likely ? No

- Can you have clinical sig. but not stat - yes
  - Approval likely ? It depends
    - Phase 2 results
    - Statistical design may become inappropriate
    - Safety advantage, Other
    - Clinical benefit is the goal!

FDA Oncology Drug Approval

- Regulatory consequences of Demonstrating Efficacy
- Regular Approval if: clinical benefit endpoint
  – OS, QOL, DFS, and occasional other
- Accelerated Approval if:
    - Benefit over existing therapy – if any; <u>and</u>
    - If a surrogate, then "reasonably likely" to predict, <u>and</u>
    - Must verify clinical benefit later
- If efficacy uncertain – ODAC likely

Evidence for Accelerated Approval

- <u>Substantial evidence</u> from well controlled clinical trials regarding a surrogate endpoint

- NOT: <u>Borderline evidence</u> regarding a clinical benefit endpoint

FDA Review Times

- Assuming a complete application and no substantive amendments submitted during the review

- Priority review completion: – 6 months
  - May fulfill an unmet medical need
  - Substantial improvement
- Standard review completion: – 10 months

Ages of Oncology Drug Approval

- Historical Era
  - Response rates - approval
- Current Era
  - Statistical refinements
  - Clinical Benefit and surrogate endpoints
- Molecular Era

Molecular Era (1)

- **Characterizing both Disease and Patient**
  - Individual Patient characteristics
    - Individualized dosing – PG profile of each person including CYPs, receptors, transporters
  - Individual Tumor characteristics
    - Receptors, transporters
    - Targets
      - Enriched populations with target
      - Study designs to assess role of the target
    - More selective drug effects
- **Individualized therapy**

Molecular Era (2)

- Phenotype to Genotype: will redefine the disease, the patient, and the indication
- Phenotype to Genotype - examples
  - MCL: Cyclin D1 over-expressed <u>or</u> t(11,14) CD20 B cell lymphoma of nodes, spleen and marrow
  - NSCLC:

    "Taressa" indicated for EGFR Exon 20 activating mutation, Bcl-2 overexpressed, cancer in lung or kidney except for CYP2D6 slow metabolizers
- Hope – we no longer have to tell someone –

    there's a chance this therapy may help you – but we can't predict …

Oncology targeted therapies 2005 (3)

Monoclonal Antibodies: <u>approval</u>   <u>target</u>   <u>label ?</u>

	approval	target	label ?
Rituxan (Rituximab) – lymphoma	1997	CD20	yes
Herceptin (Trastuzumab) - breast	1998	p185neu	yes
*Mylotarg (Gemtuzumab) - AML	2000	CD33	yes
*Campath (Alemtuzumab) – CLL	2001	CD52	no
*Erbitux (Cetuximab) – colon	2004	EGFR	yes
Avastin (Bevacizumab) – colon	2004	VEGF	no

Label ? - Is a test for the target included in the label indication? (May not be exactly the same test as the target assay)

(Radio-immunoconjugates- Zevalin (2002) and Bexxar (2003): anti-CD20)

*AA products - Comparative, randomized trials demonstrating increased survival or clinical benefits such as improvement in disease-related symptoms have not yet been conducted.
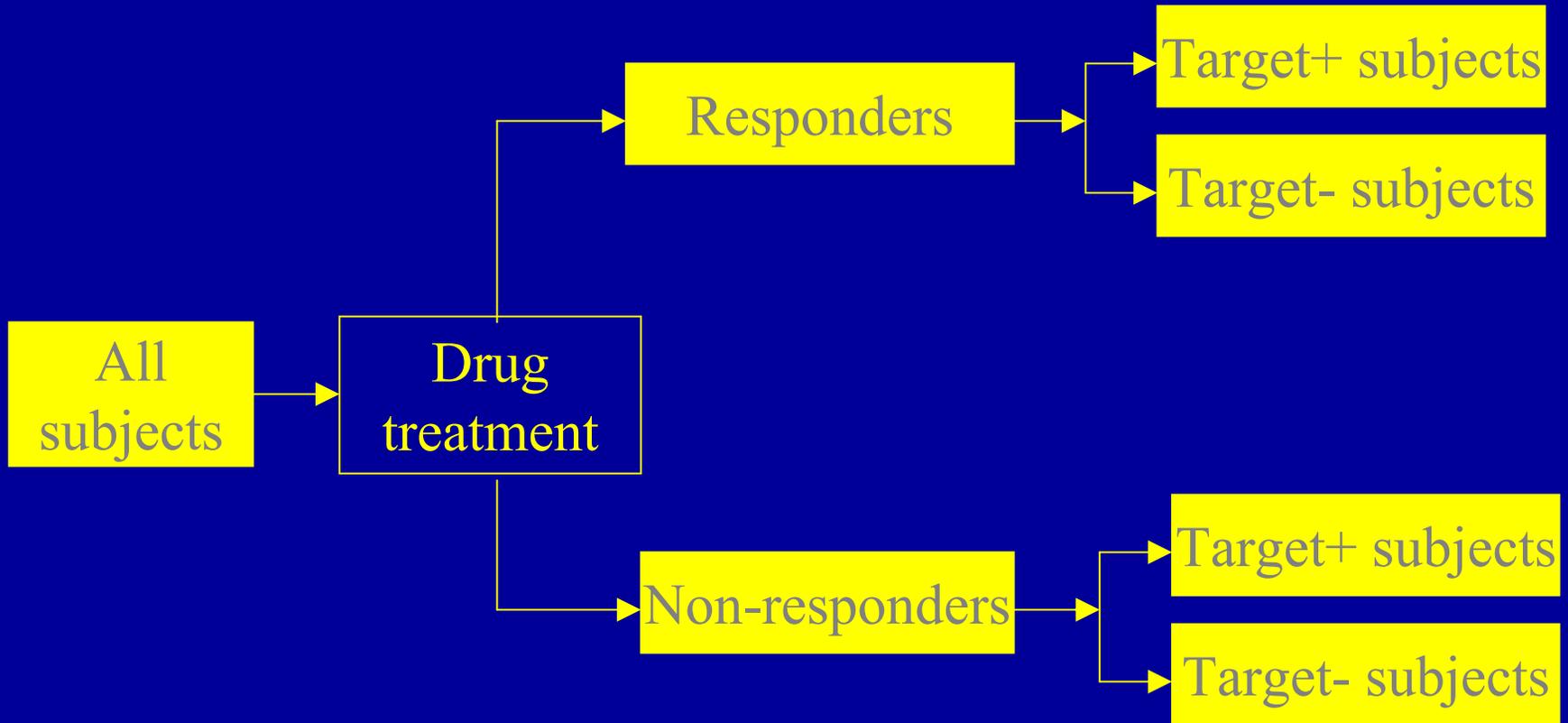
Oncology targeted therapies 2005 (4)

- **<u>Small molecule inhibitors</u>**   <u>approval</u>   <u>target</u>   <u>label ?</u>
  - **Nolvadex (Tamoxifen)**-Breast 1977   ER   yes
  - **Vesanoid (ATRA)** ----- APL   1995   RARα   yes
  - **Gleevec (Imatinib)** ---- CML 2001   bcr/abl   yes
  - ***Gleevec (Imatinib) --** GIST 2002   c-kit   yes
  - ***Iressa   (Gefitinib)** ----- Lung   2003   EGFR?   no
  - **Tarceva (Erlotinib)** ---- Lung 2004   EGFR?   no

Label ? – Is a test for the target included in the label indication?

*AA -comparative, randomized trials demonstrating increased survival or clinical benefits such as improvement in disease-related symptoms have not yet been conducted – AA

Usual target study plan - Retrospective

Problem: retrospective and subgroup analysis- Imbalances

Prospective, Stratified:
assess effect in Target POS and NEG patients

For target assay utility where predictive value unknown or well below 100%
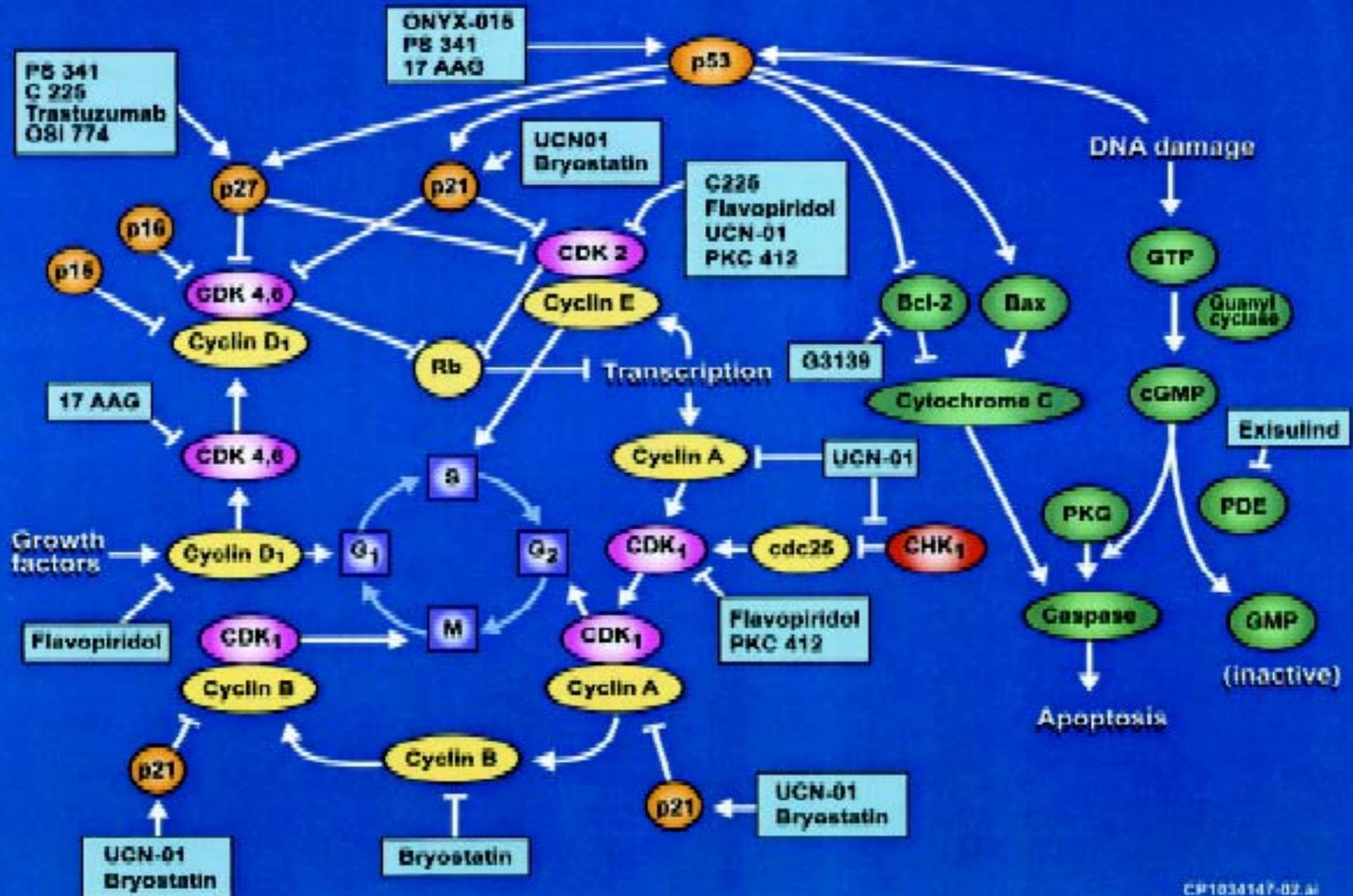– focus is on the target

® = randomization

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Targeted Therapy - Problems

- Which target(s) is the target?

  Herceptin target-gene amplification not protein "expression"

- Can't measure the target – EGFR

- Can't correlate target inhib. with outcome
  - Wrong target for the disease state
  - Target may not be in the disease pathway
  - Variable "expression" "over-expression"
  - Target present but non-functional or variable $f(x)$

- Can't validate target
  - "Inconclusive" study design

Cell Cycle Regulatory Pathways

FDA Oncology Drug Approval

- Appropriate Endpoint

- Appropriate Design

- Appropriate Conduct (FDA will verify data)

- Appropriate Analysis

- Demonstrate Efficacy and Safety (Benefit/Risk assessment)

=> Marketing Approval

Why Bad Things (non-approval) can happen to Good Drugs

"Tortured Data Will Eventually Confess"

Some Examples of Clinical Trial Conduct "problems"

- Inadequate or no controls
- Missing or unclear selection/eligibility criteria
- Small sample size - underpowered
- Randomization process concerns
- Lack of objective outcome assessment
- Improper handling of dropouts
- Inadequate adjustment for prognostic factors
- Improper or misleading tables and graphs

"Complementary and Alternative Statistics"

- ## Some improper statistical methods
  - Disregard of multiple comparisons
  - Improper (selective) censoring, exclusions
  - Post-hoc hypothesis selection (data-dredging) usually on a subgroup analysis not pre-specified
  - Claiming subgroup results when the overall study fails

FDA Website for Endpoints
www.fda.gov/cder/drug/cancer_endpoints/default.htm

FDA Guidance on Effectiveness
www.fda.gov/cder/guidance/index.htm

Under "clinical/medical"

"Providing Clinical evidence of Effectiveness…"

FDA-NIH-NLM registry of Clinical trials
http://clinicaltrials.gov/

Notes:
Basis for New Drug Approval - NDA

- Demonstration of efficacy with acceptable safety in adequate and well-controlled studies   CFR 314 - NDA Regs
- Ability to generate product labeling that
  - Defines an appropriate patient population for treatment with the drug
  - Provides adequate information to enable safe and effective use – prescribing of the drug
- Analogous rules for Biologics - BLA

notes

- ODAC 1977:
  - Approval to be based on survival or, possibly, improved quality of life
- Supreme Court 1979: US vs. Rutherford (Laetrile)
  - to be <u>effective</u>, a cancer drug must either improve survival, improve the quality of life, or relieve pain
- ODAC March 24, 1983:
  - Reaffirmed above, and added "objective tumor response could also be used if a positive correlation between tumor response and: survival, QOL, or relief of pain could be shown."
- ODAC June 28, 1985:
  - Prolonged disease-free survival is an important goal of adjuvant studies and is sufficient for approval of a drug for adjuvant therapy of breast cancer

Notes

- FDA Moderniz. Act 1997: For unmet medical need
  - FDAMA – 312 subpart E
  - Fast track – process for meeting with FDA
  - Priority review – 6 month NDA review time frame for products addressing unmet medical need
  - Endorsed possible <u>one</u> high quality study

- SPA – clinical protocols for phase 3 studies forming primary basis for efficacy for NDA; 45 d.

FDAMA 1997 – one study for efficacy

- 1998 FDA Guidance:
Characteristics of a single study to support effectiveness (with independent substantiation from related study data):

a. Large, multicenter study

  no single site or investigator disproportionately responsible for result

b. Consistency across study subsets

  consistency across key subsets, i.e. severity of disease, stage, age

c. Multiple studies within the study –

  pairwise comparisons within the study

d. Multiple endpoints involving different events

  somewhat unrelated endpts i.e. MI and death

e. Statistically very persuasive –

  very low p values   (not 0.045!)

U.S. Legal Process

- <u>Regulations</u>: CFRs
  - Interpretations of laws
  - by the Executive Branch Departments
  - FDA Regs: Full power of laws when adopted

- <u>Guidance</u>: Issued by individual agencies (FDA or CDER) to reflect current thinking, not binding.

General NDA Review Procedure for a New Drug

- Separate reviews by disciplines
  - stat, med, pharm-tox, Biopharm, CMC
- All primary data reviewed
- Analysis of Benefit versus Risk in the context of the disease process.
- Applications may be discussed before an advisory committee (ODAC) at an open public meeting