Harmonizing Research Goals with Meeting Clinical Needs:

Patient perspectives on clinical trial design

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The views expressed are the results of independent work and do not necessarily represent the views of organizations to which the author is associated, or all patients with cancer.

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1) Good morning. I'd like to start by talking briefly about the role of advocates. Advocate groups are people closely touched by a disease, such as cancer … We represent those who suffer the disorder and face the limitations of treatments … We interact with the patient community in order to discover and understand needs. We also communicate about the human costs, and patient concerns, … trying to keep the urgency alive, which is many times lost when you look at the disease in the abstract.

In memory of

Rick Stimmel, Denise Stafford, and Dan Stevens

Rick Stimmel

just 50 years old, caretaker for his elderly mother, died from severe sepsis, a complication of the toxic side effects of chemotherapy

Dx: 7/00; Deceased: 2/05

Denise Stafford

Just 51 years old
Dx: 10/03;
Deceased: 3/06
6 R-CHOP + 2 R-CVP - PR

9/04 4 x R - PR

10/04 RICE x 3

1/05 ESHAP x 2

6/05 Fludara + R + Doxil

7/05 2nd treatment - continued improvement

8/05 3rd treatment - 3rd time the charm?

Dan Stephens

just 44 years old, leaves behind a wife and infant son. He passed away when aggressive treatment failed to stop high-risk disease.

Dx: 12/02; Deceased: 3/05

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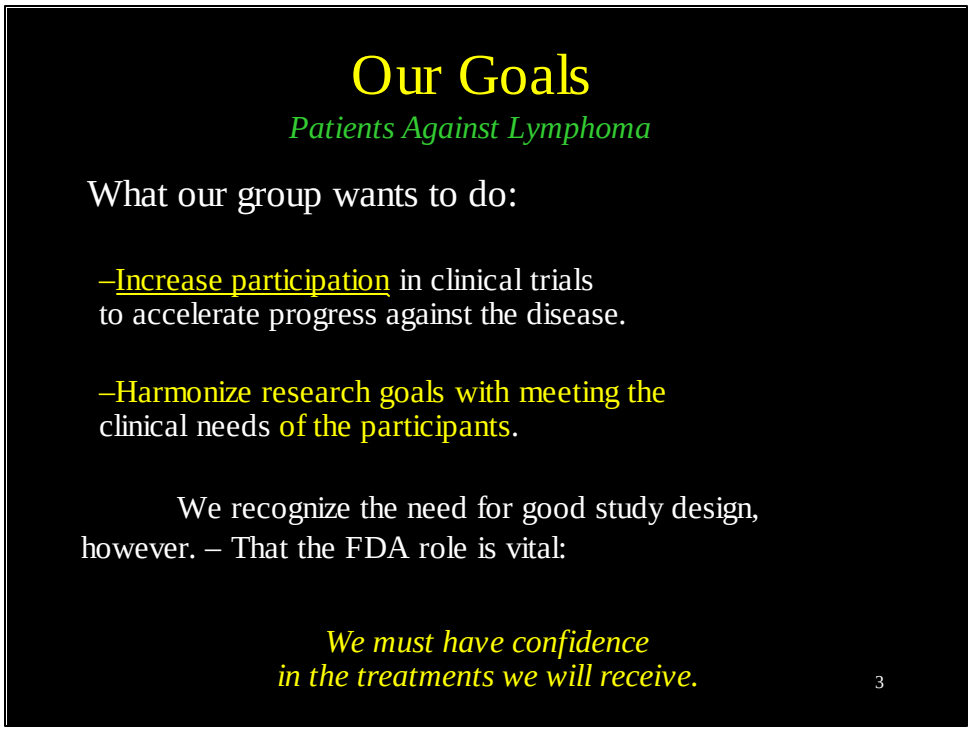
2) Our group is dedicating this talk to the memory of Rick Stimmel, Denise Stafford, and Dan Stephens …

… lymphoma patients, and valued colleagues, who recently passed away.

Each provided generous support to other patients.

Their unexpected short survival saddens us, …

Their passing is also a sobering reminder about the <u>danger</u> we face.

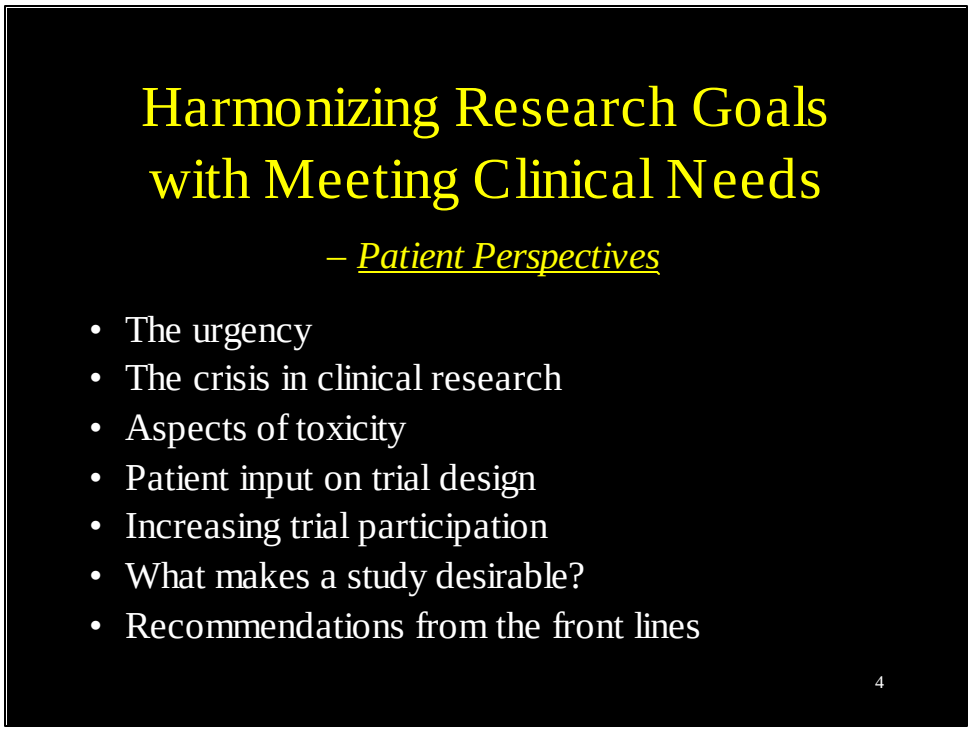


3) Our group recognizes that clinical studies are essential to making progress,
and that they must be designed in ways that produce reliable information, …

so that we can have confidence in the treatments we receive.

… but patients should not be asked to sacrifice themselves
for the "greater good." Study participation should be a reasonable
treatment decision … Good science and good medicine.

We know that there is often a tension between these ends.
One goal does not always complement the other.



4) Here's an outline of the talk:

I'll provide some background about the crisis in clinical research, and the urgent need to make progress. I'll describe aspects of drug toxicity, from the patient's perspective. I'll make the case for involving patient consultants in the design phase of clinical trials.

And provide some data about trial participation … what patients are looking for in clinical trials, and what they tend to avoid. Finally, I'll share a few proposals from the patient community, specific to lymphoma.

Urgency: every family

Cancer will affect virtually **every family**

Lifetime risk:

1 in 2 men

1 in 3 women *

* *SEER 2002*

560,000 new cases this year

Reply to patients who severely mistrust the system: "*Regulators, doctors, drug developers, and scientists also get cancer … and their children, parents, spouses, and loved ones. We are in this together. There is no conspiracy.*" ~ Len Rosen

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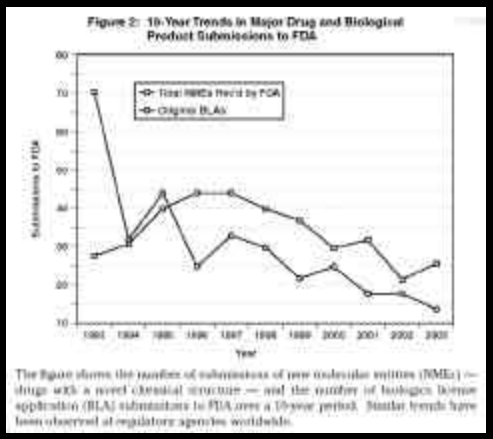
5) The data tells us that cancer is everyone's problem.

Difficult as it may be to realize, … or want to: 1 in 2 men will get a serious cancer, and 1 in 3 women.

That is to say: we are all future patients or caregivers – and that it's in everyone's best interest to make clinical research as efficient as it can be.

Crisis in Clinical Research: the promise of *innovation*; the evidence of *stagnation*

"If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical revolution may not deliver on its promise of better health."



1. *Innovation / Stagnation – Challenge and Opportunity on the Critical Path to New Medical Products ~ FDA (2004)*

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6) This slide is about the crisis in clinical research … as described in the FDA publication, "The Critical Path"

The chart showing the number of new applications submitted to FDA has declined significantly despite the promise of innovation – the exponential increase in our knowledge about cancers. It's a frightening report, I think, … for cancer patients … present, and future.

Crisis: Competition for Patients

Factors:

- Increasing **number of clinical trials**
- Need to recruit mainly **untreated patients**?
- The need to enroll **large numbers of patients**? to prove benefit for indolent lymphomas?

"it was the best of times, it was the worst of times"

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7) There's irony in this aspect of the clinical research crisis: that is, that the sheer number of new agents is an obstacle to progress, as each study must compete for patients from the same small pool - less than 5% of the patient population. Today there are about 680 studies for lymphoma listed on ClinicalTrials.gov, but no easy way to evaluate them all.

For cancer vaccines there could be a need to recruit patients who are not in need of immediate treatment. This group will be more cautious and selective. And for indolent cancers, we may need to enroll larger numbers of patients in order to get reliable answers.

Crisis: Preclinical Models

What's Wrong with Our Cancer Models?

"Response rates among unselected cancer patients in phase I studies are seldom more than 10%." [1]

"Nine of ten attempts to bring a cancer drug to market fail." [1]

1. What's wrong with our cancer models? Alexander Kamb, Norvantis Inst. For Bio. Med.

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8) Here's another aspect of the crisis in clinical research: The inability of preclinical cancer models to predict toxicity or efficacy … leading to a high failure rate.

Given the low response rates in phase I studies shown here, … and that one in ten attempts to bring a cancer drug to market succeed, … we might conclude that low enrollment in clinical trials indicates good judgment by patients and by their treating physicians.

Aspects of toxicity …

- Can contribute to death
  - Bone marrow toxicity and subsequent infection is a leading cause of death in lymphoma patients. [1,2]
- Can limit treatment choices

1. *Ten-year survey of incidence of infection as a cause of death in hematologic malignancies: study of 90 autopsied cases. Acta Haematol. 1995;93(1):25-30. PMID: 7725846*

2. *Causes of death in children diagnosed with non-Hodgkin's lymphoma between 1974 and 1985. Arch Dis Child. 1992 Nov;67(11):1378-83. PMID: 1471892 | Related articles*

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9) Starting here, I'll cover important aspects of treatment toxicity, again,
from the patient perspective, … which could help to inform or guide the direction of clinical research and trial design.

…

There are two aspects of toxicity that are well-known to cancer patients: that side effects can contribute to your death; and also narrow your range of future treatment options.

In fact, for lymphomas, bone marrow toxicity, leading to infection, might be the leading cause of death … and for indolent lymphomas it seems that we don't run out of options so much, as the ability to tolerate them.

Toxicity leading to "*a narrowing range of choices*" …

" In a sense Billy's no longer at the helm, the conditions are, and all he can do is react.

If danger can be seen in terms of a ***narrowing range of choices****, Billy Tyne's choices have just ratcheted down a notch."*

~ The Perfect Storm.

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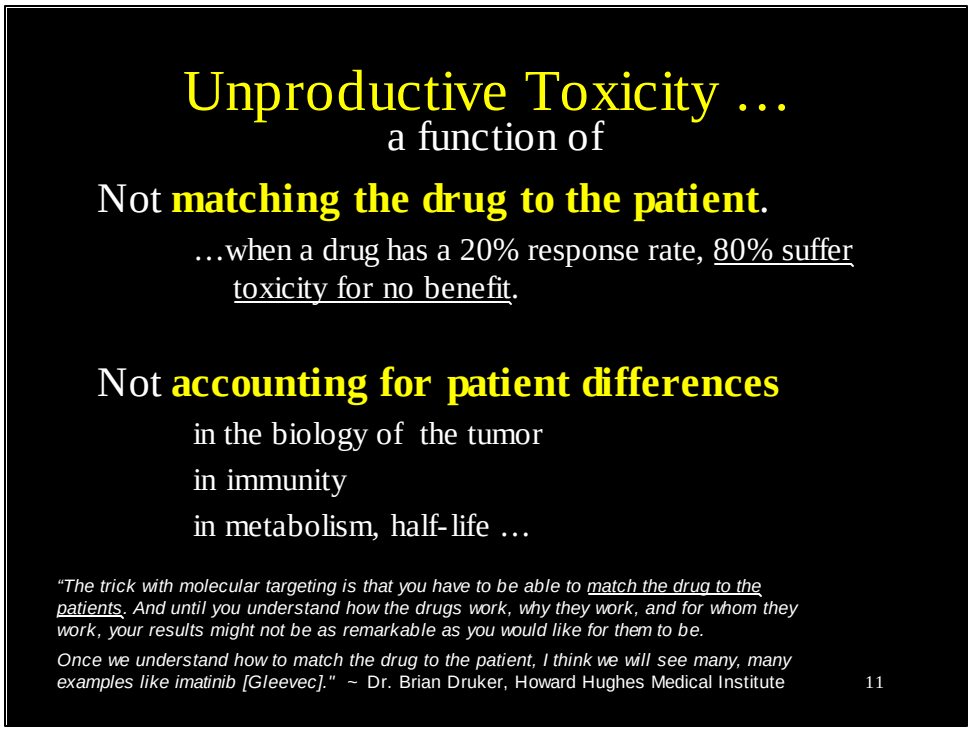
10) In the "Perfect Storm" the narrator defines DANGER as a narrowing range of choices. In the clinic, patients and physicians call it "burning bridges" When designing clinical trials investigators should be mindful of this aspect of a study protocol, for it can have a significant impact on enrollment.



11) Obviously, toxicity is bad, but what can be worse than unproductive toxicity –
getting only the side effects of the drug and no benefit … and often significant harm?

Unfortunately, for some cancers this risk is common, and considered better than having no chance at all. It appears that unproductive toxicity is a function of not accounting for patient differences:

- **in the biology of the tumor,**
- **or in immunity,**
- **or in how the drug is metabolized.**

It was this quote from Dr. Druker, about matching drugs to patients that got many advocates thinking about the necessity for a new approach to clinical research.

Patient differences and unpredictable toxicity

- Vincristine pharmacokinetics: … *"although significantly influenced by diagnosis, largely remains* ***unpredictable****."* [1]

- *"Clearance can vary from* ***23 to 85 hrs*** *for adults; and from* ***10 to 40 hrs*** *in children."* [2]

1. **Vincristine pharmacokinetics after repetitive dosing in children.; Gidding CE, Meeuwsen-de Boer GJ, Koopmans P, Uges DR, Kamps WA, de Graaf SS.** PMID Cancer Chemother Pharmacol. 1999;44(3):203-9.
2. **bccancer.bc.ca**

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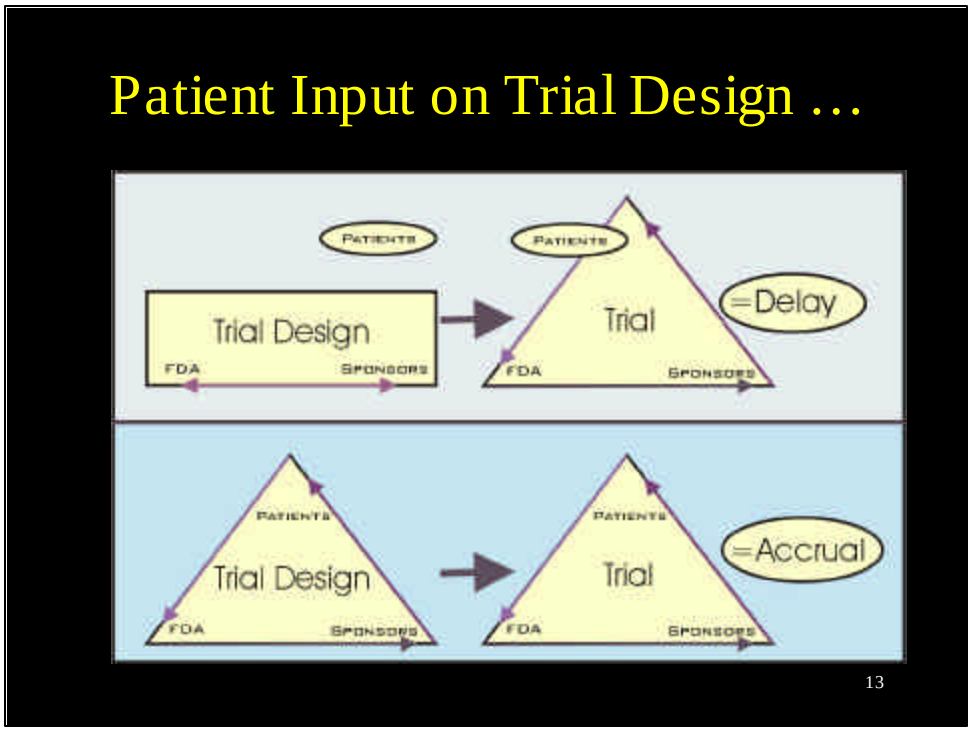
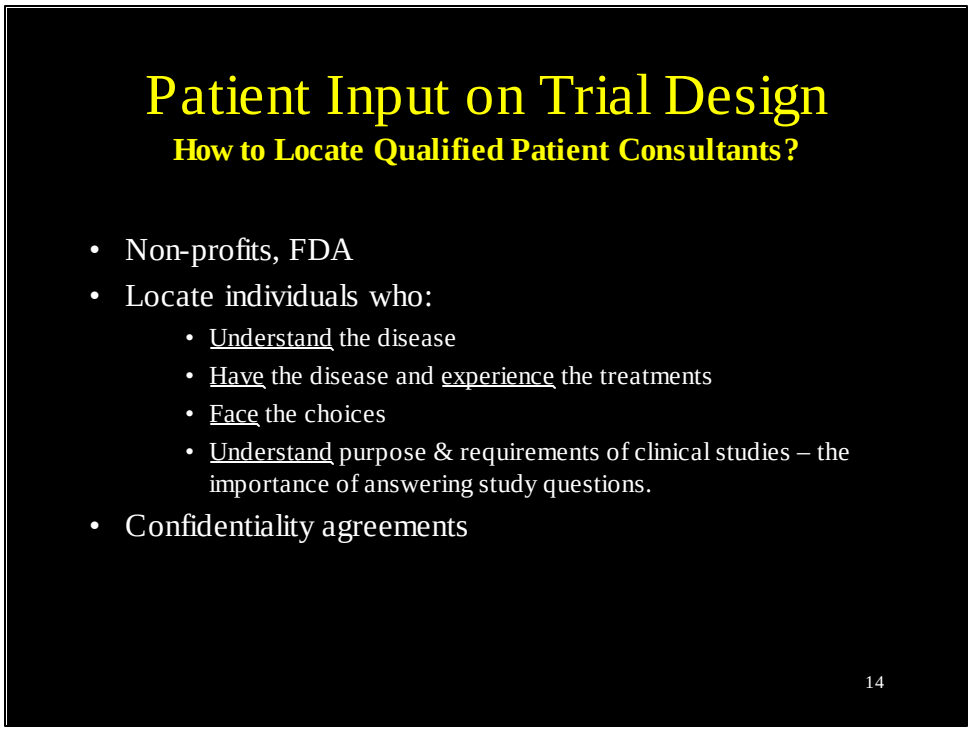
12) Here is yet another aspect of toxicity: that it can be unpredictable, which also relates to patient differences. I know that some patients treated for lymphoma can suffer painful and irreversible neuropathy, because of how slowly
their body clears Vincristine. Note that the clearance of this drug can vary significantly in children and adults.



13) This slide simply illustrates the logic of involving patient consultants
<u>early</u> in the design of clinical trials. We think that <u>including the primary stakeholders</u> is bound to result in fewer surprises and faster accrual.



14) Probably the best way to locate qualified patient consultants is to contact one of the many non-profit organizations. To safeguard intellectual property, you can require that consultants sign confidentiality agreements. Note: The FDA is beginning to provide patient consultants to participate in End of Phase II meetings.

We need each other

- **Importance of timely participation** – delays are costly to sponsors and to patients.

If patients fail to sign on in adequate numbers …

… the **assessment of the therapy** will not be made no matter how well the study is designed from the point of view of regulators and scientists.

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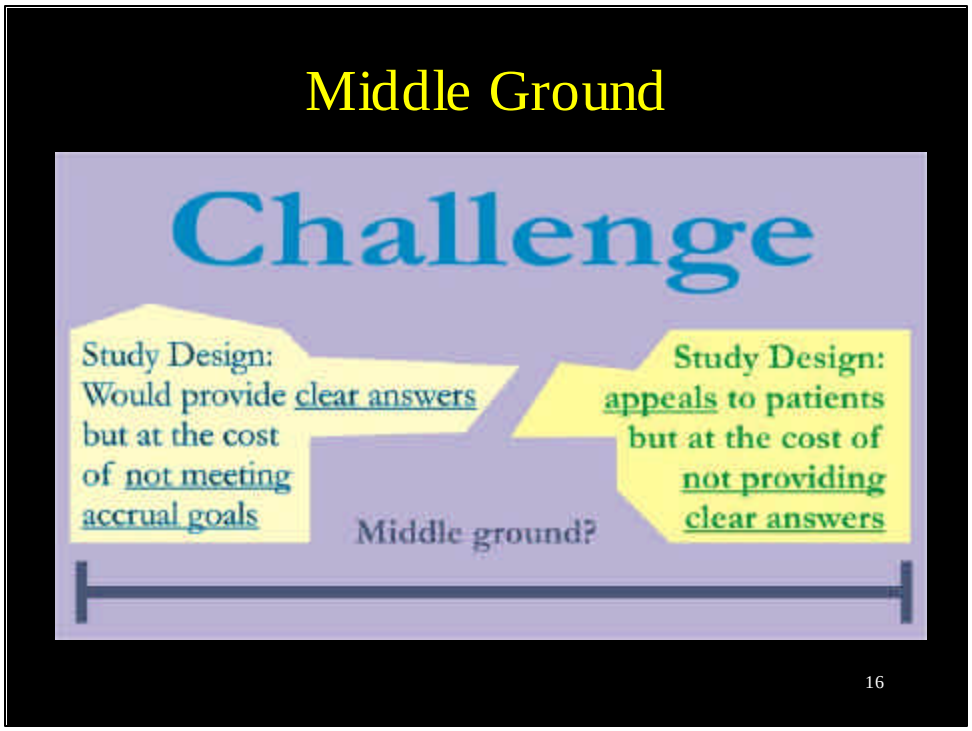
15) I think it's evident that we need each other, and that we need to communicate better. Delays in trial enrollment are costly to sponsors, and to patients. Indeed, the urgency requires that the discovery and evaluation system become as efficient as it can be.

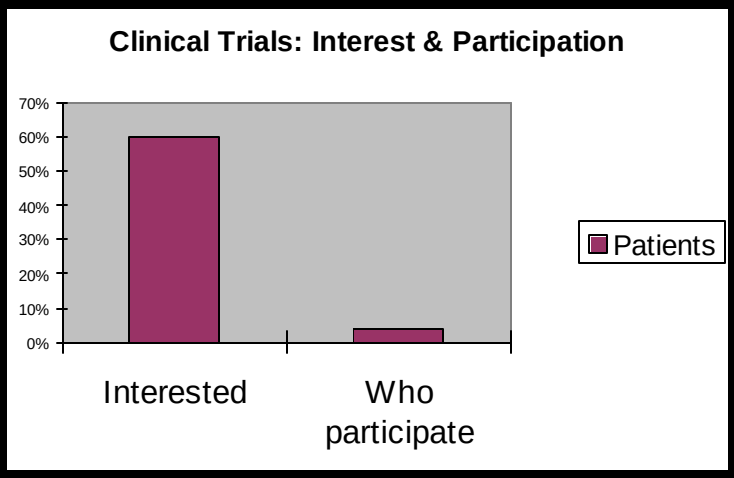


16) This slide illustrates the two ends of the spectrum of study design. Neither is acceptable, of course. The challenge is to get to a middle ground: a study design that provides clear answers in a timely manner.
Ideally, study protocols should compare favorably to available treatments, standard and investigational, for a given setting ...

In randomized trials, there should be genuine uncertainty about which arm of the study is superior. When we can't meet this condition, crossover should be provided.

We might ask: Is failing to enroll patients in well-publicized studies a marker for unethical design?

Patients Motivated, but Hesitant



* CancerConsultants.com™ - Internet Interest in trials.

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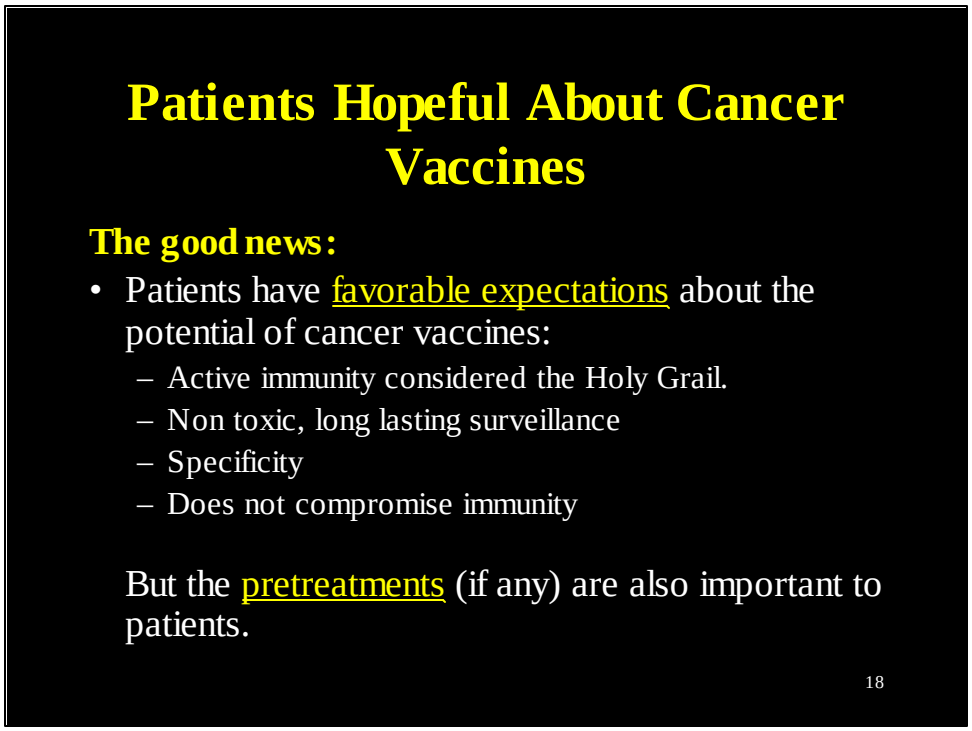
17) Here we see the results of a survey conducted by CancerConsultants.com. It found that 60% of patients are actively seeking access to clinical trials, … but that less than 5% participate. This suggests that the problem with accrual is not necessarily the attitudes of patients



18) Many patients have favorable expectations about the potential of cancer vaccines. And this expectation should translate to faster enrollment for studies of this type. And I believe experience supports this view. However, the pretreatments (if any) are key to how desirable any protocol will be.

Participation: How to Increase Patient Interest?

Ensure that the patient community learns about:

- The disease: true risks, and variable natural history
- Standard treatments, limitations[1] and benefits
- How studies monitor patients for safety
- Rationales for studies in plain language
- Alternative medicine? …caveats and poor quality of data
- Emerging therapies, potential advantages …

1. Each Subsequent Therapy Results in Diminishing Response Rate and Duration of Response in Low Grade or Transformed Low Grade Non-Hodgkin's Lymphoma. - ASCO 2001 Abstract 1165

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19) Denial is a natural tenancy that's common among cancer patients, and it works against trial participation. To increase interest in clinical trials we need to inform the patient community about: the true risks of the disease; its natural history; the limitations of standard therapies; how studies carefully monitor patients for safety;

We might provide clear rationales: Why the sponsor believes the study protocol
is a reasonable treatment decision … relative to other options … such as the favorable toxicity profile of cancer vaccines. Finally, you should know that many patients with indolent lymphomas are focused on alternative medicine, despite the lack of supportive data.

Participation: The Treating Physician

- Encourage "trial talk:"
  - **Patients** to routinely, consult physicians & *outside experts*
  - **Physicians** to routinely discuss trials with patients
- Provide physicians with:
  - Literature on investigational agents
  - Clinical trials for various settings.
  - Incentives, or communicate expectations, to:
    - Refer at least some patients to *studies*
    - Encourage consults with *outside experts*.

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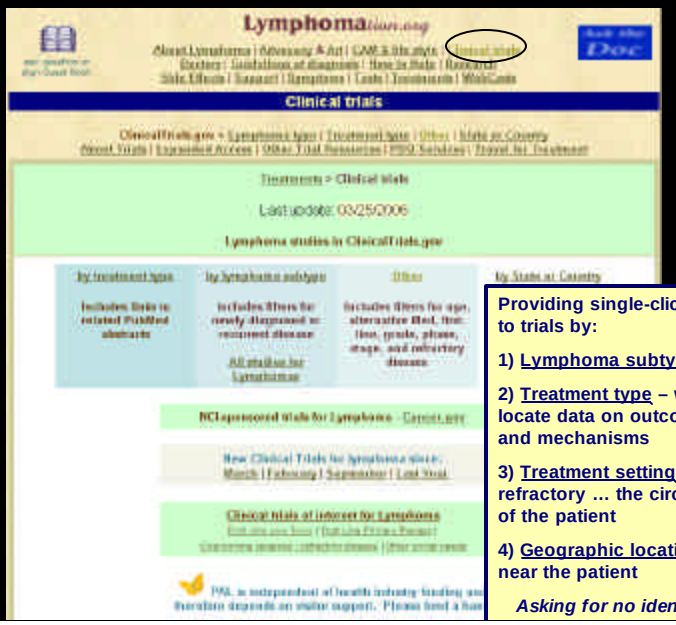
20) We need to make the discussion of clinical trials routine when patients talk to their doctors, or to outside experts, particularly when the cancer is not curable with standard approaches.

And we need to provide treating physicians with up-to-date information about investigational agents in specific clinical settings (front line, watchful waiting, relapsed, first primary, etc). Today, patients and physicians can use Clinicaltrials.gov to locate trials, but not easily by treatment setting.

Participation: Locating Studies for lymphoma

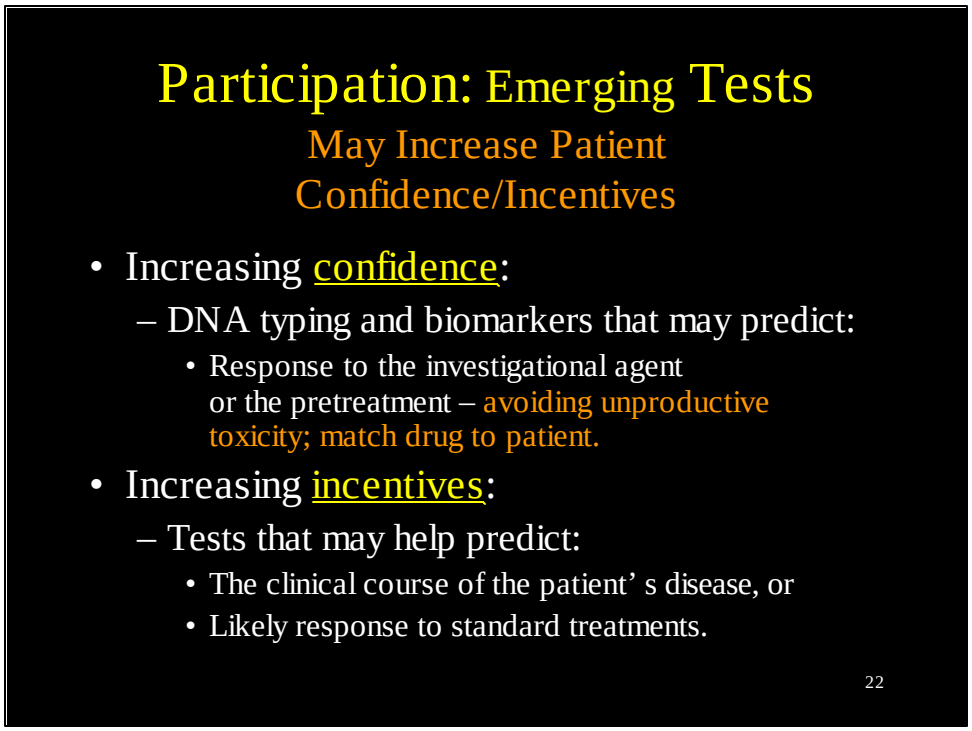


21) Obviously, you can't consider what you don't know exists. From our website, patients and physicians can easily locate lymphoma-specific studies in ClinicalTrials.gov by clicking pre-built queries. Here's a screen shot of our locator service.

From here, you can find studies by

treatment type,
lymphoma subtype,
first line studies
new studies, and much more.

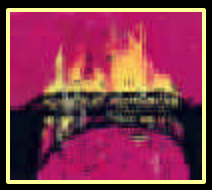
Importantly, we ask for no identifying information … and we provide tools to look up reports on outcomes, safety, and mechanisms of new agents.



22) High quality information is the basis for good decision-making. To make progress we need to better characterize the disease, which provides the context and explanation of the outcomes … we need better tests that inform about prognosis, and predict individual responses to therapies. So that we can stratify patients based on risk of disease; so that we can avoid unproductive toxicities, and better match treatments to patients … so that we can replace trial and error with rationally selected protocols in clinical research and practice.

Participation: Features of Desirable Studies

- Potential to:
  - **Cure** – particularly if risk is equivalent to standard approaches when standard therapies are not curative.
  - Increase duration of response, without adding toxicity – without precluding future options
  - Stabilize with minimal toxicity
  - Improve quality of life
- And protocols that:
  - **Use least toxic agents first**.
  - Have low risk of **unproductive toxicity**
  - Are unlikely to **burn treatment bridges** . . .



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23) These are some characteristics that patients are looking for in trials. The potential to cure is number one, of course, especially when standard therapies do not, … but the risk must be considered equivalent to standard approaches. As you can see, patients are keen to try new therapies that appear safer than standard ones. And, they don't want to limit future treatment options, and will avoid studies that appear to do so.

Other Barriers to Patient Accrual

- Lack of resources
- Health insurance restrictions
- Confusion about research and medical care, and study procedures … which study? 1
- Excessive or undesirable tests:
  - Bone marrow biopsies
  - Exposure to excessive amounts of imaging radiation
- Disqualifications

(1) Understanding Cancer Patients' Needs, Concerns is Key to Improving Clinical Trial Participation. - UC Davis Cancer Center study

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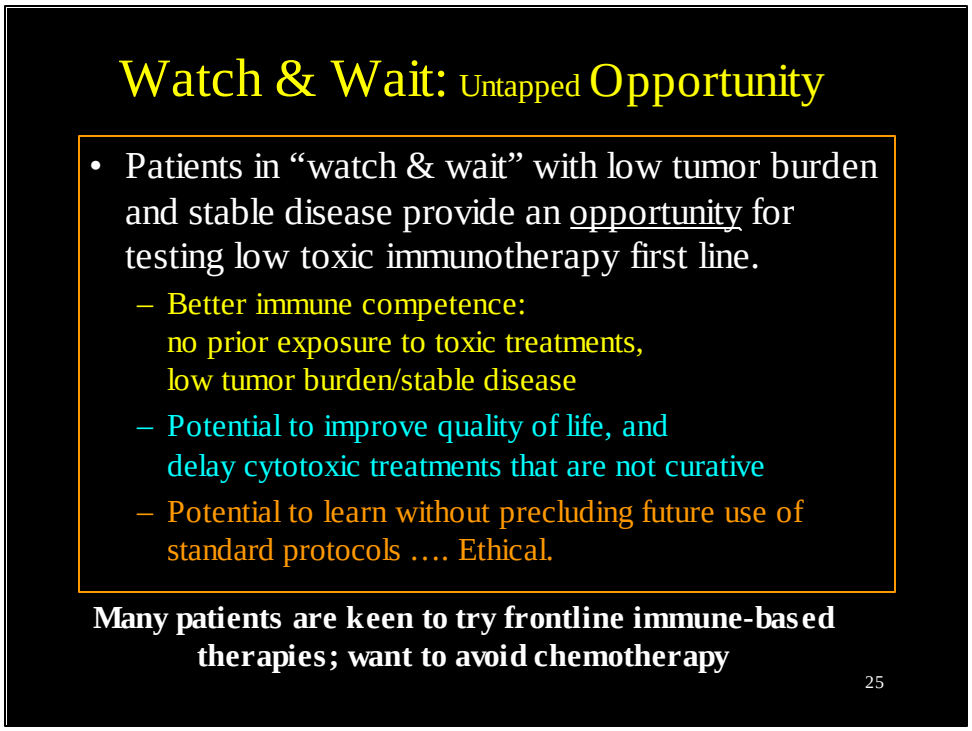
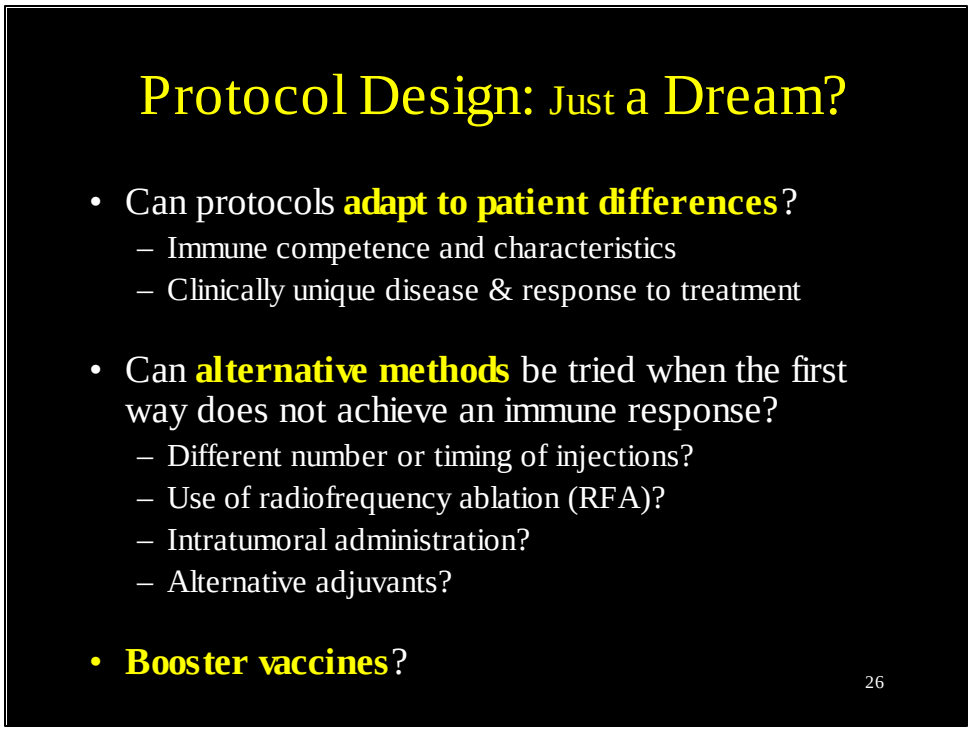
24) This slide shows some well-known barriers to patient enrollment in clinical trials.

Limited patient resources – that can make travel to a study site impossible. Health insurance restrictions , or the belief that these restrictions are present. Confusion about research and medical care, and study procedures. Patient confusion about the goals of research. Excessive or undesirable tests, such as multiple bone marrow biopsies, and frequent CT scans. And expectations that they are likely to be disqualified by one entry criteria or another.



25) Here we list some of the advantages for studying cancer vaccines first line *without* use of chemotherapy. From our perspective a sensible time to get creative is early … and when a response to treatment is not required … and when we may be more likely to benefit from the approach. Importantly, patients will be highly motivated to participate in this type of study. As an example, a pilot first-line vaccine study at Stanford completed enrollment in two weeks.

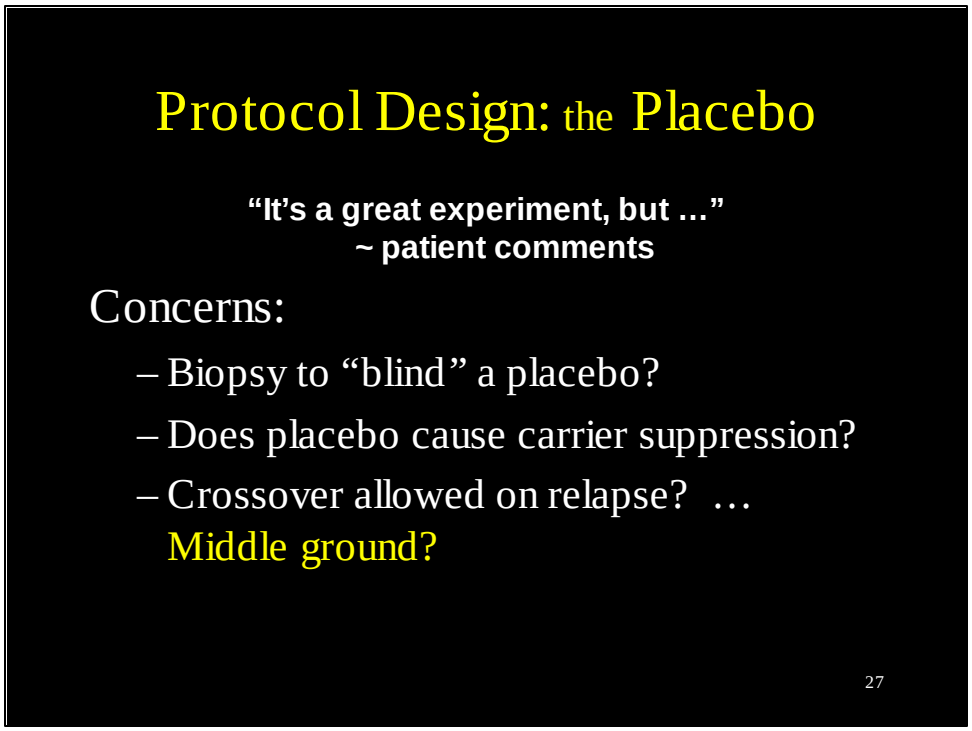
I hope you will find time to comment on our study proposal in a separate handout: To combine molecular profiling research with evaluating first-line use of cancer vaccines.



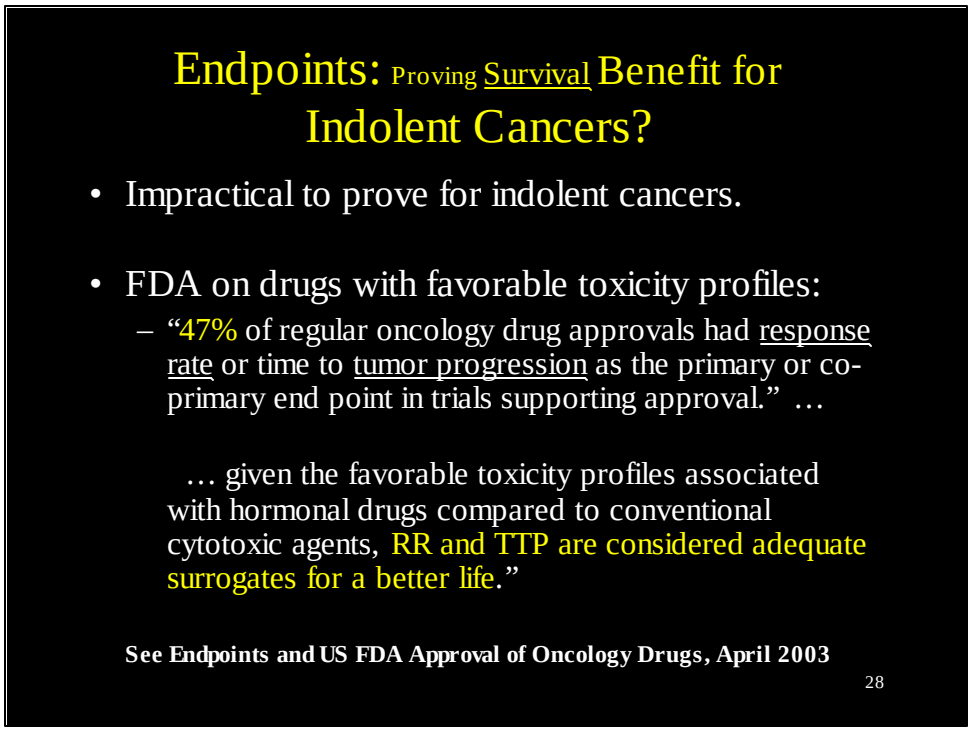
26) Perhaps this is a dream we have, but here goes.

These are questions for investigators: Can study protocols be made more flexible? Can they adapt to patient differences? Can we try alternatives when the first way fails to induce an immune response? Can we try safer localized therapy that might augment or complement immunotherapy, such as RFA?

We understand that these proposals might contribute to the difficulty of regulatory assessments. Perhaps larger studies that rapidly accrue patients can offset these difficulties?



27) Patients have technical and ethical concerns about placebo vaccines. Is the resection of a lymph node an ethical way to blind a study? Can exposing patients to the conjugates in a placebo vaccine preclude them from benefiting from the cancer vaccine in the future, should it win marketing approval? Can the pretreatments do the same? Can crossover provisions be used to relieve patient concerns? From our perspective, placebo vaccines are bound to slow accrual and delay assessments.

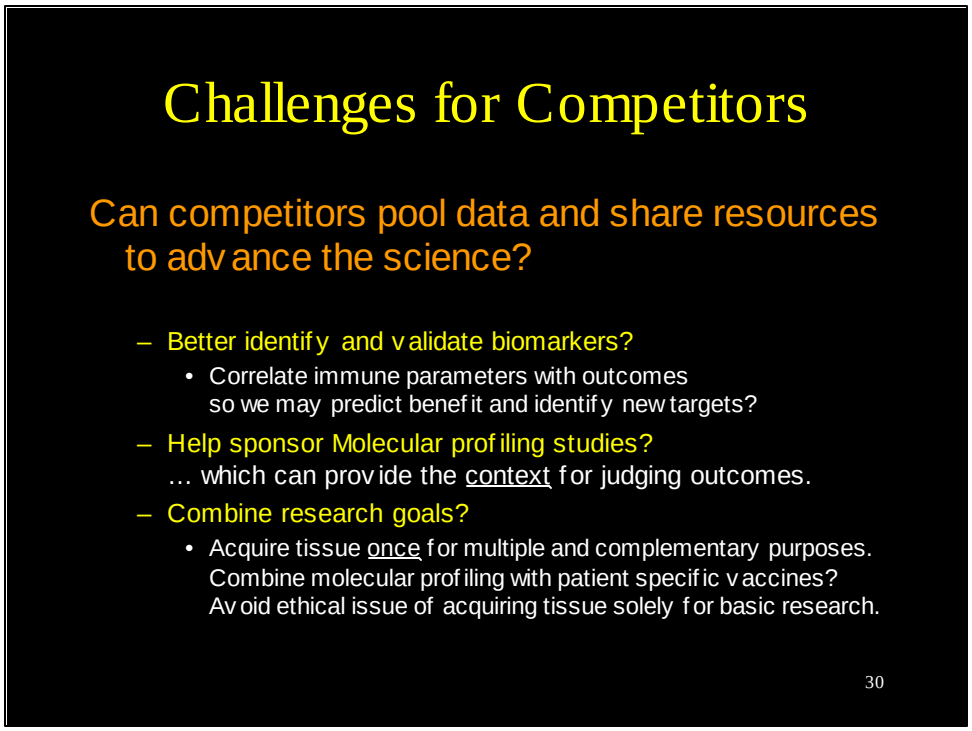


28) For patients with indolent cancers, survival is not an ideal endpoint for proving clinical benefit. Assessments will be confounded by patient access to numerous treatments, including investigational treatments on relapse. The good news is that the FDA seems to agree that drugs having a favorable toxicity profile may win approval by other means, as shown here.

29) We believe that cancer vaccines are good candidates for <u>accelerated approval</u> based on what they potentially do <u>not</u> do:

Preclude the use of subsequent standard treatments; impair immunity, or general health; undermine quality of life.

But, cancer vaccines must be proven to provide clinical benefit as well.



30) Our group is concerned that each individual study will be too small to validate important biomarkers – and that only by pooling the data can we hope to be as efficient as we can be and advance the science. The industry needs to augment competition with cooperative efforts…. and to pool certain kinds of data, and share resources.

DISCUSSION POINTS: Not easy to merge data from different sources

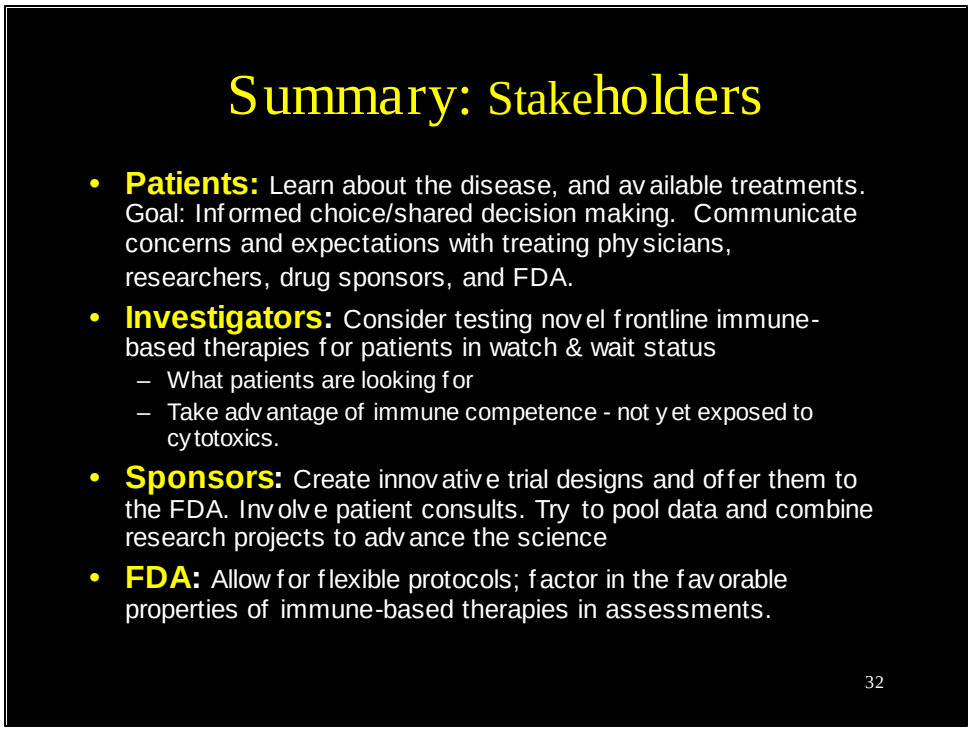
Differences in protocols may lead to information that's not credible to the FDA. Importance of standardization of methods.

31) To summarize:

Include patient consultants in study design, so that you avoid unanticipated obstacles to enrollment. You can contact non-profits to identify qualified consultants. We ask that you work to design studies that are in harmony with patient goals and needs:

Is the study protocol: a reasonable treatment choice? As flexible as it can be?

Does it increase danger … by narrowing the range of future treatment options?



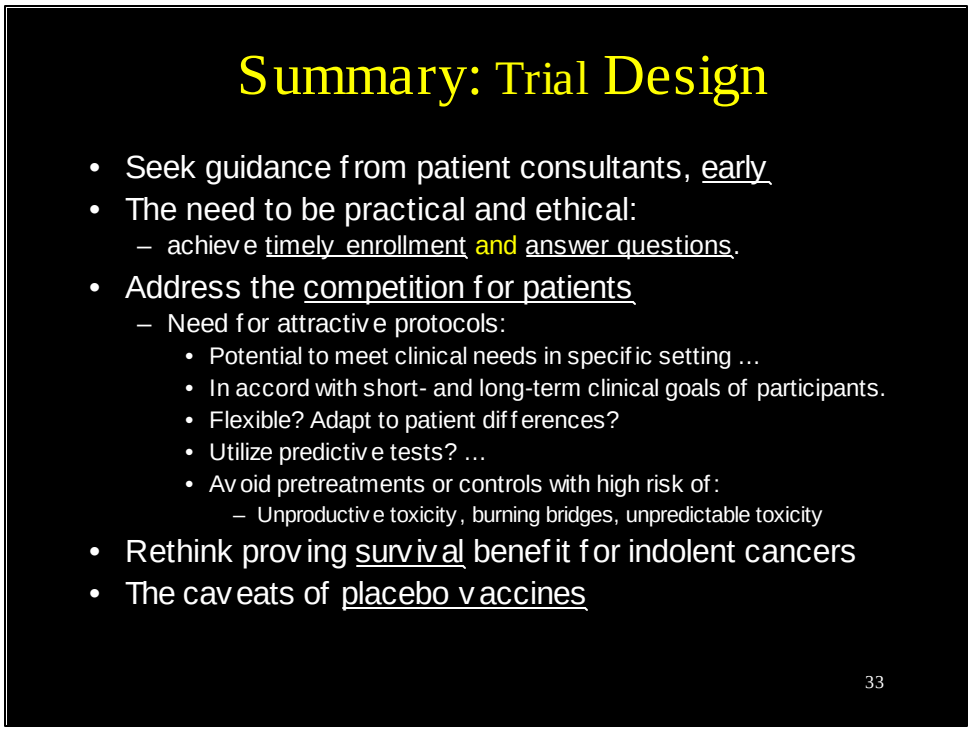
32) Regarding the various stakeholders: We try to inform patients about the natural history of the disease, about the limitations and benefits of standard approaches … about the potential and risks of emerging therapies.

We urge sponsors to create innovative trial designs and offer them to the FDA. We urge sponsors to pool data, share technologies, and standardize methods when possible …

… to advance the science – to compete with lead products, but cooperate where and when you can.

For example, sponsors might pool data that helps identify markers associated with clinical benefit from vaccines, and how tumors might escape or suppress immunity. We will continue to urge the FDA to allow for flexible protocols, and to factor in the favorable properties of immune-based therapies in assessments of benefits and risks.

We propose that sponsors combine research goals with the NCI. For example: Characterize the molecular biology of follicular lymphoma while testing the clinical effects of cancer vaccines.



33) Patient interest is an important starting point for study design. Patients must enroll for the answers to be found. Competition for patients is increasing. Study protocols should compare favorably to other available treatments. There should be genuine uncertainty about which arm of a randomized study is superior – or has the greater potential.

Avoid, when possible, protocols that may burn treatment bridges. Fully consider the caveats of placebos to the participants and the study.

Summary: Patients & Treating Physicians

Patient interests and concerns:

- Minimize risk of unproductive toxicity … (averse to risk)
- Minimize risk of bridge burning
- Interested in targeted therapies that may be less toxic, and matched to the tumor's molecular profile
- Interested in protocols with curative potential … when realistic.
- HIGH interest in immune therapies to manage or consolidate response to standard therapy.

The role of the treating physician:

- Guide patient … best protocols at best time.
- Do what is best for patient; not to advance the science, or to help win marketing approval of individual agents.

Note: Providing incentives and finding better ways to recruit patients will not fix an underlying problem: the appeal of the clinical trial to the patient as a treatment decision.

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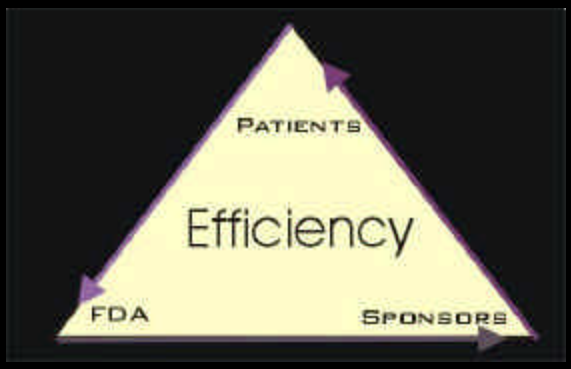
34) Cancer patients will be very careful about treatment decisions. Always. Each patient has one life to experiment with, … and the role of the physician is to do what is best for their patient; it is not to advance the science, or to help win marketing approval of individual agents.

These are my impressions: Therapies with low expected toxicity will enroll patients the fastest.
As demonstrated by the rapid enrollment in a pilot vaccine study at Stanford. Obviously, patients with high-risk disease need potentially curative protocols that sequence and combine complementary therapies.
Patients seeking to manage low-risk disease will not be interested in trying new single agents, unless they are targeted, immune-based, and expected to be low toxic.
Providing incentives to physicians and seeking better ways to recruit patients – remedies often proposed by different parties – will not fix an underlying problem: the appeal of the clinical trial to the patient as a treatment decision.

Think like a patient.



Consult patients!

The end.

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35) Thank you for listening. It's appreciated …

as is the important work you do on our behalf.