Lessons about Options from a Pharmaceutical R&D Project

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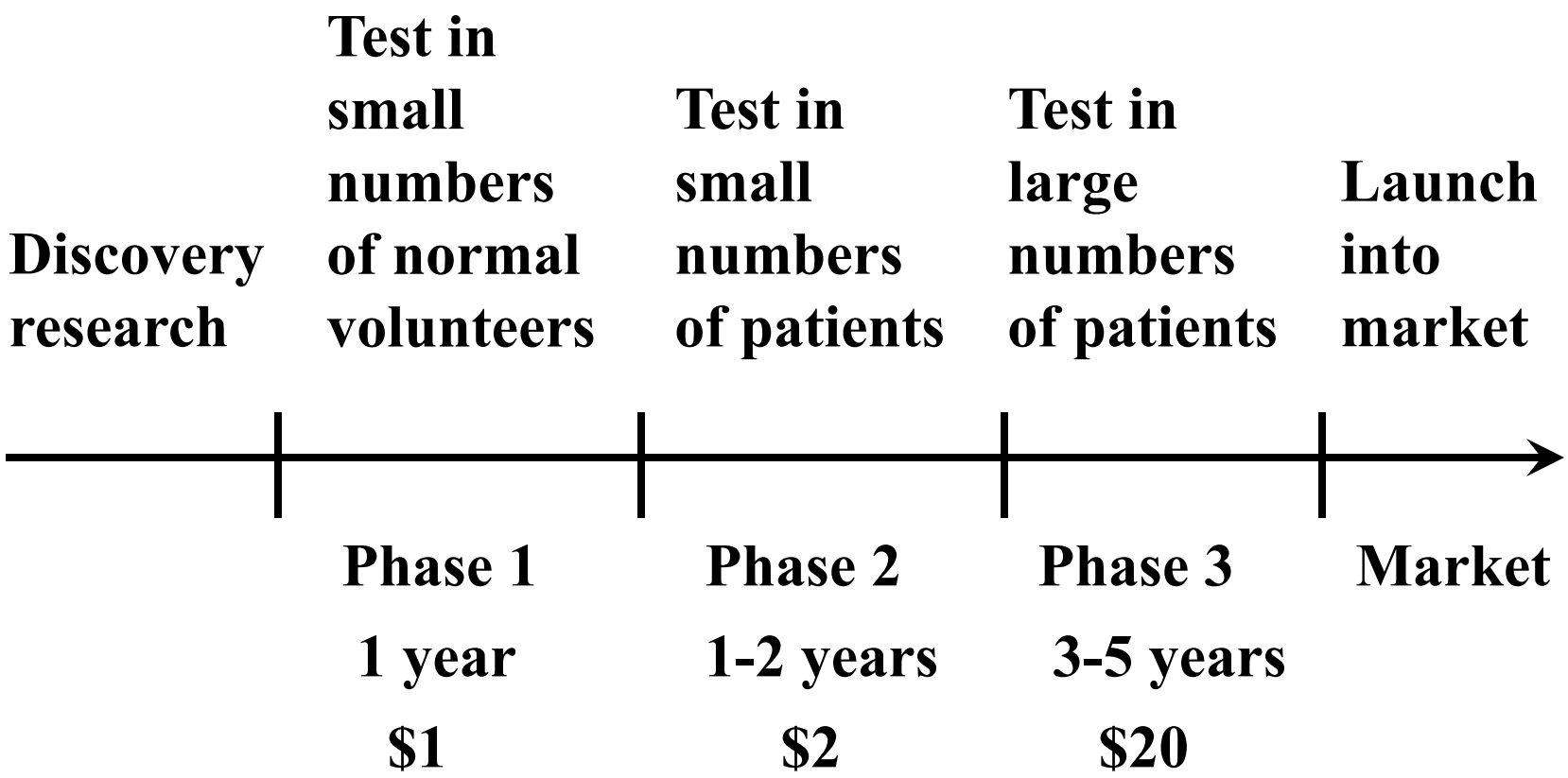
Our agenda

- The drug development process.
- Representing that process as a sequence of options.
- An example of an R&D project.
- Insights arising from consideration of the options.

Options and decisions

- **A decision is defined as the allocation of resources.**
- **An option is a decision made after the revelation of information. Purchasing an option is also a decision.**
- **To be meaningful, our conversations about options must be focussed on decisions.**

Drug Development



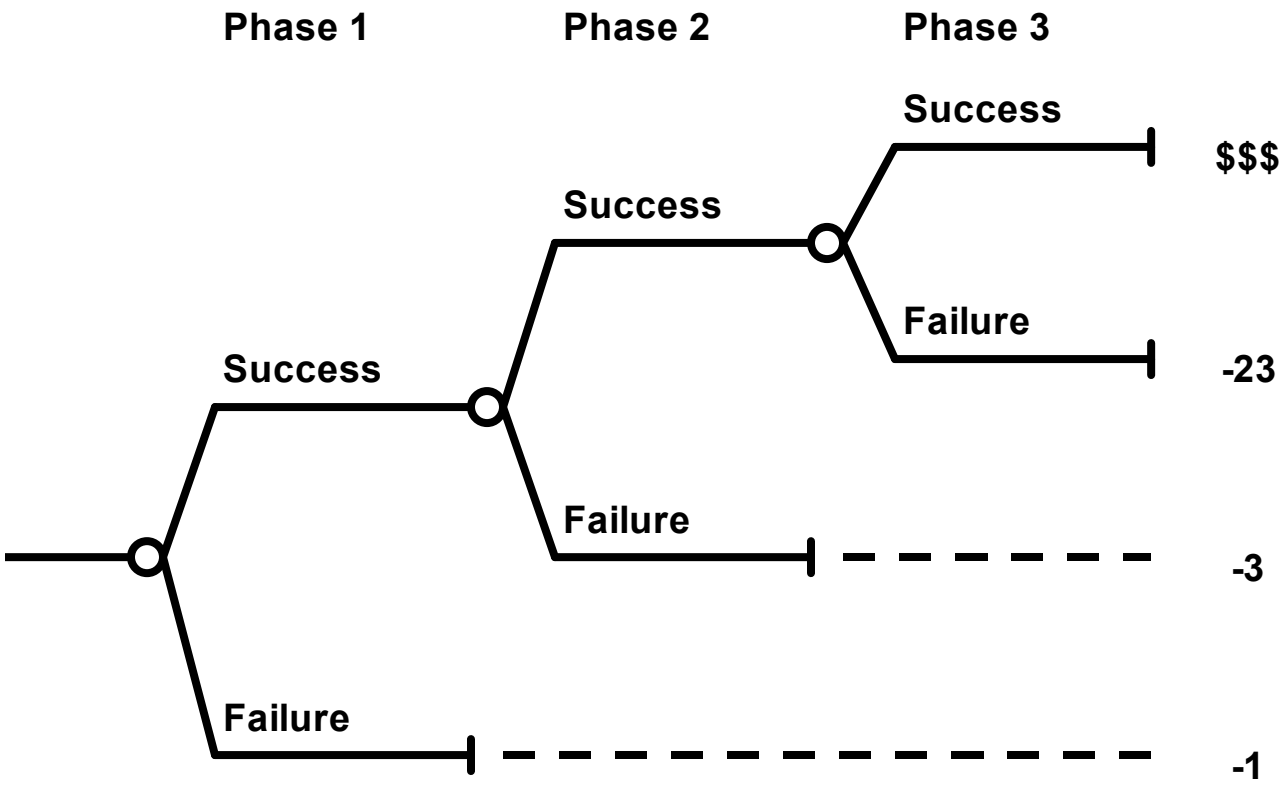
We have a collection of these

- At any given time, a company has a portfolio of opportunities at various phases in this process.
- This is the lifeblood of the industry, but it also adds to the complexity of decision making.

Why do we go through this process?

- It is a rite of passage, a series of steps one must take in order to get the regulatory approval to enter the market.
- For an opportunity at any given point in the process, to proceed down the path adds more value (on average).

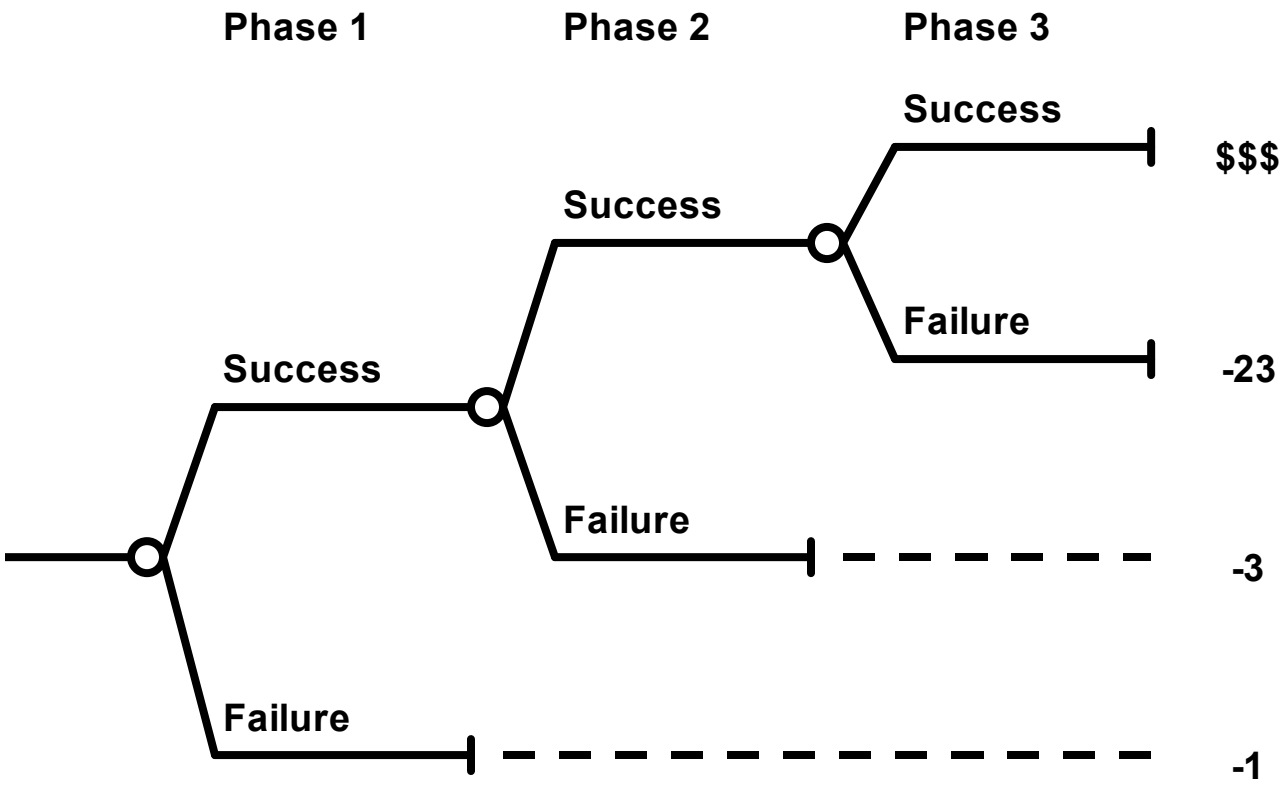
The process in tree form



Observations on this view

- People spend many hours estimating $$$ and probabilities of the various branches.
- This is used to generate a discounted cash flow estimate of "the value" of the opportunity.

What defines success?



What defines success?

- The word "success" suggests that it is random, a matter of chance.
- And that is also consistent with our efforts to estimate its probability.
- A study of the tree shows that success is the passage from one phase to another.

How does one make the choice to proceed into the next phase?

We let ourselves be guided by critical success factors.

Critical Success Factors

- Project management has developed this concept, according to which one specifies ahead of time how he will make the decision.
- The critical success factors define the circumstances under which a project will pass from one phase to the next.

More on critical success factors

- They can be complex: "A must be true, and either B or C must be true, and etc..."
- They are almost always of a scientific nature.

The critical success factors are often not followed in decision making.

- A project that does not meet its factors might be continued.
- Or one that does meet its factors might be terminated.

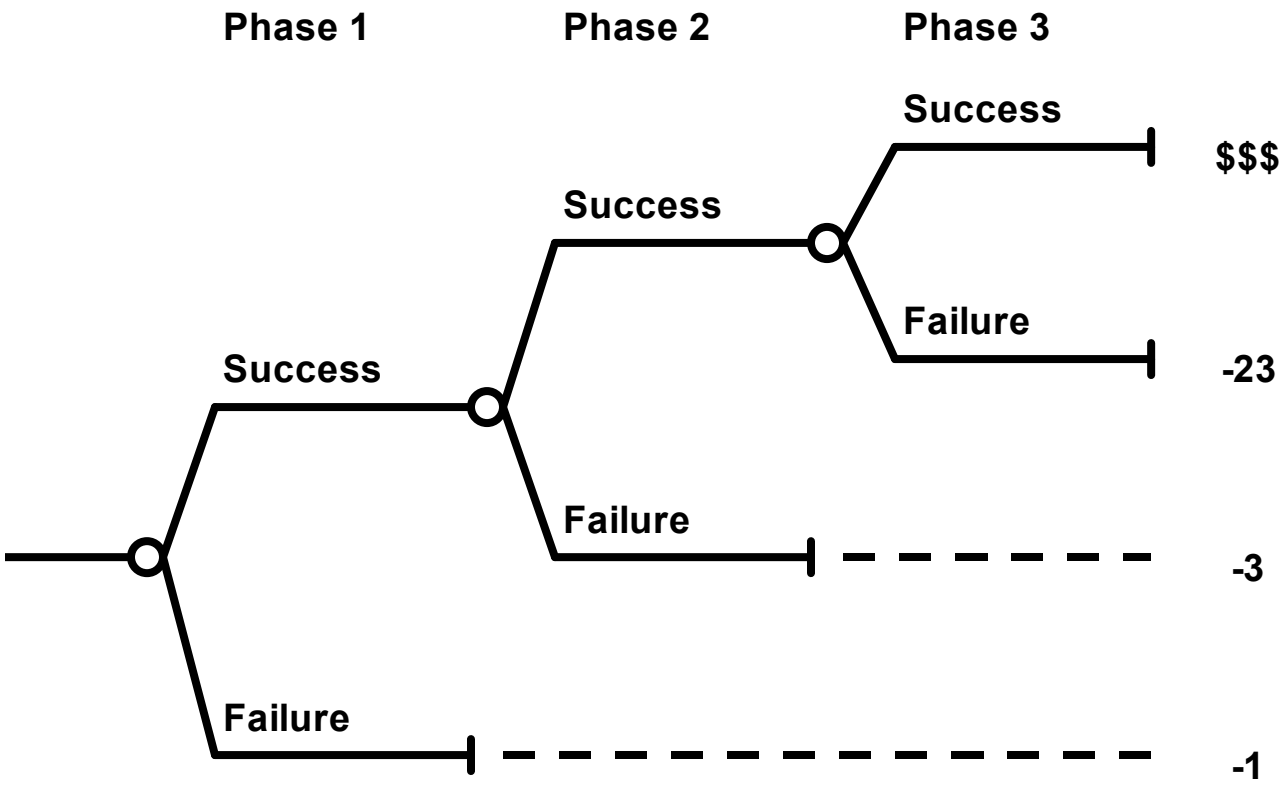
Why would one violate the critical success factors?

- Perhaps one of the criteria is almost, but not quite, satisfied.
- Perhaps one has new insights into the situation.
- Perhaps an important factor was omitted.

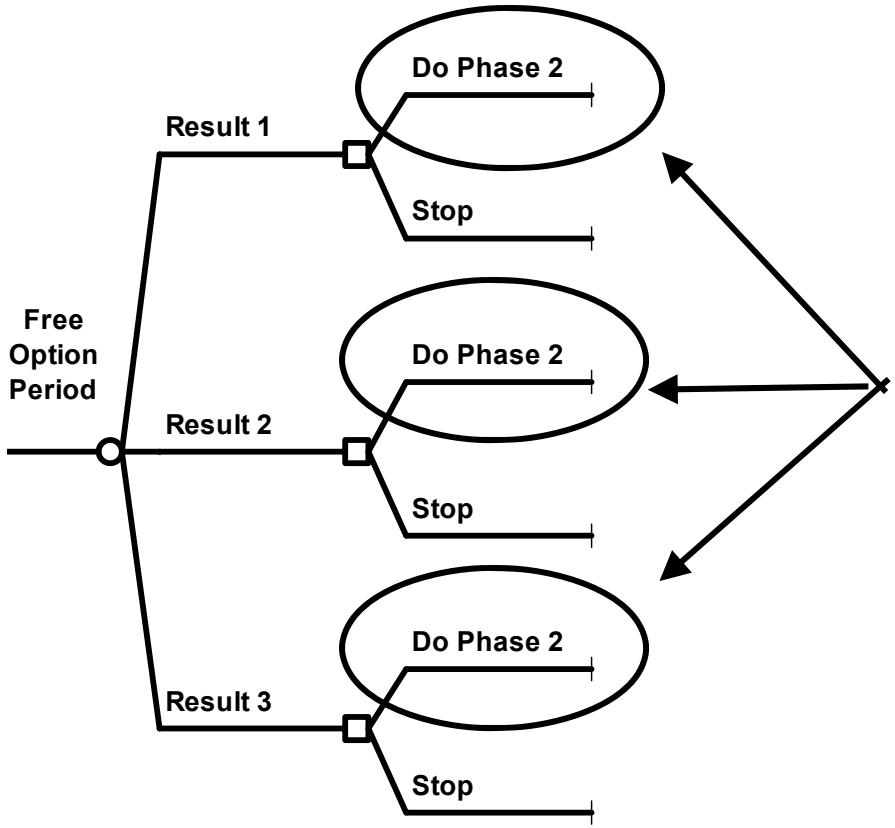
The pattern of our behavior

- ***Decide (commit resources)*** **to enter a new phase;**
- **Observe results and think;**
- ***Decide (commit resources)*** **again.**
- **Etc.**

The process in tree form

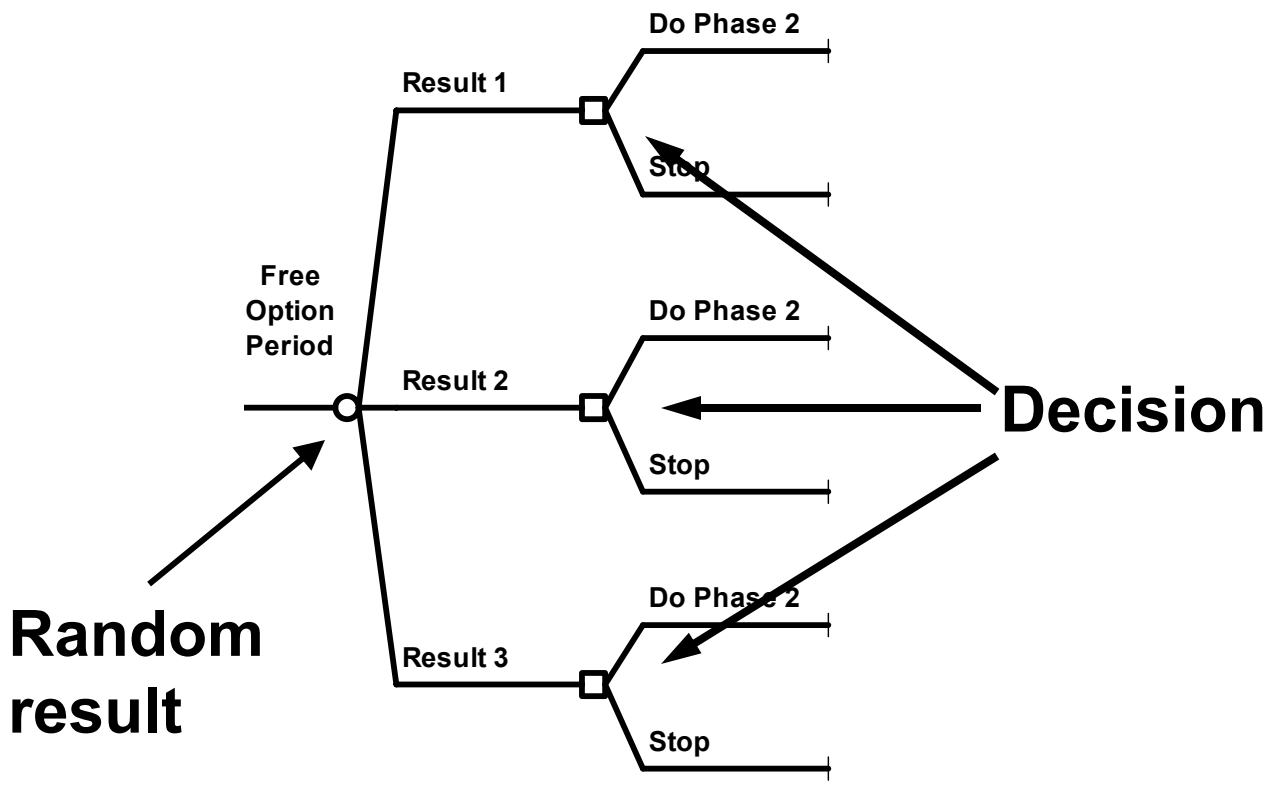


A close-up of Phase 1



These 3 branches are normally thought of as "success."

A close-up of Phase 1



This is a more realistic view of the process

- It separates the result of phase 1 from the decision whether to do phase 2.
- It explicitly captures the fact that we get to make choices in the course of drug development.
- By including those choices explicitly, we can think of options and their value.

Taking stock...

- **The R&D process consists of periods of action (decision, investment) separated by information collection.**
- **This is how it actually happens, and it is how it should happen.**
- **Why does our evaluation not reflect this paradigm, and should it?**

Example: Lillymycin

- was hoped to be useful in treating a common, serious, chronic disease.
- There is a well-established scale for measuring the effectiveness of drugs in this disease.

Lillymycin and the market

- **The marketplace was crowded, but there was excellent opportunity for a drug with the right kind of effectiveness.**
- **On the downside, a drug like all the others would have little chance of success.**

Current status

- **Phase 2 clinical trials were underway, in which we were to get our first look at the effectiveness of the drug.**
- **The project team asked me to help them estimate the value of Lillymycin, because it was to be compared with other opportunities.**

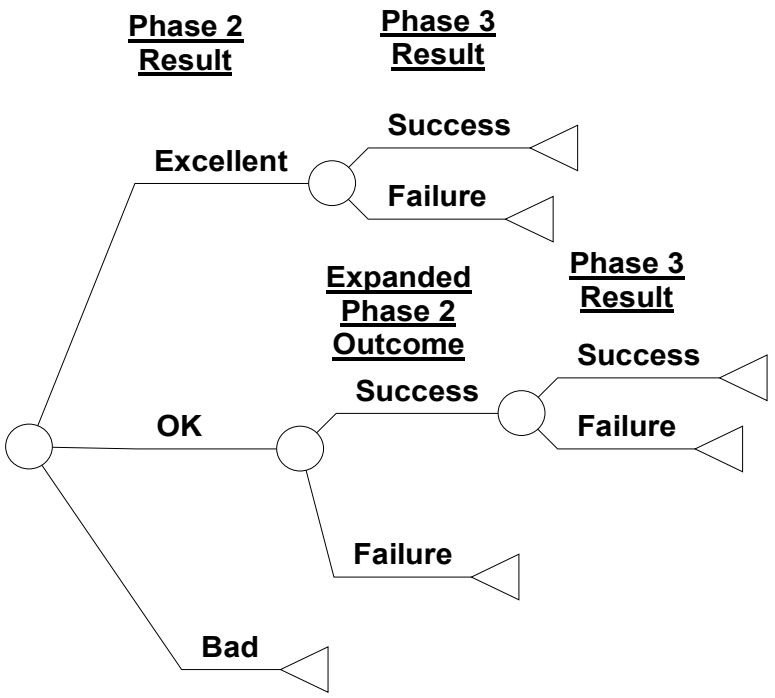
The team had defined Phase 2 outcomes

- The best result on the standard scale was defined as "excellent."
- A lesser result on the standard scale was defined as "OK." Currently existing drugs were in this class.
- An inferior result was defined as "bad."

The team had defined critical success factors

- If the phase 2 result is bad, we stop.
- If the phase 2 result is excellent, we would do phase 3.
- If the phase 2 result is OK, we will do an expanded phase 2, meant to help us make a better phase 3 decision.

Early "decision" tree



We agreed we had an option

- **We were to decide how to proceed *after* seeing Phase 2 data.**
- **We needed to think what courses of action we *<u>might take</u>* when the phase 2 data would become known.**

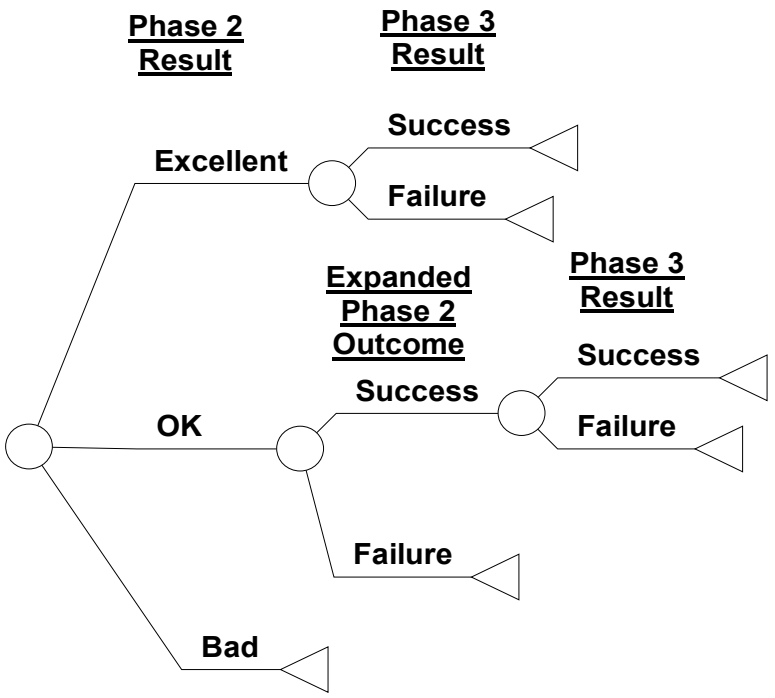
"Your decision can be no better than the best alternative you think of."

from Hammond, Keeney, Raiffa, Smart Choices, Harvard Business School Press, 1999.

The dark side of critical success factors:

- At the time to make a decision, we need to search for new, creative, courses of action for consideration.
- To specify decision rules ahead of time inhibits creativity, as it leads people to believe "the decision making work is done."

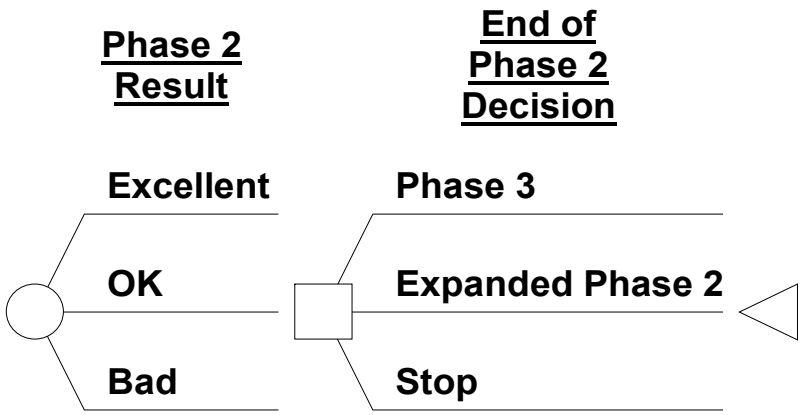
Early "decision" tree



In the case of Lillymycin

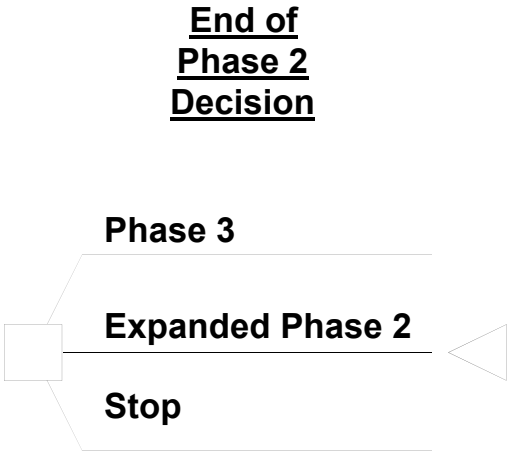
- We tried to think of some new alternatives.
- We will consider only 3 alternatives in this presentation.

A better decision tree

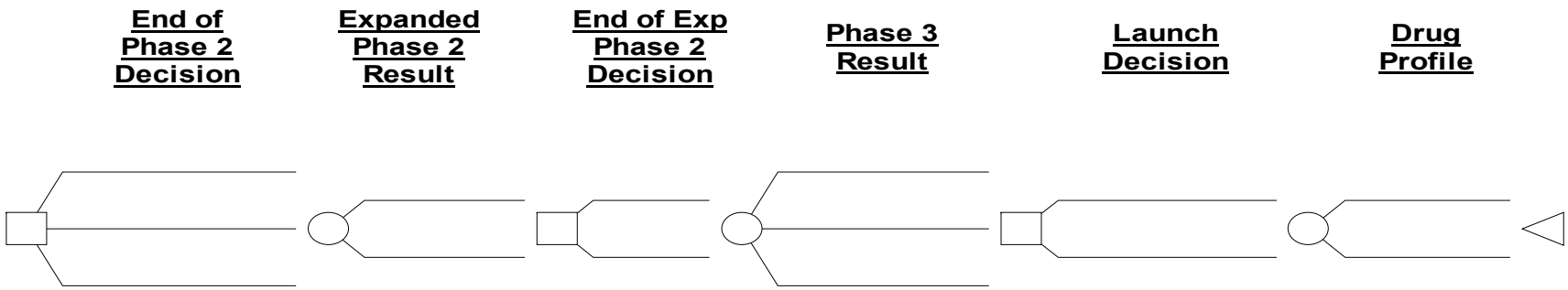


An even simpler view

The Phase 2 result uncertainty can be removed, as it will be resolved before the decision is to be made.



The full tree looks like this.



The project team attempted to look into the future.

Once the team understood that the decision was in the future, after Phase 2 data were examined, we attempted to have them imagine that they were indeed at that point in time.

Imagine phase 2 finished

- it is time to decide what to do next.
- What should we base that decision upon?
- We try to look into the future at the consequences of the various alternatives we face.

What do we try to predict in R&D?

- We might try to predict the outcome of the next experiment.
- There is no reason to try to predict future decisions.

We are *really* interested in predicting the market value of the drug.

- Every potential new drug has a market value.
- This is the value (in $NPV, for example) if the drug were to be launched into the marketplace.

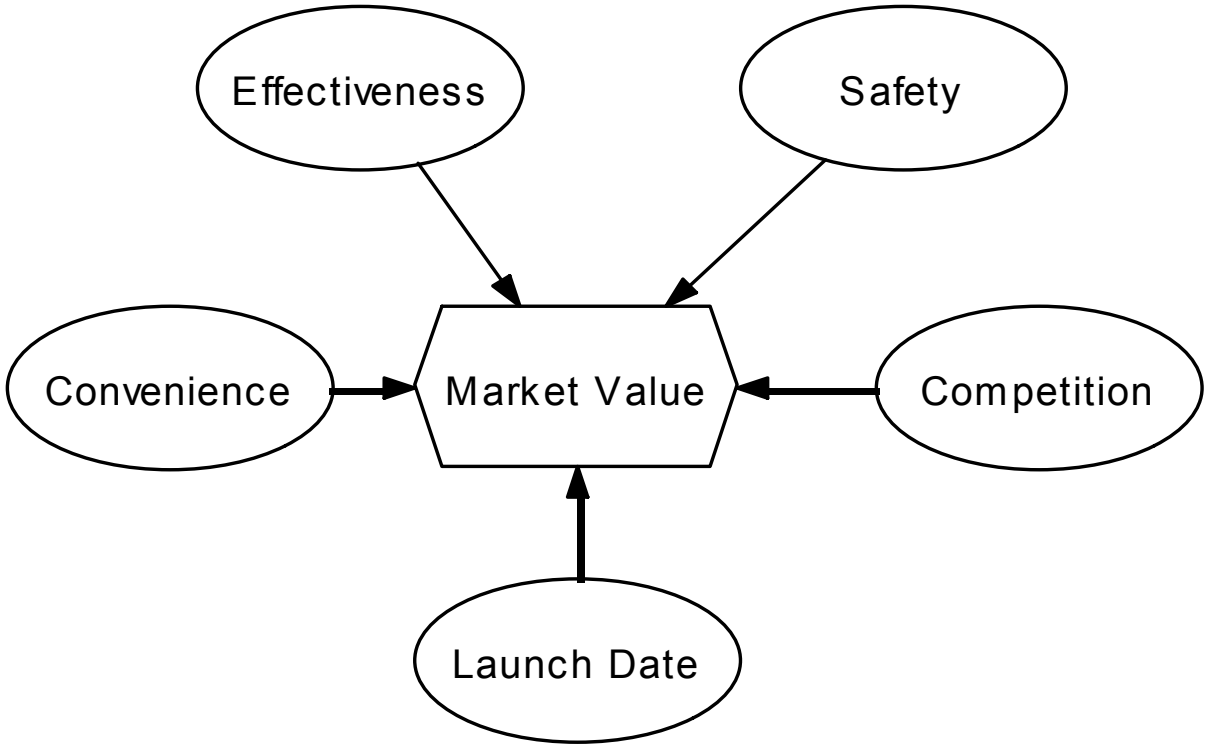
Observations on this very important concept.

- **Every new drug has a market value even if it never reaches the market to realize it.**
- **Regulatory approval is the key which allows us to have a look at the market value.**

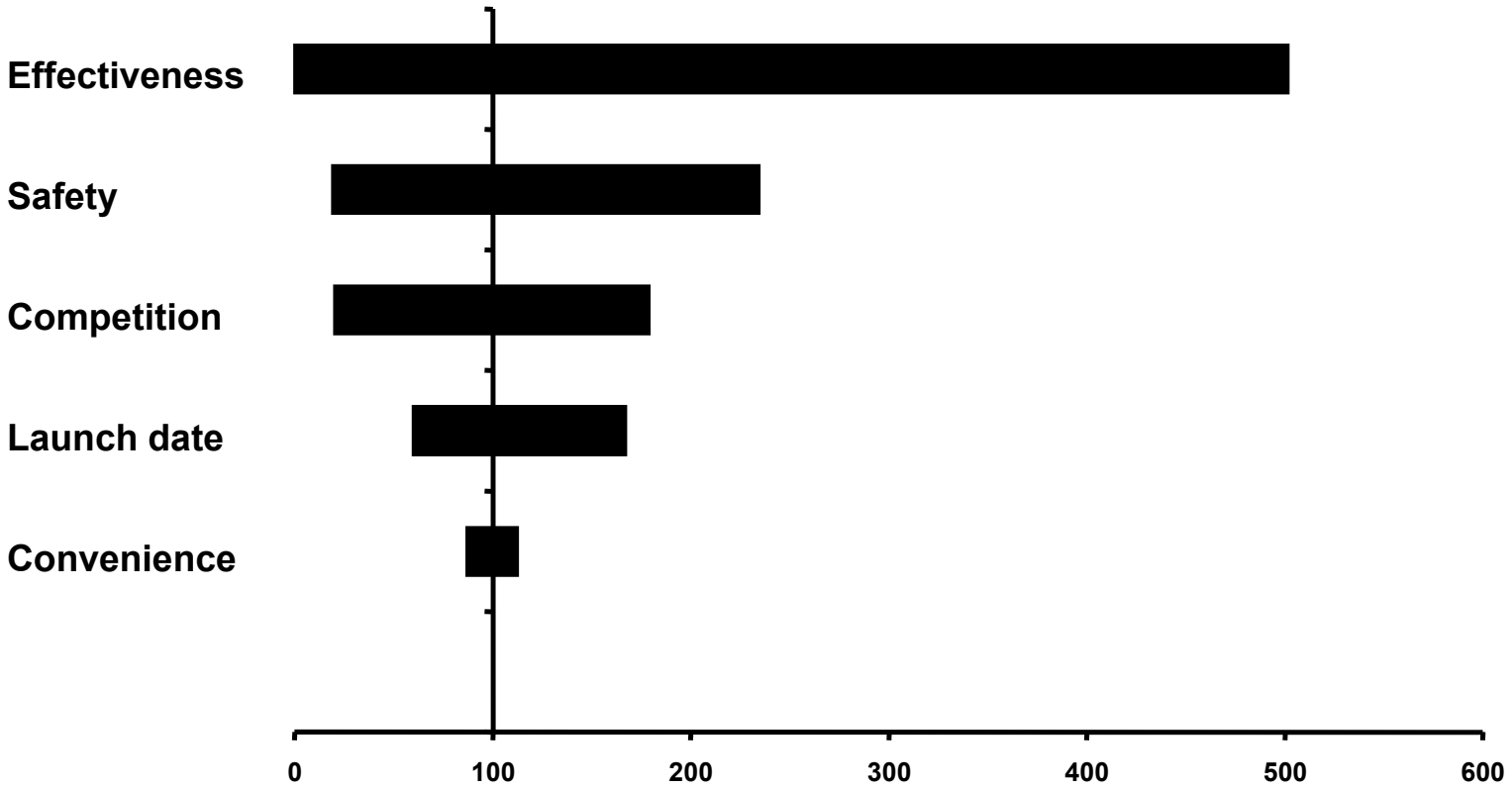
What will determine the market value?

- Effectiveness
- Safety
- Convenience
- Launch date
- Competitive situation
- etc., etc., etc.

One can model this value



Understand drivers of value



Then devise a few possible product profiles

Profile	Effectiveness	Safety	Competition	Value
Blockbuster	Excellent	like water	none	1000
Good	Very good	like water	2nd to market	500
Fair	Fair	side effects	several players	200
Poor	Fair	side effects	commodity	-150

In the case of Lillymycin

- **We assumed that the key determinant of value will be effectiveness.**
- **If it is unusually effective, then it will be highly rewarded.**
- **If that unusual effectiveness is not present, then it will lose money.**

Unfortunately

- **The testing does not determine the effectiveness.**
- **Instead, the effectiveness influences the results of the testing.**
- **Therefore the testing gives only a distorted view of the effectiveness.**

R&D is like diagnosis

Consider a diagnostic test for a disease affecting one in a million. The test gives the correct result 99% of the time. If a random person has the test done, and it comes out positive, how likely is it that he has the disease?

By the same token

- a new drug that will ultimately fail in the market may appear very good in clinical trials.
- Or, one destined to be embraced by the market might appear not very good in research.

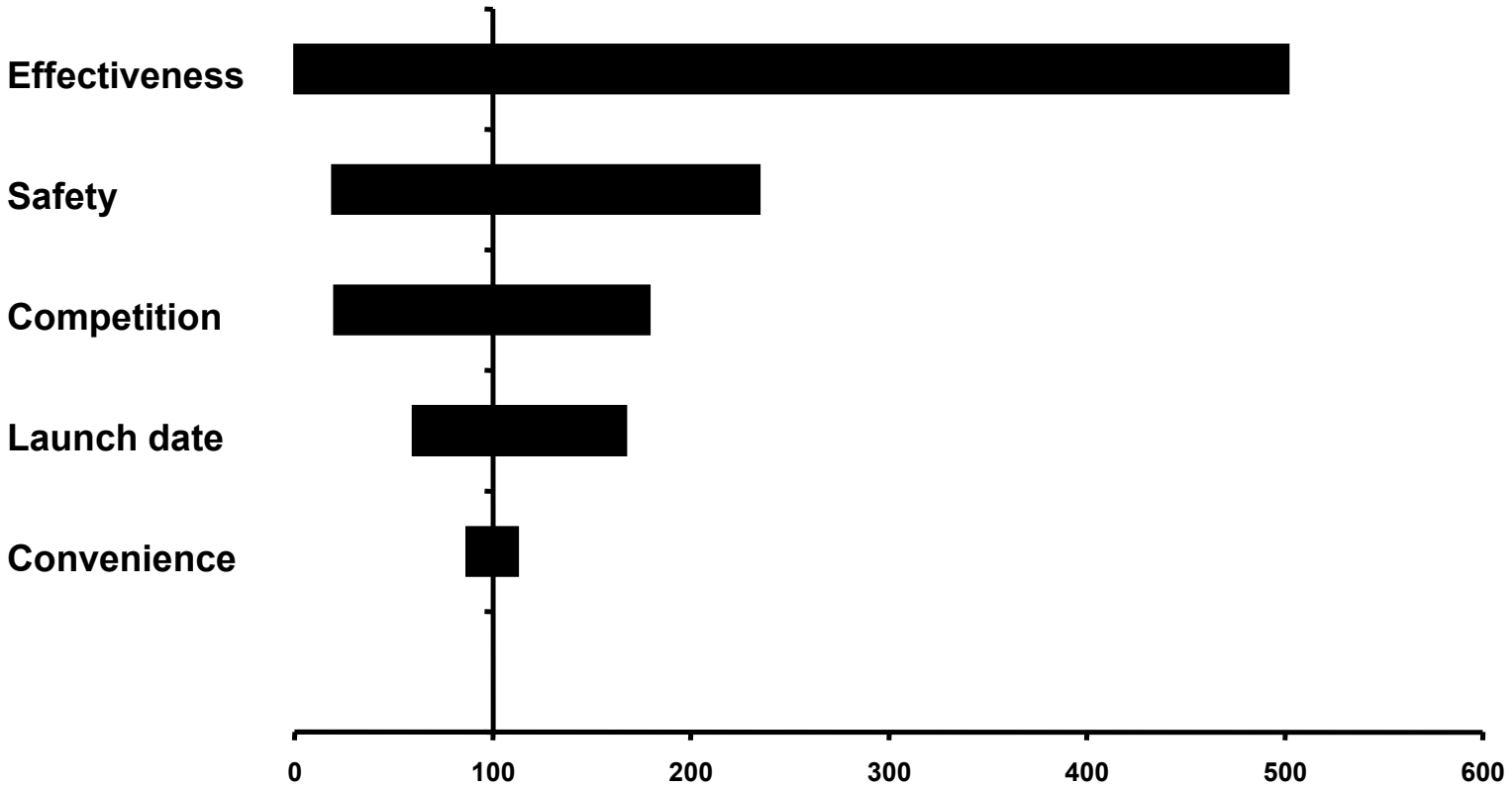
Therefore I conclude

- **Our R&D gives us only an imperfect picture of product profile.**
- **Since product profile strongly influences market value, we incorrectly estimate market value.**

And hence

- As we plan our R&D, we should aim toward optimizing that prediction of product profile.
- The R&D must be directed toward predicting the important determinants of market value.

Important determinants of market value



Our process

- We defined the levels of effectiveness which would determine the value.
- For each such level, we considered the possible results of the testing, and how likely those possible results were to happen.

Levels of effectiveness

Effectiveness	Value
Excellent	1000
Ordinary	-100

Results of testing

Phase 3	Expanded Phase 2
Exciting	Better than Phase 2
Satisfactory	No better than Phase 2
Disappointing	

And their likelihoods

Excellent effectiveness

Phase 3	Probability	Expanded Phase 2	Probability
Exciting	0.6	Better than Phase 2	0.7
Satisfactory	0.3	No better than Phase 2	0.3
Disappointing	0.1		

Ordinary effectiveness

Phase 3	Probability	Expanded Phase 2	Probability
Exciting	0.3	Better than Phase 2	0.4
Satisfactory	0.5	No better than Phase 2	0.6
Disappointing	0.2		

Observations on the process

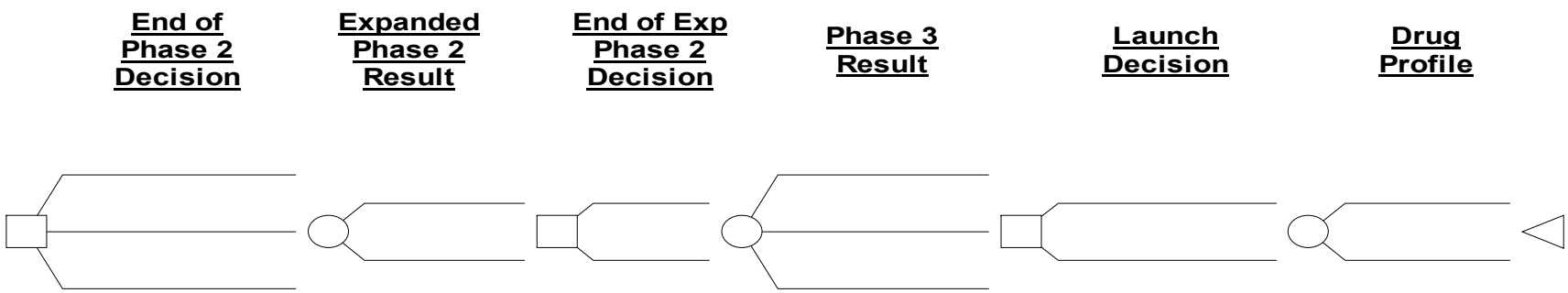
- It is essential to have precise definitions of the levels of effectiveness and results of testing.
- All of the above can be done while we await the results of phase 2.

When the Phase 2 data arrive

one can assess from the experts their judgment as to the likelihoods of the various profiles for the new drug.

Effectiveness	Probability
Excellent	0.3
Ordinary	0.7

Then one can solve the tree.



Results of solving the tree

- We receive an estimate of the potential risk and reward of pursuing each of the alternatives.
- We win insights on future decisions.

What did we learn about Lillymycin?

- Given our state of knowledge about the effectiveness, we would prefer to initiate phase 3 directly.
- Other insights from this analysis give us guidance not only on Lillymycin but on other similar projects as well.

The current decision

- If one chose to perform the expanded Phase 2 study, then
  - if its result is better than the Phase 2 study, one would do Phase 3.
  - If its result were the same as Phase 2, one would do Phase 3.
- Therefore the expanded Phase 2 study simply added expense & delay.

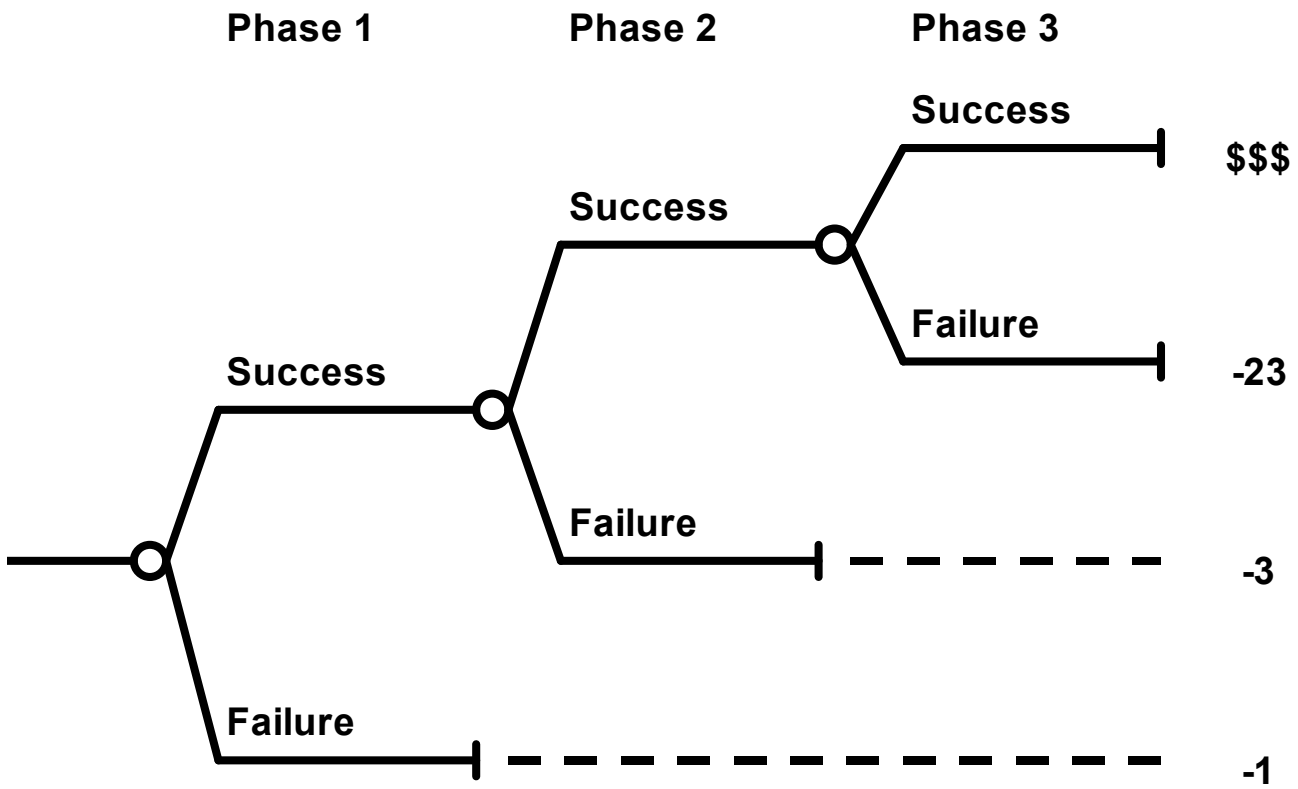
What this finding suggests

- **If our proposed expanded Phase 2 study cannot justify itself by its ability to predict market value, is there a different expanded Phase 2 study that might do so?**
- **I infer that other possibilities should have been among our alternatives.**

Another insight

- **Given our current state of knowledge, one would not launch the drug into the marketplace if the Phase 3 study were to yield a "disappointing" result.**
- **As a corollary, in this case one would not seek regulatory approval for marketing.**

This option was not captured in the earlier view of R&D



As a consequence

the value of Lillymycin was underestimated in comparing it with other opportunities.

Yet another insight

- **This analysis exposed the common error in human judgment which causes us to place too much credence on new evidence.**
- **It is important to weight new information correctly, namely according to Bayes Law.**

Lillymycin is only 1 example

- "Full speed ahead" into Phase 3 was preferable to a temporizing step.
- I believe this finding is generalizable, at least in pharmaceuticals.
- If confirmed, then decision making in such cases would be easy.

But decision making should not always be easy.

If decision making is easy, we need to be thinking of more creative alternatives.

A portfolio frame

- for problems like this might acknowledge that, yes, faster is better for such opportunities, one at a time.
- But for which combination of opportunities is "faster" most rewarding?

And especially

- **is there a combination, some faster, some slower, with even greater value?**
- **This might be the case, particularly if some have R&D methods that are excellent predictors of market value.**

In summary, we discussed

- staging the R&D process as options,
- what things we need to think about in approaching these options,
- some important elements of research design, and
- why one might wish to think of such opportunities in a portfolio frame.