Who are clinical trials for: Guinea Pigs, Test Pilots or Prize Poodles?

By D. Ross Camidge, MD PhD

Developmental Therapeutics and Lung Cancer Programs,

University of Colorado Comprehensive Cancer Center,

Aurora, Colorado

Contents:

1) Introduction:

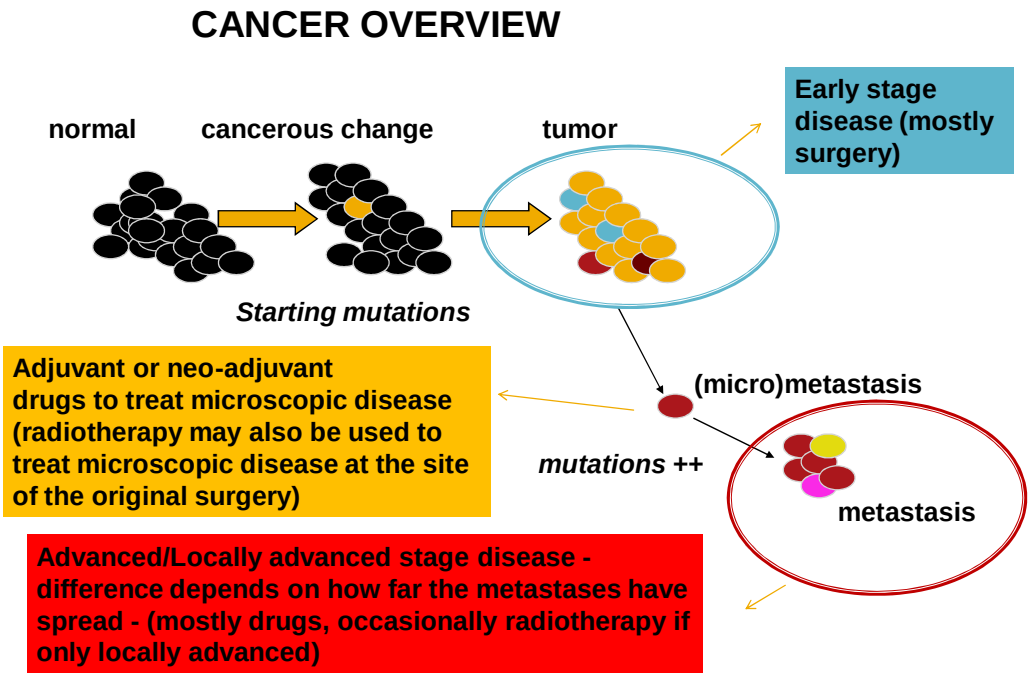
While everyone with a diagnosis of cancer wants to get the best treatment, how does anyone know what the ‘best’ is?

A hundred years ago, when a salesman would stand on the back of a wagon and hold up a bottle of snake-oil, the ‘best’ medicine, at least at first, was often the one associated with the grandest sounding story of its discovery, or with the most impressive (paid) testimonials from those it had miraculously healed. Sadly, we still have snake-oil salesmen even in the twenty-first century. Although, these days they tend to operate from the internet rather than the back of a wagon. Fortunately, we are not dependent on them as our sole source of information. Instead, over many years a rigorous, evidence-based process for establishing and justifying the claims associated with any licensed medical product has evolved – a process involving the participation of patients in formalized clinical trials.

In this article I aim to explain why and how such clinical trials are performed in oncology. However, even if we recognize the value of objective data from clinical trials, this is, of course, not the same as automatically wanting to be a participant in the process yourself. Therefore, I also aim to give you some tips to help you and your family/friends decide on whether a particular trial is something that you, personally, should consider entering into at any stage of your cancer treatment journey.

2) Defining our cancer treatment terminology from the outset – stages of disease and lines of therapy:

Cancers come in all varieties, and in all shapes and sizes. Treatment for cancer ranges from surgery to radiotherapy to drug-based treatments - either on their own or as combinations of the different approaches. When a cancer has not spread very far around the body, perhaps only to the nearest set of lymph nodes that cover a given area of the body, or to no lymph nodes at all, it is usually referred to as an early stage cancer (this usually includes what is formally referred to as stage I or stage II cancer). If many different lymph nodes, or lymph nodes that are further away from the cancer, are involved, the cancer may be called locally advanced (this comprises most of what is called stage III disease). If the cancer has spread to other organs or structures in the body, such as the liver, bones or brain, then the cancer is considered even more advanced, and it is then usually called ‘metastatic’ or stage IV disease.



2a) Early stage cancers:

In general, early stage cancers tend to be the most curable. The definitive treatment for these cancers is surgery, although high-dose radiotherapy, sometimes called radical radiotherapy, may be just as good in some situations. However, as most of us would rather have the cancer out of our bodies completely, radiotherapy, as an alternative to surgery for early stage disease, is usually reserved for those not fit enough for surgery or for those who don't wish surgery for other reasons. Chemotherapy, other drug-based treatments, radiotherapy or any combination of these is sometimes given before an operation. This is called 'neo-adjuvant' treatment and is usually to help shrink larger cancers down, either to make the operation easier and/or to increase the chances of getting rid of the cancer completely. Instead of, or in addition to, any neo-adjuvant treatment, after the operation a defined course of chemotherapy and sometimes radiotherapy (to the site of where the cancer once was) may also be given to reduce the chances of the cancer coming back. This is to treat microscopic disease that may be there, but that is too small to be detectable at the time. This is usually reserved for cancers with a higher risk of recurrence based on all of the available information after the cancer has been removed. This kind of 'insurance policy' approach, trying to maximize the chances of cure by giving extra therapies after an operation is called 'adjuvant' treatment.

2b) Locally advanced cancers:

While some locally advanced cancers may be removable by surgery, with or without the benefit of any associated neo-adjuvant and/or adjuvant treatments, other stage III cancers cannot be operated on. For example, in non-small cell lung cancer – one of the most common serious cancers - this is usually because the cancer has spread to involve lymph nodes on both sides of the middle of the chest, or to the lymph nodes behind the collarbones. However, the exact location of the lymph nodes that distinguish between Stage II (early stage disease) and Stage III (locally advanced disease) will vary depending on the particular type of cancer and the part of the body affected. For cancers starting in the pelvis, like prostate or ovarian cancer, the lymph nodes that determine how far the cancer has spread will be very different from, for example, those relevant to a breast cancer that starts up in your chest wall.

Operations for locally advanced cancers have traditionally not been undertaken, although there are exceptions. This is because the risks of not removing all known deposits of the disease and of there being hidden metastatic disease in other parts of the body are considered to be very high for cancers that are locally advanced. Surgeons usually don't want to put patients through a large operation that will ultimately not cure them. Instead, a combination of high-dose radiotherapy to all known sites of disease, complemented by chemotherapy, is currently considered the standard of care for most inoperable stage III disease. The chemotherapy in this setting acts both to make the radiotherapy more effective and to treat any hidden microscopic disease in other parts of the body. Although some patients with stage III disease can be cured by this approach, the relapse rate is unfortunately still very high.

2c) Advanced/Metastatic cancers:

In contrast to both early stage and locally advanced disease, advanced or metastatic disease is usually not treated with either surgery or high-dose radiotherapy, except under rare circumstances when there are very few sites involved (so-called 'oligo-metastatic disease'). Instead, when the disease is in multiple different places in the body, or in other areas difficult to localize precisely (for example, in fluid around the lungs), drugs, such as chemotherapy, that can circulate around many different places, are the mainstay of treatment. Treatment in this setting is not usually considered curative; instead it acts as a means to control the cancer. Control in this setting means several different things. For example, a slowing of the cancer's progress or a reduction in the amount of cancer in the body, for example shrinkage in the size of any masses seen on scans. Control may also mean an improvement in symptoms, if symptoms are present at the start of treatment. It may also mean a change in the natural history of the disease such that an individual with an incurable serious cancer lives longer. This sometimes can be very difficult to comprehend as a treatment goal. If you can't cure me

– why even bother? Aren't you just dragging out the inevitable? There are two answers to these important questions. The first is purely pragmatic – if you have symptoms from the cancer and a treatment can improve these, or postpone their development, no matter how much time you have left it will be better quality time. However, there may be side effects associated with anti-cancer treatments and their severity and duration will always have to be weighed against the symptoms associated with the disease they are designed to treat. Pure symptomatic care that does not attack the root cause, for example treatment as needed with pain-killers, oxygen, anti-nausea medication, etc can also be used, and may be part of a treatment plan, or form the entire treatment plan itself. The second answer relating to why treat the underlying cancer if you can't cure it is more philosophical and each of us may have very different reactions to it. For myself, I tend to think about a number of different things including:

- Many serious and potentially life-shortening conditions are not curable, but we still treat them to maximize both our actual and potential quality and quantity of life – conditions such as HIV, diabetes, heart disease, asthma or COPD. Drawing analogies between cancer and other serious life-changing diseases such as HIV, severe heart disease or severe COPD probably seems pretty reasonable. However, for some subtypes of cancer, even the analogies with asthma and diabetes may become achievable goals within the next few years.

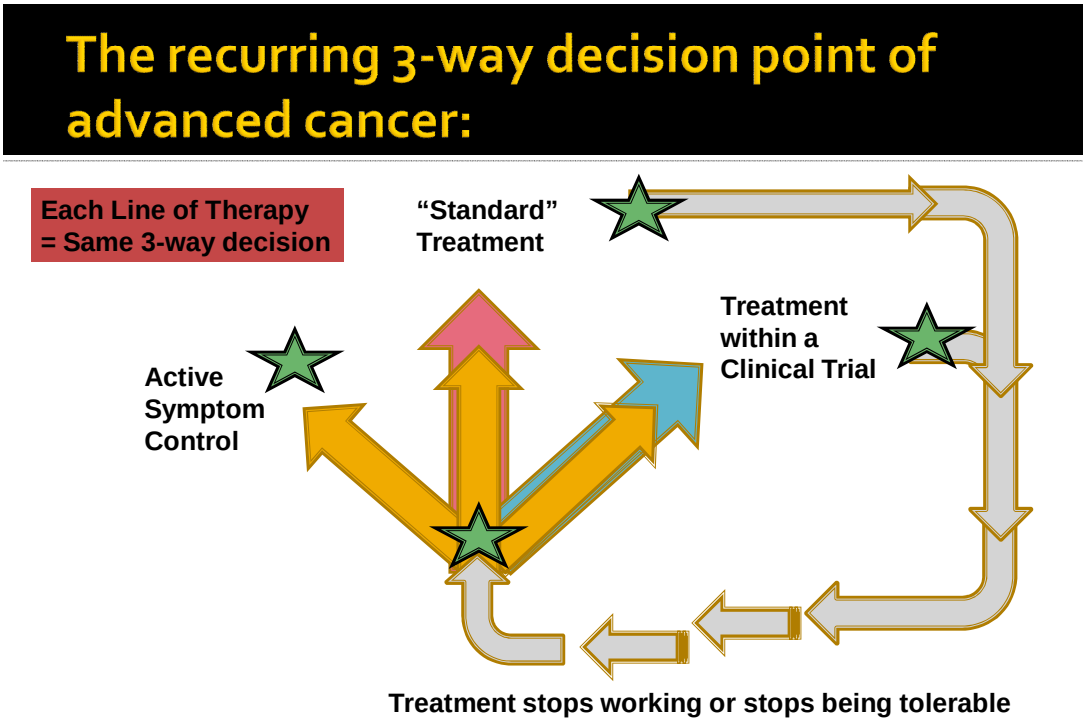
- In the worst case scenario - if the disease was going to end my life in a relatively short space of time - if the treatment could increase my chances of getting to a specific goal, an event I wanted to see or participate in on a specific date, like a wedding, Christmas or a family gathering, or just to give me time to set my affairs in order, I would consider it.

The treatments for most advanced cancers are not cures but attempts to control the disease. Even if control can be achieved, it does not last forever. Instead, multiple different treatments, called the first, second, third, etc 'line' of treatment are usually employed. Each may produce or not produce control, and the extent and duration of the disease control produced by each one can vary enormously.

Consequently, treatment for advanced cancer is characterized by a recurring three-way decision point that, as the patient, you find yourself coming to/back to at the consideration of each new line of therapy: (1) Just treat the symptoms, (2) Treat the symptoms and have standard anti-cancer therapy, or (3) Treat the symptoms and have anti-cancer therapy within a clinical trial (Figure 1). Which of the three pathways is most attractive to you or most appropriate will vary. Each time it will depend on your own fitness, your own state-of-mind and the details of the side-effects, inconvenience and

chances of success from the anti-cancer treatments that are available at that particular line of therapy/point in time.

FIGURE 1:



NB Active symptom control may be a standalone treatment decision or be a part of either 'standard' or clinical trial-based anti-cancer treatments

3) Clinical Trials - Overview:

Assume for a moment that you are not a participant in a trial, but just a consumer of the data coming out of them. Clinical trials establish for all of us a means to determine the best treatment for a specific condition, in a specific indication, at any particular point in time – for this cancer or that cancer, in the early, locally advanced or metastatic setting, in the metastatic setting in the first, second, third line of therapy, etc. This is established based on good evidence and free from prejudice, through a highly regulated, multi-step process. It aims to put decision-making on an objective level, above that of the whims of those who just want to sell us something, or of those who just have a gut feeling that something is right or wrong for us.

BUT… In the middle of dealing with a diagnosis of cancer, when your doctor brings up the idea of a clinical trial that you yourself might be involved in, it can be a source of enormous stress:

- *I don't understand this – it's too much to think about.*
- *What if it's a dumb idea, how can I tell?*
- *I don't want to upset my doctor/my family.*
- *I don't want to be a guinea pig.*
- *What if I get a placebo (dummy treatments)?*
- *What about the side effects?*
- *Who is paying for this?*

So let's look into clinical trials in more detail – what they are, and what to look out for.

4) Where do clinical trials fit in?

Most clinical trials for cancer are in the advanced disease setting, fitting in as a treatment choice at a particular line of therapy. Clinical trials in early stage and locally advanced disease also exist, but are rarer and are usually only large phase III studies (see below). This is because cure is considered a more realistic possibility in these settings, so any new drug or other treatment change has to have a large amount of evidence behind it before anyone usually considers messing with a potentially curative standard approach.

Although there can be trials of anything – from a diagnostic test, to surgery, to radiotherapy, to symptomatic care, to counseling – most anti-cancer clinical trials involve the development and integration of new drugs. Therefore, for simplicities sake, from here on we will only illustrate this article with reference to anti-cancer drug trials. A clinical drug trial can be:

- *A new treatment on its own.*
- *A new treatment added into a standard treatment.*

- *A new treatment on its own, or added into standard treatment ,compared to standard treatment alone (randomized study).*

Randomized studies may be open-label – where you know which of the available treatments that are being compared you are getting - or it may be 'blinded'. A 'blinded' study is one in which the study is 'placebo-controlled' – whereby you may be getting a dummy treatment or the new treatment, either on its own or added into standard therapy - but you, and probably your doctor too, won't know which of the two you are getting (although, code numbers will reveal it at a later date to the organizers of the study). It is also important to note that sometimes, where something is being compared to a "standard treatment", the standard may, in fact, be active symptom control alone, i.e. there is no standard anti-cancer treatment for that disease in that particular setting.

5) Do I qualify for a clinical trial?

Generally speaking, there is no point even looking at a trial that you do not qualify for. Most trials are asking specific questions and do not have too much room to bend their particular rules of eligibility. Therefore your doctor should have identified you as at least potentially eligible before mentioning any specific trial to you, so that neither of you waste time and energy thinking about something that this is never really going to be an option. Each trial has specific inclusion and exclusion criteria associated with it that your doctor can look up in advance to see if you are likely to be eligible. While sometimes eligibility or ineligibility is easy to determine straight away – for example, if you have colon cancer you won't qualify for a study designed only for those with breast cancer, or if you have early stage disease you won't qualify for a study designed for advanced stage disease, etc – other issues on which people fail to qualify for clinical trials may not be apparent until more information or more test results about you become available. The three most common reasons that cause people with cancer to fail to qualify for clinical trials are inappropriate line of therapy, inadequate fitness for participation, and, less frequently, inappropriate insurance coverage. Dealing with each in turn:

5a) Line of therapy: A line of therapy is a full course of treatment, usually involving multiple different repeated exposures (cycles), with a specific drug or combination of drugs for advanced cancer. Each new drug or set of drugs that is tried to get your cancer under control is a line of therapy and is numbered sequentially – first line, second line, third line, etc. Using non-small cell lung cancer as the example again, a combination of carboplatin and paclitaxel for six cycles would be a common first line treatment (the two drugs being counted together as the first line regimen). Then this might be followed by, say, multiple cycles of pemetrexed started when the cancer begins to grow again (second line treatment), which would then be followed by erlotinib

tablets (Tarceva) at the point when the pemetrexed stops keeping the cancer under control (third line treatment). For different cancers the specific drugs and number of cycles will vary, but the principles of naming each new regimen of drugs used to try to get the cancer under control as sequentially numbered 'lines of therapy' ('lines of defense') remains the same. Of note, the same drug can be part of different lines of therapy in different individuals. For example, maybe Mr. Smith gets pemetrexed with carboplatin as part of his first-line treatment, instead of the paclitaxel, whereas Mr. Jones gets pemetrexed after his carboplatin and paclitaxel combination, in which case the pemetrexed would be his second line treatment.

Not all clinical trials are written in the same way, but most Phase II and III studies are constrained to only look at a particular line of therapy, i.e. you may be eligible if you have had two previous different treatments but not three, or one but not two, etc. Phase I studies (see below) are a notable exception to this and are often open to people regardless of the number of lines of therapy they have had. Areas of controversy that vary between studies include (a) whether any drug exposure counts – even if the treatment is then abandoned early because of side-effects or allergic reactions- or whether it has to be shown to not be working on the cancer by scans showing that the cancer is growing despite the treatment, (b) whether any treatment given around the time of surgery (adjuvant or neo-adjuvant treatment) for early stage disease counts if you later relapse with more advanced stage disease, and (c) whether all drugs count the same or whether, for example, only chemotherapies are counted and so-called 'targeted therapies', such as erlotinib, are somehow 'counted' differently. The reasoning behind this last point is that when cancers become resistant to one type of chemotherapy there can be a spill-over effect such that they also become partially resistant to other chemotherapies (this is why line of therapy is perceived to be important to level the playing field for any new drug in a particular setting). However, 'cross-resistance' to chemotherapies may not affect drugs that work very differently, such as highly targeted therapies where the presence or absence of a specific molecular factor may be a much more important determinant of the drug's activity or inactivity, and, as such, line of therapy may be a much less important variable affecting activity for these types of drugs.

5b) Fitness for participation: In some ways all participants in clinical trials are acting like test-pilots – putting a new drug or combination of drugs through its paces, and figuring out what they do well, in the form of anti-cancer activity, and what they don't do well, in the form of side-effects or treatment-related 'toxicity'. As the number of people who have tried out a new drug will vary over time, just as in the real world of test-pilots, it makes sense to only allow your best and fittest test-pilots to try out the most experimental of your airplanes. In the world of clinical trials these means setting some

benchmarks of fitness that patients need to achieve in order to be eligible for particular studies, for safety reasons to allow them a good chance of being able to cope with unexpected severe or serious side-effects should they occur. Fitness requirements are usually highest for Phase I studies and lowest for Phase III studies, as knowledge and confidence relating to the new drug increases over time. 'Fitness' doesn't necessarily mean physical fitness – although a patient's general 'performance status' is one thing that is considered – instead it often means simply that your kidneys and liver are working fine, or that you are not on medications with a strong potential to interact with the study drug, or that you do not have particular risk factors putting you at increased risk of side-effects from the drug, such as a recent heart attack or stroke. Increasingly, 'fitness' for some of the newest targeted drugs may also mean having a test performed on the original biopsy of your cancer that may be stored away in a lab somewhere, in order to see if your cancer expresses a marker that makes it more likely that you will respond to the new drug or at least reduce the chances that you will be resistant to it – these molecular tests are sometimes called 'predictive biomarkers'. Perhaps the most frustrating thing about the fitness hurdles that an individual may have to clear in order to be eligible for a particular clinical study is that some of them are outside the control of the individual. You can be made ineligible on the basis of a simple blood test, even though you may feel like superman or superwoman at the time. While occasionally, at least from a Clinical Trialist's perspective, some studies are written too cautiously, in general, most of these rules are put there with the best intentions of protecting the patient from excessive risks associated with their entry into a particular study.

5c) Insurance coverage: There are many different trials, different sponsors of trials and different insurance programs. However, in general, the payment of costs associated with most clinical trials tends to follow the same basic principles. Firstly, if the trial includes elements of standard care – for example, standard chemotherapy drugs in

addition to, or as an alternative to, any experimental drugs, routine visits to the doctor or routine scans to assess whether the treatment is working - these will be billed to your insurance. If you normally have co-pays for these things then that will not change. For 'extra' things associated with the study – research blood tests or research scans, any experimental drugs, even any extra visits to the clinic – usually these are not billed to your insurance but are absorbed by the sponsor of the study (usually either a pharmaceutical company or an academic individual or institution with a grant from the government or another organization that funds research, such as certain charities). Some insurance programs will not cover any aspects of clinical trials. However, this is the exception rather than the rule. If it happens, sometimes your doctor can explain matters to your insurance company, sometimes they can't. Since we are talking about costs, one thing that it is important to ask is if you need emergency care because of something directly related to the study - from an extra visit to your doctor to address side effects, to admission to hospital because of the severity of these side effects – would this care be perceived as standard, or as study-specific costs. The other thing to clarify is that, if you are receiving benefit from continued use of the study drug, you will still to be able to receive the drug for free, even if it ultimately gets licensed and other people starting on it are then being billed for it.

6) What does being in a trial involve?

Being in a clinical trial involves different things at different stages. At the beginning it involves taking on board some additional stresses – will you pass the screening tests? There are usually more unknowns about the side-effects and efficacy of the treatment than with standard treatment – do these risks seem acceptable in return for the potential benefits of being in the study? Are any extra visits or tests acceptable to you in terms of the additional time commitment they involve?

To help you in making these decisions, all clinical trials involve the potential participant being shown a detailed 'consent form' that outlines what is known about the study and any alternative treatments. It also describes what being in the study might involve and the risks associated with the decision to enter the study. You should then have the opportunity to read the consent form and to ask any questions you may have before deciding on whether this is something you want to take further.

The concept of 'informed consent', i.e. giving you as much information in advance to help you decide about whether you give your consent to be screened for a given trial or not, is at the heart of all modern clinical trials. The amount of information on any particular new drug will vary depending on whether the study is a Phase I, II or III study. The later the stage, the more is known about the drug. It doesn't necessarily mean the

drug is any better or worse – just that the number of ‘knowns’ and ‘unknowns’ about it change as time goes by and more people are treated with it.

The other core concept is that you can withdraw consent at any time. The signing of a consent form doesn’t force you into anything – you can always change your mind. The only consequence being that, if you do withdraw consent, you will then be withdrawn from the study and all or part of its associated experimental treatments. Most study teams try to be flexible – we all have to live in the real world and sometimes you can’t make a particular appointment on a particular day – but in general there is an expected mutual agreement to try to abide by what the trial involves as much as possible. If you start to compromise the essence of the study too much, the investigator also has the right to withdraw you from the study too.

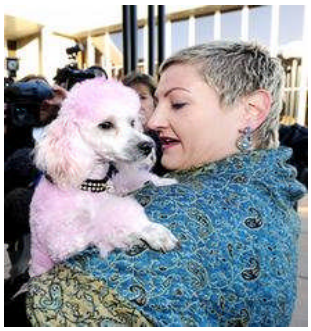
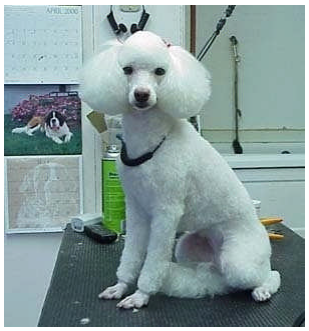
Being in a study, after you have passed any screening tests, involves a mutual relationship of good two-way communication between you and the study staff (nurses, nurse practitioners, study coordinators (sometimes called CRAs – clinical research assistants), and physicians). It involves agreeing to report any side-effects, any improvements, perhaps keeping track of whether you miss any doses of tablets, etc and feeding these all back to the study team – just like a test-pilot would frequently radio back to the control-tower about how a new airplane was handling.

7) What are the potential advantages of being in a clinical trial?

Broadly speaking, there are three main advantages to being on a study:

1. The evolution of new knowledge that may help others know what is the best available treatment for their condition in the future.
2. An individual on a study may get access to a better (more effective or less toxic) new treatment than is currently available outside of a clinical study. However, it is important to remember that a new treatment may NOT be better than what is already out there (otherwise we wouldn’t need to do the trial to prove it). It is also important to remember that, if you are considering a randomized study (see below), you may end up getting the same standard treatment that you would get off-study and not getting the new treatment at all.
3. Being in a clinical study involves forming a close relationship with a dedicated team of experts focused on your care that may bring many general health benefits – such as having a larger number of named individuals to contact for help or advice, or spotting and acting on other conditions, symptoms or side-effects earlier than might happen with standard medical care. For this reason, I clearly recall one trial participant commenting that in her clinical trial she

didn't feel at all like a guinea pig, but more like a prize poodle - with her own entourage of people fussing over her and making sure everything was just as good as it could possibly be.


8) How do I know if a particular trial is a dumb idea or not?

Despite other reasons, most of us will still only be considering a trial for the express reason of getting access to something new. So how do we tell if new is better? When you're not a doctor or a molecular biologist, how do you tell if a trial is looking at something promising and that it's not just some crazy idea that could be wasting your time?

Firstly, we should be reassured that all clinical trials, in the USA and in most other developed countries, are very carefully regulated. Since the Nuremberg trials of the Nazis', international consensus on how clinical trials should be conducted has existed. International guidelines, for example within something called the Declaration of Helsinki, are regularly updated and expected to be followed. For an individual trial, once the trial is written and before any patient can be entered onto the study, it has to be approved by a series of local committees – usually involving some kind of scientific review and some kind of ethical review to confirm that it makes sense and is in concordance with such international guidelines. If it involves a new drug, then it also has to encompassed within an Investigational New Drug (IND) listing registered with the US Food and Drug Administration (FDA). So crazy ideas for clinical trials, in theory, shouldn't get anywhere near you.

However, it is still vitally important to ask your doctor two questions about any particular study:

1. ***How much is known about this new treatment?***
2. ***What are my options if I don't go on this study?***

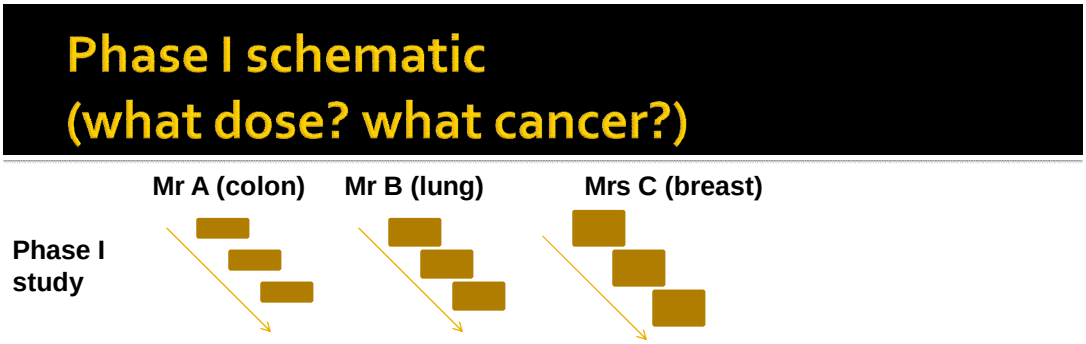
More than almost anything else, the answers you get to these simple questions will help you to decide if a clinical trial in a particular setting is really the right thing for you to participate in or not. So let's deal with each in turn:

8a) What is known about this treatment? – Phases I, II and III.

Whether a study is labeled as a Phase I, Phase II or Phase III study generates a lot of debate. In reality it is not that big a deal. All the Phase of the study tells you is how much is known about the drug, and what being in the study might involve in terms of intensity of visits and chances of it being a randomized study – in and of itself it doesn't tell you whether a drug is better or worse than anything else. In the hands of an expert the right drug for you may be accessed through any Phase of clinical trials.

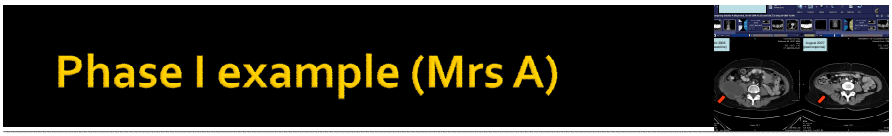
i) Phase I studies:

All drugs, when they are first given to humans, have to explore the correct dose to give – either on their own or in combination with other drugs – these dose-finding studies are called Phase I studies. Because they happen early on in the life of a new drug, there are more unknowns than in later Phase studies, and they are, by definition, the most experimental of studies. Phase I studies tend to be open to anyone with any type of advanced cancer at any line of therapy. Traditionally, they were for those individuals who had exhausted most, perhaps even all, standard treatments. However, in recent years, as specifically targeted drugs that may have particular promise in certain diseases have been developed, in some situations Phase I studies of new drugs, or new drugs in combination with established first-line treatments, may be considered much earlier on in the treatment journey of some individuals.



Small studies:
-Most experimental
-May be first time drug tried in humans
-Used to determine dose and side effects
(different patients get different doses)
-Any advanced cancer
-Any line of treatment
-Must be relatively fit to cope with the unexpected

As Phase I studies are dose-finding studies, participants who enter the study when it first opens will get a lower dose of drug than participants who enter at a later time point. In general, the dose of the drug is increased with each new group of participants entering the study, with an individual tending to stick at the dose they started on. Some people worry whether, if they are in the first few dose levels, they will get effective doses of the drug. On the other hand, if you are in the last few dose levels, people worry about whether they will get too much in the way of side-effects. There isn't a simple response to reassure participants as to these worries. However, it is important to note that some of the newest drugs can achieve efficacy at levels well below those that produce side-effects. Also, to remember that side effects are very carefully monitored at all times during these studies, to try and ultimately choose a tolerable dose to take forward to other studies, not an intolerable one. Participants have to be fairly fit to enter Phase I studies in order to cope with the unexpected. Also, the number of study-specific visits and tests tend to be more than in any Phase of clinical studies. In general, observations and tests are more intensive at the start of the study. Then, after about a month on study, they become much less frequent as it is clear at that point how well you are tolerating the treatment. For safety reasons, after a certain number of patients start at a particular dose there is usually an observation period (about 3 weeks) during which they are treated and when no one else can join the study, until it is clear how well that particular dose level is tolerated. All patients on all Phases of clinical studies should have routine scans or other assessments to confirm that their disease is being kept under control or is responding to treatment. If the drug is not working for you, or you cannot tolerate the drug, usually you will come off the study and return to the three-way decision point outlined above with regard to what you should do next.

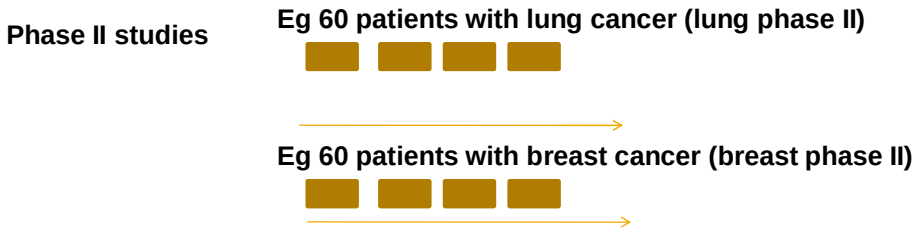


- Advanced sarcoma
- Exhausted standard chemotherapy
- Came to UCCC Phase I practice
- One of the first 50 people to try experimental drug
- Seen every week for the first month, now every few months
- Possible side-effects: intermittent fatigue; previous area of radiotherapy became inflammed
- Activity: Slow progressive shrinkage of tumors, great disease control for almost 2 years now

ii) Phase II Studies

Once a Phase I study is complete, the drug - at the doses determined as appropriate to take forward based on the results of the Phase I study – is then explored in a series of Phase II studies to get a good feel for its activity in different cancers at that dose. Of note, if you started on the Phase I study and the drug is still working for you, you stay in the Phase I study. It is the drug which expands to start a new study, not you. Within Phase II studies all patients receive the same dose of drug and, because more is known about the side effects and tolerability of the drug, the fitness requirements for entry tend to get more relaxed and the number of study-specific visits and tests also get less. However, at this point the manufacturer of the drug is starting to look for a specific license for the drug, so Phase II studies are usually restricted both by tumor type (there may be several parallel Phase II studies, each in a different tumor type) and by line of therapy (usually first, second or third line of therapy, but not beyond this).

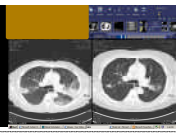
Phase II schematic
(does it work in a specific cancer?)



Medium sized studies:
-Dose determined from phase I
-Several phase II studies for a drug, each in a different advanced cancer
-More restricted by line of treatment (usually 1st-3rd line)
-Fitness constraints a little more relaxed
-May be randomized compared to standard treatment to get flavor of differences in side effects and anticancer activity

Phase II studies may be randomized (see below), comparing two different doses of the same drug or different treatment regimens, or to get a first look at the new treatment compared to some standard treatment. However, although randomization is becoming more common, most Phase II studies are still not randomized. Instead, most randomized studies are Phase III studies.

Phase II example (Mrs B)



- Advanced lung cancer that had responded to one treatment but then grew again
- Phase II study looking at new tablet that looks promising in lung cancer (second line treatment)
- Dose determined from previous phase I study
- Side effects: rash and diarrhea
- Activity: Dramatic improvement in scans, came off oxygen, and good disease control for 2 years to date

iii) Phase III Studies:

Once a drug has (a) its dose determined from a Phase I study and (b) some signal as to which tumor type it might work in from the Phase II studies, in order to get a license from the FDA, it has to be shown to be at least as good or better than what is already available for treating a particular cancer. This kind of large comparative study, almost always randomized against some current standard treatment, is called a Phase III study.

Phase III schematic (does it work better than what we have?)

Phase III Studies (randomized)

Eg 100s of patients with breast cancer comparing standard treatment to new treatment

<u>Very large studies:</u>
-Drug looking for a specific FDA licensed indication
-Very restricted by line of treatment (usually 1st-2nd line)
-Fitness constraints more relaxed
-Always randomized compared to standard treatment

As this may be the final step before a drug is licensed, Phase III studies are the most restrictive in terms of tumor type and line of therapy. Although, as they are trying to develop something for use in the wider community and knowledge about the specific new drug will have increased from the time of the earlier studies, they may be less restrictive in terms of general fitness. Everyday pilots, in addition to the very Top Gun test-pilots, may be eligible to participate.

- First-line treatment of advanced lung cancer.
- Standard chemotherapy alone or with addition of Bevacizumab ('Avastin' - affects blood vessels)
- Randomized study
- Side effects – severe bleeding in 1-2% of patients who got bevacizumab
- But addition of bevacizumab improved overall survival rate
- Overall good outweighs bad = new license/new standard of care!

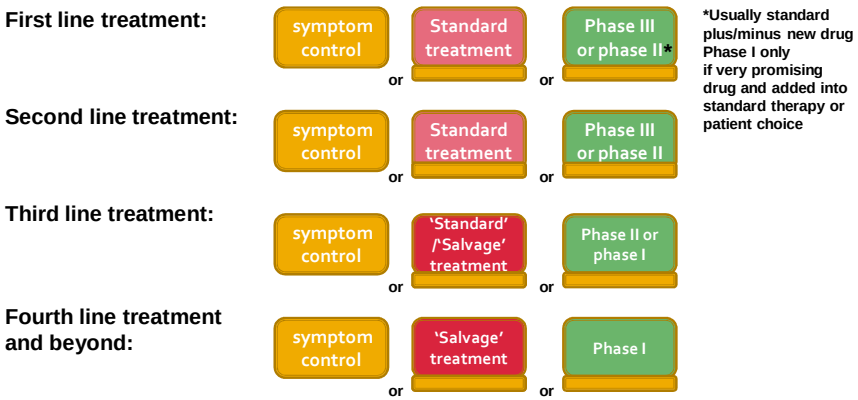
In general, if you are in the first or second line of treatment for advanced cancer, you will mostly be considering Phase II or Phase III studies. If you are at third line or beyond you will mostly only have Phase I studies open to you. However, as mentioned previously, the Phase of the study really only tells you how much is already known about the drug and the level of intensive investigation/extra visits/extra tests and/or the chances of the study being a randomized study. It doesn't tell you if a drug will work or not and an expert physician may seek out the best drug for you in studies of any Phase. Being cared for in a center where the doctors have expert knowledge of your disease and a large palette of available studies to choose from in order to select the best drug for you at each line of treatment is therefore something to be strongly considered. If you have the means, the insurance, the fitness and/or the inclination to travel, then a large list of clinical trials – complete with a search engine to allow you to narrow down to your particular tumor type and line of therapy – can be found at www.clinicaltrials.gov. Your physician will not know every trial that is going on around the country, so it's perfectly acceptable to do some homework in your own time and ask your doctor's opinion on the different studies. However, unless there is a true breakthrough out there that has to be searched out and is only available within a clinical trial, most people do not travel too far for clinical trials – especially if the trial they were considering traveling for is a randomized trial with a chance that they could end up getting exactly the same as they would have got nearer to home.

Phase I-III – does it matter?

Tells you about:
- Level of data
- Chances for extra research tests
- Chances for randomization

It does not tell you for certain:
- If it will work/not work for you
- If you will get side-effects, or what they will be

Treatment options by line of therapy (Advanced Cancer Generalization)



In the Figure above, 'salvage' treatment usually means other kinds of 'traditional' chemotherapy that are available, but that may not be formally licensed in your particular cancer. Sometimes there is still a 'chink' in the cancer's armor that these different variants of traditional chemotherapy can exploit. However, sometimes cancers develop cross-resistance to many different chemotherapy drugs, such that increasing lines of traditional salvage chemotherapy start to manifest the law of 'diminishing returns'. My own opinion is that, sometime before you start exploring traditional drugs that are somehow 'left in the cupboard,' you should have at least explored your options for treatment within clinical trials too. The drugs left in the cupboard will still be there for you to explore after considering clinical trials, but you may be excluded from some clinical trials if you've had too many different chemotherapies, or your fitness has slipped too much while you are working your way through these salvage treatments.

8b)What are my options if I don't go into this study? If it's a randomized study, what might I be randomized to?

Having got your head around what a clinical study is, what informed consent means, and whether you might qualify for a study, the single most important question to understand is what your treatment options are if you don't go on the study.

In part, this is to help you finalize your thoughts on whether you want to enter the study – how many visits and tests would you have if you weren't on the study, is there a standard treatment that you would miss out on if you went on the study, etc. However, the most important reason to ask this question is if this is a randomized study.

More than almost anything else, randomization – a computer tossing a coin and determining which of two or more different treatments you will end up getting – causes the most stress when an individual is trying to decide on whether to enter a clinical study or not. When it's a placebo- controlled study – i.e. you may be getting a dummy treatment instead of the real treatment – this just increases the stress levels even more.

So why do studies bother with randomization? The short answer is it's the only way to be certain if a new treatment is really better or not. People talk about the 'placebo effect', when our minds make us think we're feeling better (or sometimes worse) after taking a particular treatment, even when it's just a sugar tablet. So if you want to really prove to the FDA that your drug actually works, you have to eventually compare it to something in a head-to-head, pepsi-cola versus coca-cola kind of challenge. Placebos (which can be dummy tablets or dummy injections) are sometimes used to distinguish drug effects from the side effects of just taking any kind of tablet or injection, and to minimize the risks of people withdrawing consent from a randomized study if they don't end up randomized to the arm they want. Although the possibilities of randomization and of placebos can be stressful things, they do have their roles to play in helping us all out in terms of truly determining the next best treatment. To deal with these stresses though, consider the following checklist to ask your doctor about any study:

1. Is this a randomized study? If it is, you have to be told what the possible treatments are and your numerical chances of being allocated to each treatment 'arm'.
2. If it is a randomized study, is there a placebo arm? If there is, as part of informed consent you have to be told this in advance, and your numerical chances of getting the placebo (e.g. 50:50).
3. If there is a placebo – is it the whole treatment (i.e. could you be getting just symptom control) or does everyone get some kind of anti-cancer treatment and the placebo or study drug is then just added in on top? Either is possible,

mostly depending on whether there is a perceived standard that everyone should be getting at that line of treatment.

4. If there is a placebo arm to the study and the drug doesn't work – will your doctor be able to find out (quickly) if you did get the placebo and offer you the other treatment? This is called 'unblinding' and 'crossing over'. Its availability varies but is a nice aspect of a study if it's there – a second chance.
5. If there is no placebo, just a comparison of two different treatments – pepsi-cola versus coca-cola – it is VERY important to clarify if the 'standard' treatment arm is the same standard that you would be offered if you weren't on the study.

I cannot emphasize this last point enough – On a simple level, let's say there are normally two different standard chemotherapies, both equally effective at treating your cancer, but one is given half as often as the other (less visits) but it also makes your hair fall out, whereas the other one doesn't. If you weren't in the study, you would have a choice between the pros and cons of these two treatments. Within a randomized study of new drug X added into standard chemotherapy, it is likely that only one of these standard regimens will have been chosen. In the study, you may be randomized to standard chemo (the one that is given less frequently, but that makes your hair fall out) or to the same standard chemotherapy plus new drug X. Here, by knowing what your options 'off-study' are, you can make the choice of whether you want to go in the study to potentially have the benefits of the new drug and/or the general benefits of being in a study, but limit your choice of the standard chemotherapy you receive to only the one that makes you lose your hair (which may or may not be a big deal to you – but, either way, it should be part of your informed decision-making process).

On a more complex and more serious level, knowing what your options off study are is incredibly important because randomized studies can sometimes get out of date while they are still going on. Let me explain what I mean by this. Let's say the standard treatment is chemotherapy with drugs A and B combined, and you are being offered a randomized Phase III study of A plus B compared to A plus B plus X (where X is a new drug). Phase III studies require hundreds, sometimes thousands, of patients to be recruited and their results analyzed to determine whether the addition of X (or its equivalent) is worthwhile in terms of its extra side effects and any extra anti-cancer efficacy. If you look at www.clinicaltrials.gov or surf the internet at all looking for anti-cancer trials you will see that there are many different trials all going on at the same time. So what happens if, over night, A plus B is no longer the appropriate standard? What if someone finds out either that A plus B is no longer safe for people like you, or that C plus D is actually a better treatment than A plus B for your particular kind of cancer? Your planned randomized study may still be going on – it is only if its way 'out

there' that the FDA will shut it down – however, the new information is something that you probably would want to know to weigh up whether the chances of getting access to new drug X with A plus B, still outweighs the new information relating to C plus D as the new standard treatment for your disease. Therefore, the single most important thing to do is:

Ask your doctor: "If I don't go into this study, what would you treat me with?"

Only when you have asked this question (and are happy with the answer!) can you truly weigh up the pros and cons of being entered into a randomized clinical study.

9) What if the 'best' treatment is redefined while I am on a study – can I, or should I, change treatment?

This is a tough one to answer. It is imagining a situation in which you have started on a treatment plan (which may, or may not, be part of a study) and suddenly there is a breakthrough announced that there is another treatment, or something added into the kind of treatment you are already on, that may be better than your current treatment plan. I think here I would discuss it with your doctor and, if it's safe and you are not on a trial, ask about whether you can 'upgrade' to the new standard. If you are on a clinical trial, you probably have less flexibility as the study will probably not update that quickly. Instead you have to decide if the advance could make enough of a difference that you should consider withdrawing from the study to change to this new standard. The things to think about here are firstly, how much longer you may have to go on the study treatment, particularly, if it is only for a defined number of cycles. If you only have one more cycle to go there is probably no point jumping ship at this point. Secondly, to recognize that if in the clinical trial you are not just on the original standard treatment, but on the standard plus something else, you won't know if the 'new standard' is, in fact, better than the even 'newer' regimen that you are being treated with. If you are on a randomized study then you need to ask if you are definitely getting the new treatment or not. If you and your doctor don't know (i.e. if it is a 'blinded' placebo-controlled study) you would have to weigh up the chances that you are actually receiving the study treatment against the pros and cons of coming off the study to switch to the new standard that has just been defined. In reality, these situations don't come up very often and in the past the 'new' standards, at least in my experience, have not been such big breakthroughs that I usually recommend changing horses mid-stream. However, it's important to have the discussion and to make the decision you feel most comfortable with. If you've already completed the treatment, changes to what that standard was will cause you some stress, but there's not much you can do. While it may be appropriate

for you to try the new treatment in a later line of therapy, you cannot change what has already happened.

10) If I go on a study how long am I on the study for?

In general you would stay being treated within a study until one of the following occurred:

1. The drug was proven to not be working for you (usually on the basis of some unfavorable change in your disease, for example demonstrating tumor growth on your scans)
2. The side effects of the drug meant that it wasn't tolerable for you – Sometimes the dose of the study drug can be reduced and retried at the lower dose, but after a couple of dose reductions, if you're still having problems most people would have to walk away from a drug that they just couldn't take.
3. You have completed a fixed number of cycles of treatment predefined by the study – for example 4 to 6 cycles of many traditional chemotherapies is about all that most people can tolerate and about all the good that can be done by the chemotherapy is completed within that time. However, this is not the case for some of the newer treatments, which are both better tolerated and work in a very different way from traditional chemotherapy. For example, defining a fixed numbers of cycles would be very unusual for most of the latest, so-called targeted agents.
4. You change your mind and withdraw your consent.

However, even if you are not being treated, most studies will still be collecting some information on you. For example, the time it takes for your cancer to start to grow again, whether your cancer has returned or not, or simply that you're still alive and kicking. Laboratory tests on blood samples or tumor specimens that you may have given permission for may also be ongoing for years after you have completed treatment in order to determine, in retrospect, what the people who did well or who did badly had in common on a molecular level.

Clinical Trials Decision Guide

- Do I qualify?
- Will my insurance cover the standards of care?

- What are my options if I don't go in this study?
- What is known about the side-effects?
- What has been seen so far to make you think this may or may not work?
- How many extra visits/tests are involved?

(answers to most of above will vary with Phase I-III)

Randomized Study Decision Guide

- Is this a randomized study? (will I definitely get the new treatment?)

- If this is a randomized study will I know which treatment I am getting? (is there a placebo)

- If this is a randomized study and I get the standard treatment is this any different from what you would give me if I wasn't in the study? (v. important!)

11) In summary:

Clinical trials are essential for progress, to help each of us know the best treatment for different diseases at any given point in time. Sometimes, the information we generate

from being involved in clinical trials helps others. Sometimes, by being involved in the trial ourselves, there are general benefits from the more intensive care received. Sometimes, there are specific benefits if the trial involves access to a new treatment that actually is better. However, it is important to realize that new is not always better (otherwise we wouldn't need to do the trials). Also, to know that, in randomized trials, you may not automatically get the new treatment, or know if you are getting it or not.

Deciding whether you enter a trial can be a stressful task and the best thing to do is to ask lots of questions, seek opinions from friends, relatives or other professionals and understand the principles of informed consent – you should never feel like a guinea pig – guinea pigs do not get a choice – you always do – and you can change your mind.

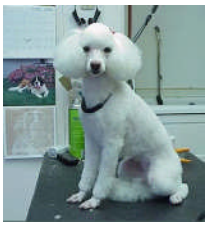
Ideally, as there are always some unknowns associated with being in a clinical trial involving any new treatment – you should be fit enough to cope with some level of unexpected side-effects, just in case you are the one person in which they do occur. Being in a trial means forming a close working relationship with the doctors and other staff associated with the study – good communication about what the study involves and how you are doing on the study – just like a test-pilot's relationship with the control tower. Sometimes, being in a trial, even if you don't get one or other treatment, is beneficial in itself just because of the close relationship you form with your medical team – becoming one of the 'Prize Poodles' described in the title of this paper.

Entry into a trial is sometimes the right thing to do and sometimes not – and that may change over time - in part with the specifics of the trial, the current alternatives available and where you are in your own treatment journey. However, it is often something to at least consider discussing with an expert every time you find yourself at the recurring 3-way treatment decision point described earlier.

Without the test-pilots and prize poodles (and hopefully not too many guinea pigs) who have gone before, we would still be listening to snake oil salesmen on the back of wagons. Within the last decade, I have already seen amazing things start to happen in our fight against many different types of cancer – progress that will increase as we all work towards the same goal: doctors, scientists, drug companies, study teams, test pilots and prize poodles all pulling together to make cancer a footnote not a headline in people's lives in the future.

Listings:
Central national database -
www.clinicaltrials.gov

Thank you to all the Test Pilots and Prize Poodles who continue to help define (and redefine) the State of the Art in Cancer Care each and every year



About the Author:

D. Ross Camidge qualified in Medicine from Oxford University in the UK, with a PhD in Molecular Biology from Cambridge University. He trained in both Medical Oncology and Clinical Pharmacology and is an expert in the development of new anti-cancer drugs. He joined the University of Colorado in 2005, initially as a Visiting Professor and then as full-time Faculty from October 2007. He is the Clinical Director of the Lung Cancer Program, as well as being a specialist Attending Physician within the Developmental Therapeutics Program, at the University of Colorado.