WEBINAR TRANSCRIPTION:
THE "CANCER INDUSTRY" AND PHARMACEUTICAL POLICY IN GERMANY

Presentation by Dr. Karl Lauterbach, MD, ScD, MPH, January 2016

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THE "CANCER INDUSTRY" AND PHARMACEUTICAL POLICY IN GERMANY

January 27, 2016

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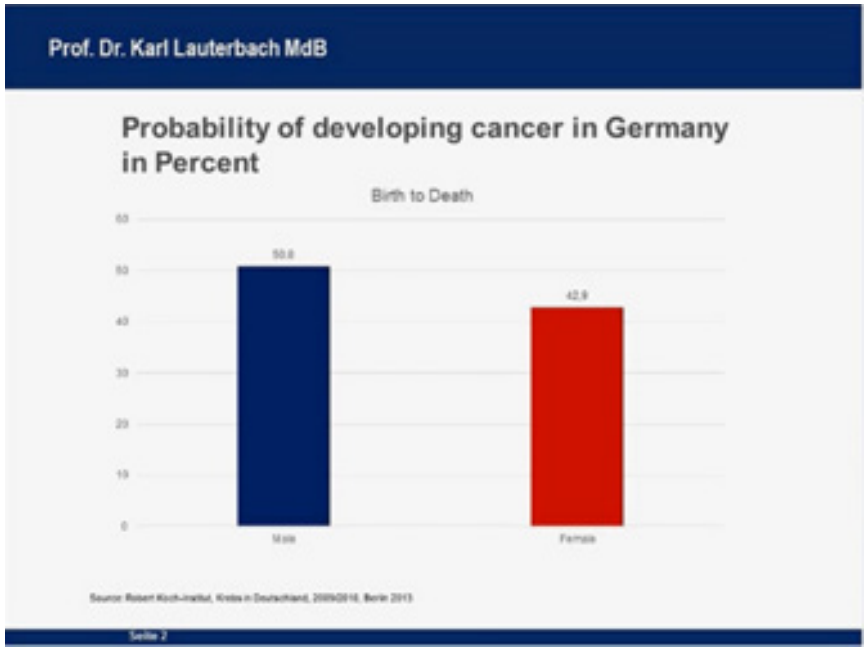
(Min 02:43)

I will start by explaining why the topics of cancer, the cancer industry, and also pharmaceutical policy regarding cancer, are important topics in Germany, as well as in the U.S., in Europe and in many Latin American countries. These topics will become even more important in the future. I will explain why I think this is the case and what the challenges and the possibilities of the future will be.

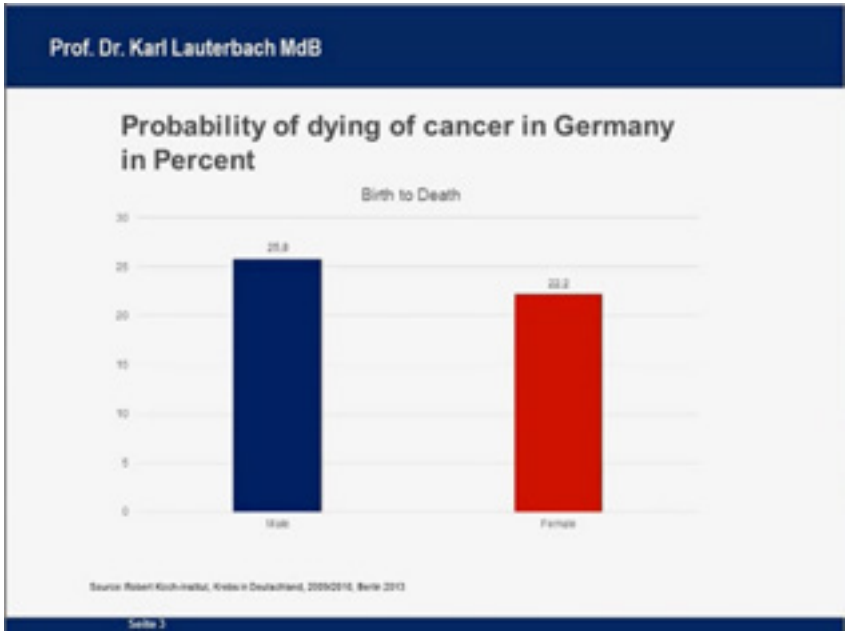
I have written a book on the topic, which has not yet been translated into English, but the translation is currently under negotiation. The information included in this presentation is further developed in my book. I will also soon publish a couple of articles on the topic, so that the information will be better available to the English speaking community. The biggest issue regarding cancer in Germany, Europe, and in many other countries, is that cancer is more difficult to prevent and also more difficult to treat than many other diseases, in particular cardiovascular diseases. The risk factors for cardiovascular diseases are known by now, and many of them can be tackled very efficiently. For example, hypertension is a mayor risk factor for strokes and also for cardiovascular diseases in terms of coronary heart disease and heart attacks. Yet, we now have very important, effective and fairly inexpensive drugs available for the treatment of hypertension. In terms of hypertension it is important that we treat as many people as possible. For those patients that we treat, we have a very successful treatment available, and the same goes for patients who have higher than normal cholesterol levels, who have high triglyceride or patients who are overweight. All of the risk factors that are important for heart diseases and for strokes are well known, can be treated well and there are many ways to prevent them. That means that in countries everywhere around the world, in comparison to cardiovascular diseases, cancer will become more important because cancer is much more difficult to prevent and to treat. I will come to that in a moment.



PROBABILITY OF DEVELOPING CANCER IN GERMANY IN PERCENT

(Min 05:54)

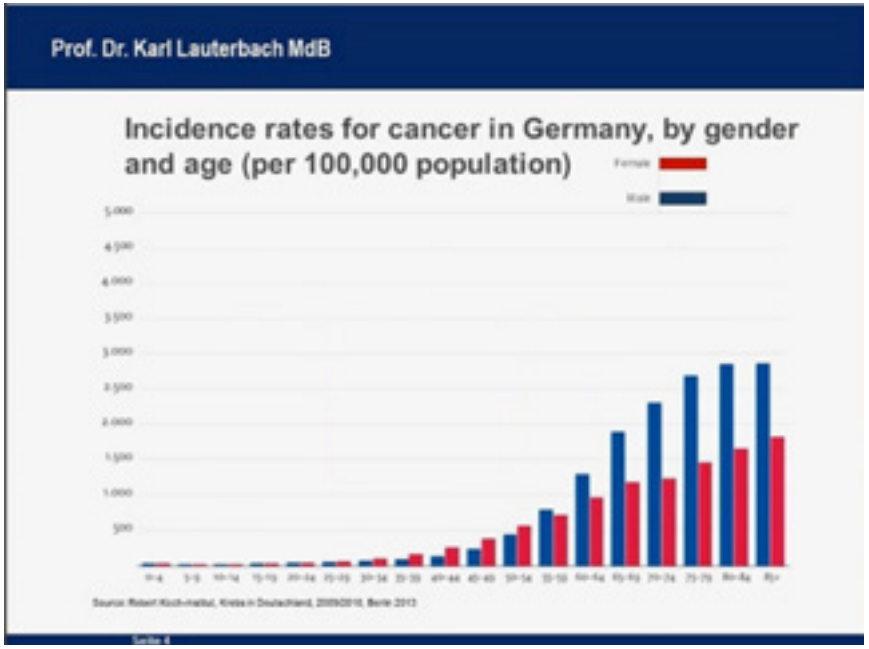
If we look at the current probability of developing cancer in Germany, we see that at the moment of birth, the lifetime risk of developing cancer for males is 50%, and for females it is 43%. The likelihood is increasing so we can expect that in the future one out of two inhabitants of Germany will develop cancer. The situation is quite similar in all European countries. Germany is not an exception but the rule. The same is also the case in the U.S. and in many Latin American countries. Even in China, in India, in many Asian countries and in Africa, cancer is becoming way more prevalent. Cancer is the most rapidly increasing disease of our times and we face major challenges in terms of prevention and in terms of treatment.



PROBABILITY OF DYING OF CANCER IN GERMANY, IN PERCENT

(Min 07:19)

The third slide shows the probability of dying of cancer in Germany as of now. If you look at the birth cohort currently born, about one in four of all males and between one and five, and one and four of all females, do not only get cancer but die from cancer. So all factors taken into consideration, everyone in two will get cancer and one in four will die from cancer. Half of the cancer cases are still not curable at the moment. About 25 percent of the population will die from cancer in Germany. That is between 200.000 and 250.000 patients per year, with an increase in numbers. This number will further increase in the future.



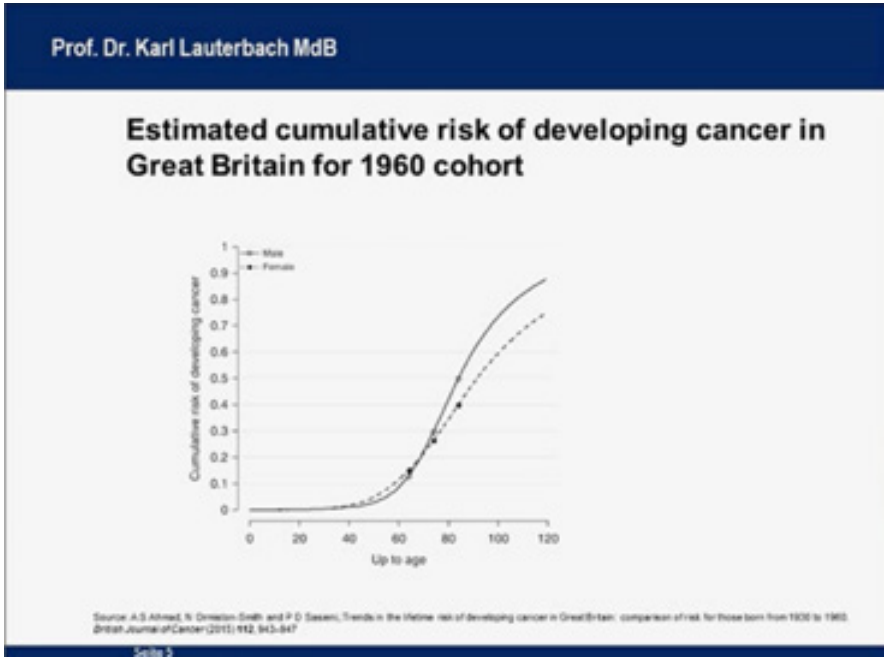
INCIDENCE RATES FOR CANCER IN GERMANY, BY GENDER AND AGE (PER 100,000 POPULATION)

(Min 08:23)

Slide four shows this in more detail. If you look at the incidence rates of cancer in Germany by gender and age,

per 100.000 people, you see that cancer incidence is rapidly increasing with advancing age. In comparison to other diseases, for example diabetes or hypertension, cancer depends much more on the ageing of the population. It is true that there is cancer in all age groups even for children and people who are younger than 50 years. Nevertheless, all things considered, most cancer cases occur in the age group 50 and higher. There is an exponential increase in the number of cancer cases between the age of 35 and 75. The curve is flattening thereafter a little bit, but this is also the case because many people who develop cancer at the age of 75, have already died from cancer.

The second problem is that the younger someone develops cancer, the more aggressive the cancer typically is and the higher the likelihood that that person dies from cancer. Obviously, this is an overgeneralization because I am speaking of cancer and the situation is actually quite different from cancer type to cancer type and from the advancement of the cancer at the moment when it is detected. If you look at all cancers by gender, you will see an age increase and this is important because it determines how many people would die from cancer if life expectancy would continue to increase. A very important study of this was published in 2015 in the British Journal of Cancer written by Ahmad, Ormiston-Smith and Sasieni.



ESTIMATED CUMULATIVE RISK OF DEVELOPING CANCER IN GREAT BRITAIN FOR 1960 COHORT

(Min 10:37)

This slide shows how many people would develop cancer if the life expectancy was to increase, according to what we

currently know about the incidence rates of cancer and how cancer is developed. We see that if life expectancy would increase to 100 years, more than 80% of all males would develop cancer. If the life expectancy would increase to 110 years, which is not completely unthinkable, the incidence rate of cancer would increase in such a way, that lifetime risk for males would almost reach 90 percent. Cancer seems to be the only major killing disease that we cannot escape by getting older. An increase in life expectancy will lead to more cases and more people developing cancer. This is particular also a major problem for the Latin American countries, where the life expectancy has recently increased tremendously. We will also see a major increase in the number of new cancer cases, especially also of severe cancer cases and cancer death. That is one of the reasons why this topic may be of some relevance to you.

HALLMARKS OF CANCER

(Min 12:23)

Let us look at the way cancer works. I apologize for bringing up a couple of medical and genetic issues. Even for those who are not trained in medicine or in modern day genetics, it is important to understand the major changes that occur in the body when cancer develops. This is important in order to explain how we try to prevent cancer and how we want to treat cancer. It is interesting that cancer was not a well understood disease even until the late 80s of the last century.

Cancer is a disease that has been around for thousands of years. Most animals also get cancer, despite the fact that they get different cancers and sometimes with a lower incidence rate. Cancer has been known for centuries. Even in the medieval ages people developed cancer. Despite the fact that cancer was around for so long, the way cancer works, is only known for the last 25 or 30 years. We have made major advances in the understanding of cancer, which made it possible to develop treatments which I will come to in a moment.

The hallmarks of cancer are the changes that occur in those cells that become cancerous cells and in the tumors. These hallmarks are universal, which means, that they are found in all cancers. They are commonalities of all cancers and they play a role in causing cancer and making cancer preventable in some cases. They also play a big role in the treatment of cancer. These hallmarks were first developed by researchers working at the MIT institute in Cambridge, U.S., Robert Weinberg and his colleague Hanahan, who is now working in Switzerland, but who has also spent many years at MIT teaching. These were the pioneers that developed the hallmarks of cancer. I am basically using the way they originally presented the hallmarks of cancer, to organize my talk. Obviously, new research has been developed since then, and there are many other and more modern ways to describe these attributes. Yet, this is still a good way to get us started and to understand cancer and the challenges of prevention and treatment.

The first hallmark is the ‘limitless replicative potential’. A non-cancer cell divides a number of times and then the cell simply dies. A cancer cell can escape this process and can grow and divide forever. This is called cell immortality. We can learn a lot about immortality and avoiding ageing from cancer cells, because cancer cells can survive even if the person, who was once the host of these cells, is long dead. We still have cancer cells that are alive and divide of patients that died more than 50 years ago from cancer. If the circumstances of division are still there, if there is an opportunity to get nutrition, oxygen and blood supply, then cancer cells of a particular patient can continue to live and grow even if the person is long dead. We also know that cancer cells are insensitive to anti-growth signals. If a typical cell is not working well, or is dividing too quickly, then signals come out from this cell that helps the cell not to divide or grow any more. In cancer cells these signals are not working. The cells are not sensitive to those signals. They are often called suppressing signals, or suppressor genes. They produce proteins which give a signal that cells should not divide any more or grow any more. In cancer cells these oppressor signals are not working and sometimes they are not even

produced, due to genetic changes in the cells which stop the typical process that limits growth. Cancer cells grow. They divide and become more and they do not get the signals to stop growing, which would typically work in a non-cancer cell. The third hallmark describes how cancer cells appear to be self-sufficient. Typically cells only grow if there is a stimulus from the outside for the cell to grow. For example, if you have a cut or a wound, skin cells get a signal from the blood that there is a wound. This triggers a growth signal and then the skin cells divide and close the wound. This stimulus comes from outside the cell. For example, the blood signals from the wound give a signal to the skin cells to grow. In cancer cells the self-sufficiency means that the cell gives the signal to grow from inside. It does not even depend on any stimulus from the outside, like a wound, or other growth signals in the body. For example, master cells grow if they get a signal that more muscle power is needed because you work out. In cancer cells even if there is no signals, the signal to grow comes from inside. It is therefore a self-sufficient cell with respect to growth signals. If the tumor grows, obviously, it needs blood vessels because otherwise there cannot be enough blood supply to nourish the tumor. A cancer cell and also a tumor need oxygen, nutrition, proteins, and minerals in the blood in order to be able to survive. If a cancer is growing, very soon it is too big to get that type of nutrition and blood from the blood vessels around. It is like a new organ of its own which is not linked up well with the blood vessel that provides the nutrition and the oxygen for the organs. In order to be self-sufficient cancer tumors develop their own basic blood vessel system. New blood vessels are formed in the tumor, and in order to do so, cancer cells have genetic privileges and angiogenetic signal waves that help the cell and the tumor to develop new blood vessels. They are like a cell system which reorganizes its own blood and nutrition supply. This maintains the tumor, even under conditions, where the oxygen and nutrition supply from other sources would be too low for the cancer to survive. This is very important. Cancer cells provide their own blood supply if they need it.

HALLMARKS OF CANCER

(Min 22:16)

If cells are not functioning because they are damaged, or they do not do what they are supposed to do, normal cells commit suicide. This is called apoptosis (programmed cell death). Cell suicide is a mechanism with which the body makes sure, that those cells that are not working, do not survive. They should not survive for two reasons. First of all, because they are not needed. Why should a cell survive, which does not function in the body? And also if a cell survives and does not work, it may actually work in the wrong direction. The body has a system which helps to protect the body against cells that do not work properly. This is called apoptosis. With cancer cells this mechanism does not work. Cancer cells obviously do not work like they should in the organism from which the come from. For example, a cancer cell which develops from the kidney is not doing the work that the kidney cells should typically do. Normally, it would then die because of programed cell death. Nevertheless, for cancer cells in the kidney the suicide mechanism does not work, despite the fact that this cell does not function as a kidney cell any more.

The sixth hallmark is tissue invasion and metastasis. Everyone has heard about metastasis. It is also called a ‘daughter tumor’, meaning that it is a local tumor which develops in a faraway tissue which is coming from the original cancer tumor. Cancer cells break away from the primary tumor, from the organ in which the primary tumor is living in, and develop their own metastasis in the surrounding tissues, also in distant body parts. This is what nine out of ten cancer patients die from. If a cancer patient dies, only in one of ten cases this person does not die from metastasis. This is a very important and very aggressive hallmark of most cancers. Not all cancers develop metastasis, but most cancers do. Ultimately, it is always important to look at the immune system. The immune system typically works against everything that in the body arrives and is foreign, or has developed in a way that is foreign, despite the fact, that it came from the body. As an example the immune system immediately attacks a foreign object in the body. If you put metal or something artificial into the body, then the immune system tries to destroy it and the process of immunity is set into place.

This is also the case if cells in the body change too much as, for example, in auto-immune diseases. The body attacks its own cells in a way that these cells are no longer recognized as body cells and then the immune system attacks its own

body in order to destroy cells which are body cells but not recognized as such. They are treated by the immune system as foreign cells. This, for example, happens in autoimmune diseases like rheumatoid arthritis, lupus, and also in many cases of asthma. Autoimmune diseases are very wide spread. The cancer cells should be very good candidates to be attacked by the immune system because they are very different from typical body cells. Unfortunately, cancer cells appear to be invisible to the body's immune system. That is the reason why the immune system is not in a position to understand the circumstances to launch a major attack against cancer cells. Cancer cells seem to be able to evade the immune defense of the body. Ultimately, most cancer cells live in very abnormal conditions with low oxygen. The new vessels that they build are not perfectly functioning so they have a deregulated metabolism, which allows them to survive under conditions that are normally not good conditions for cell survival. The deregulated metabolism means that they can survive in surroundings of the body, which are very difficult for cell survival quite generally. This is a complicated mechanism and I am not going into major detail.

NEW CANCER DRUGS – TYROSINE KINASE INHIBITORS

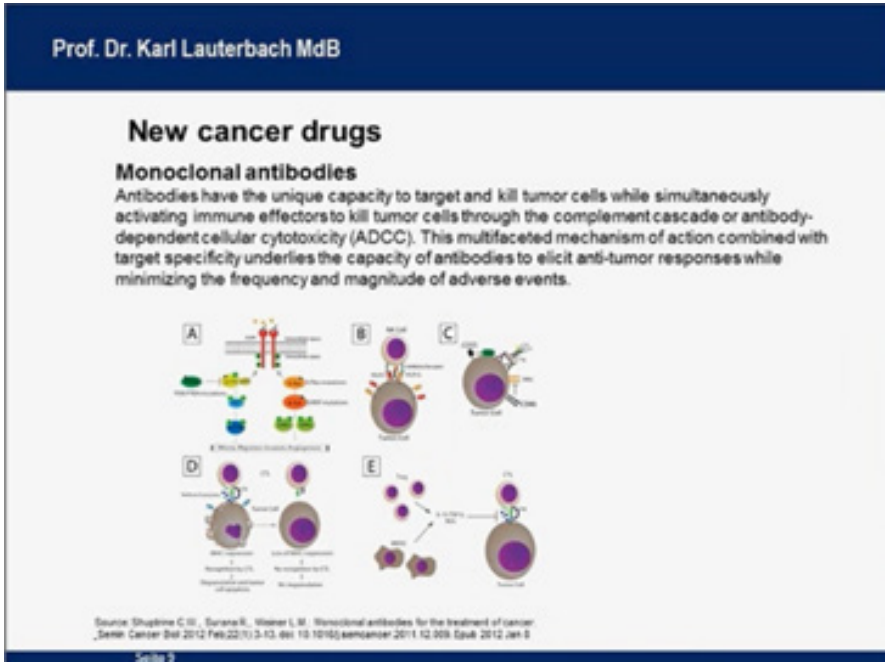
(Min 28:13)

I will only focus on new cancer drugs. I will not focus on chemotherapy, radiation therapy or surgery. I assume that you are familiar with that and it is also not my topic today. My topic is the cancer industry and, in particular, the new drugs in terms of what we can expect from them, how helpful they are, how expensive they will be and what the future will bring.

I will start with Tyrosine kinase inhibitors. Tyrosine kinase inhibitors are a very important form of drug, which focus, on what I earlier called, the immortal growth of the cells. Cells produce their own growth signals and they suppress the signals that limit growth. This is a standard hallmark of all cancer cells and, as we have learned, this is also unique because in all other cells the growth signals either come from the outside or after a while cells die automatically and there is no more growth. In cancer cells there are signals, which indicate the cell to continue to divide. In order to treat this, we need to be able to get into the mechanism, which produces this protein that provides information in the cell to continue to grow. Tyrosine kinase inhibitors are proteins that are small molecules, which go into the cell and try to block the proteins that are crucial in giving the growth signal. A small molecule enters the cell and at some place it gets into touch with a protein that is important for cell growth and in blocking cell proteins. It blocks the growth chain in the cancer cell and therefore the growth of the tumor. Hence, this is a very important group of drugs. The most important and successful drug in cancer treatment in recent years, Imatinib, is actually a tyrosine kinase inhibitor. In rare forms of leukemia there is only one growth signal not working. It is overproducing growth signals all the time and with one particular tyrosine kinase inhibitor, Imatinib (there is also another on the market), you can block this particular protein and therefore you can stop the tumor growth. This was a major success in cancer treatment. Unfortunately, this is a unique success and other cancers have many signals, which are not working, so we need more than one drug to influence more than one signal wave. This drug is also unique as it works in the long run. There is no resistance against the drug that builds up for long periods of time. It is very specific to the growth signal in this form of leukemia and it is also not becoming resistant after a while. Therefore, it works predictably, very well and for a very long time.

Most other tyrosine kinase inhibitors, have different problems and I will explain those in a couple of words. This is very complex. In a developed tumor typically the growth signals that are not working come from many different sources. It is not one growth channel that is not working but many growth channels. Typically, at least five to eight growth channels are not functioning. You would then need a couple of tyrosine kinase inhibitors that get into the cell and at the same time block all of these growth signal chains. This is almost impossible and very often we do not know exactly what type of signal chains are not working in a particular tumor. Knowledge of this is developing very fast, but we typically know one or two, perhaps three cancer growth pathways that are not working. We cannot identify all. Therefore, we do not have enough knowledge and also not sufficient

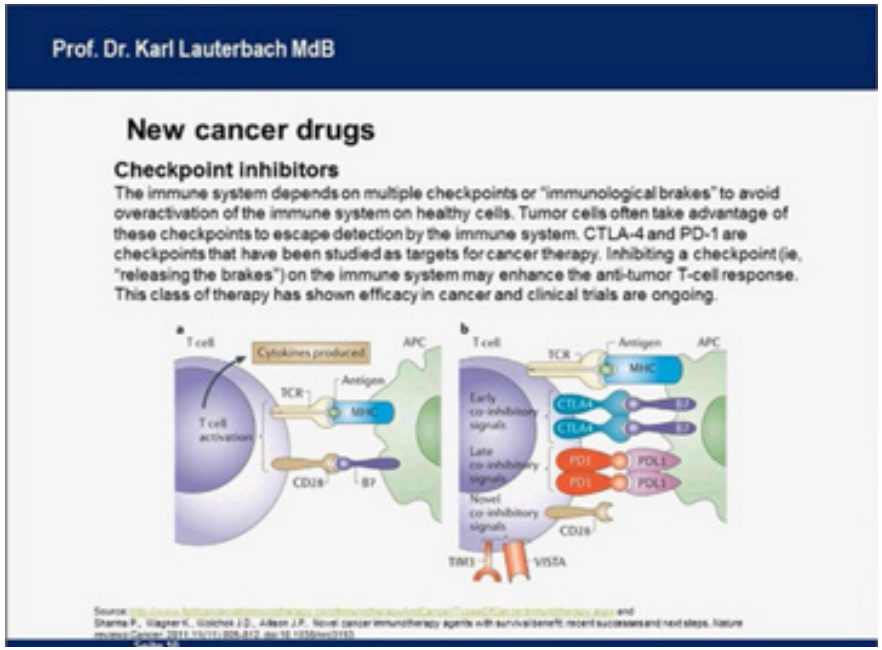
tyrosine kinase inhibitors for particular tumors. As a result, they typically only work in a limited way. They cannot cure the cancer and very often they help only for a while. Yet, they are very successful drugs in particular since they are specific to the cancer cells and do not damage a lot of tissue outside of the cancer cell. If they hit the growth signal they can be very efficient and even if they do not work forever, for the time that they do work, they can improve life expectancy and quality of life substantially. The tyrosine kinase inhibitors are important drugs but they are not perfect drugs for the reasons that I have just tried to outline.



NEW CANCER DRUGS – MONOCLONAL ANTIBODIES

(Min 34:57)

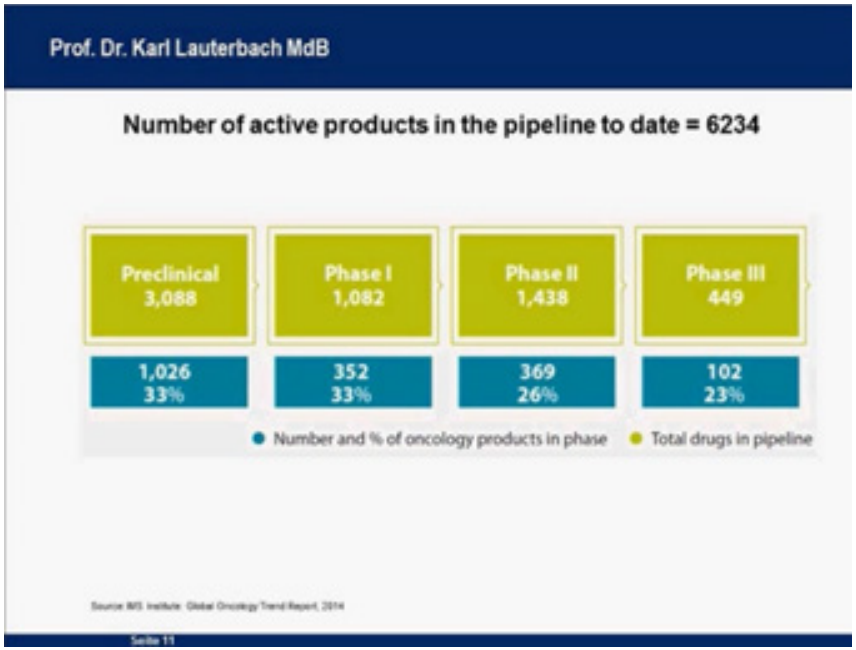
Monoclonal antibodies work on the cell surface. They very often overlap with what I have just described about how tyrosine kinase inhibitors work. Many of the growth chains in the cancer cell start outside of the cell. For example, if cells get together they may give themselves a signal to continue to grow. The monoclonal antibodies, at the cell surface, block this signal inside of the cell by docking at the key outside of the cell, like you open or close a door from outside. Once this door has been closed, inside the growth is no longer taking place. In that sense, monoclonal antibodies can be used both for suppressing tumor growth by giving a signal to those suppressor proteins to come out and do more tumor suppression work, and they can also give growth signals to continue to grow. That is what monoclonal antibodies are used for. In contrast to tyrosine kinase inhibitors, which can be given orally, monoclonal antibodies have to be injected or have to be given by infusion. They are also very important and effective drugs.



NEW CANCER DRUGS – CHECKPOINT INHIBITORS

(Min 36:50)

The third type of drugs are checkpoint inhibitors. Obviously, there is more than these three drug types in cancer research but these are the three most important ones. Checkpoint inhibitors are very important new cancer drugs that have only been developed in the last ten years. They are becoming ever more important. They help the body to recognize the cancer as a foreign cell system. I explained before, that cancer cells manage to fool the immune system by making themselves undetectable. Therefore, they are typically not attacked by the immune system. In the immune system we can find two types of cells: C-cells and P-cells. Both cell types typically do not recognize cancer cells and therefore do not attack them. With the checkpoint inhibitors it is possible to make these cancer cells and the tumors visible to the immune system, and permit an immune attack against these cells. This is a major advance in cancer treatment in particular in one of the deadliest cancers that we know which is melanoma, so called black skin cancer. This is a highly deadly disease if it is advanced. Before the checkpoint inhibitors came out it was almost impossible to treat an advanced melanoma but with these drugs it is now possible to treat this cancer for a long period of time successfully, even if it is advanced. This is an important issue and it is currently the hottest spot in research to find out whether these checkpoint inhibitors can be developed in a way that they are equally successful for other solid tumors, for example, lung cancer, kidney cancer, breast cancer and colon cancer. These are the most important cancers in terms of how many people get these types of cancer and die from them.



NUMBER OF ACTIVE PRODUCTS IN THE PIPELINE TO DATE = 6234

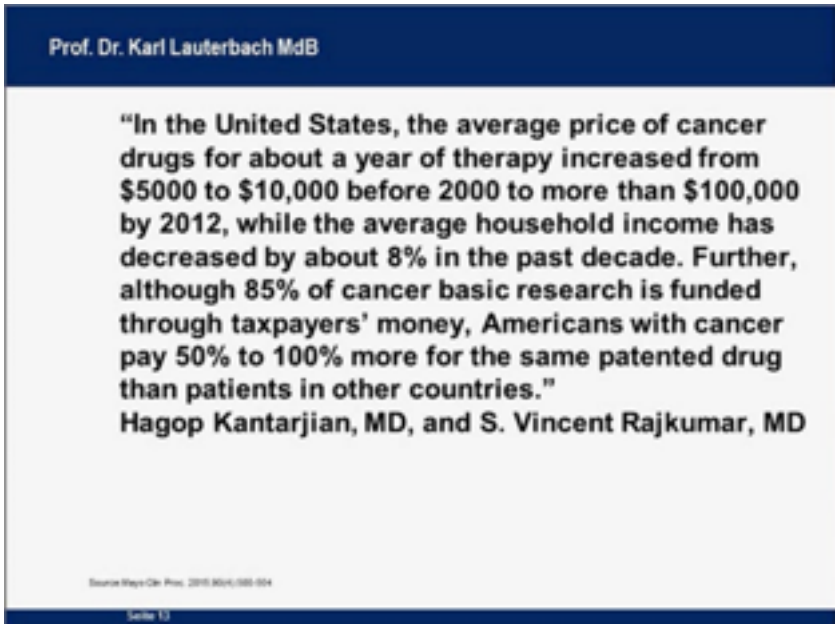
(Min 39:36)

This slide shows the number of active products currently in the pipeline. This is data from the IMS Institute, which has a lot of drug surveillance reports on the industry side. They come out yearly with a global oncology trend report. This trend is from 2014. Ever since the number of active products in the pipeline has increased. Even in 2014, if you look at the complete pipeline, more than 6.000 active products where in the pipeline. Many of those are still in the preclinical phase but more than 1000 are in phase one, 1,438 in phase two, and still 449 in phase three. This is the total number for all diseases and it is quite a substantial number. In blue you see the percentage of those drugs that are in the pipeline for cancer. Roughly speaking, in the preclinical phase and in phase one, so the earliest phases, one third of all active products in the pipeline are cancer products. Cancer is by now constituting one third of the newest development in the drug research. Cancer is becoming by far the most important research topic, development topic and economic topic in the drug industry and will become an ever bigger issue for quality regulation and cost regulation in the drug industry. In the past, cardiovascular products were the leading products in that respect. For example, you all remember the incredible importance of lipid lowering drugs like statins. Yet, in the future cancer drugs will become the hottest issues in economic, regulation and cost effectiveness developments in the drug industry. Therefore, the topic is becoming more important as we speak.

TOP 10 PHARMACEUTICAL COMPANIES BASED ON GLOBAL ONCOLOGY REVENUE UN 2014 AND 2020

(Min 42:34)

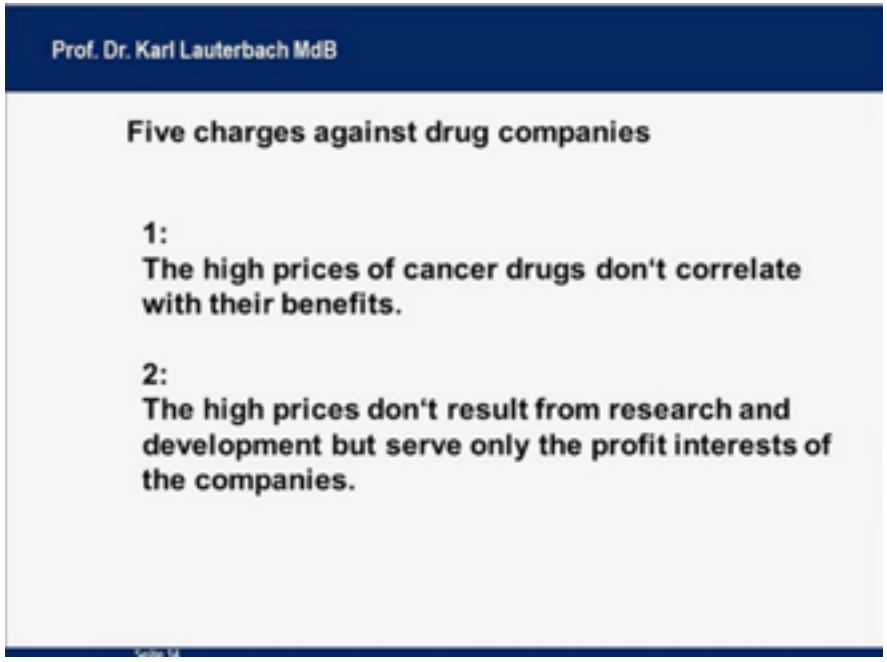
The top ten drug companies based on global oncology revenue are all expected to grow rapidly in the time frame from 2014 to 2020. If you look at this source, all of the companies that are in the drug market, and produce oncology products, are expected to grow quite considerably. Bristol-Myers Squibb expect a growth of almost three times in this time period. Celgene is expected to grow by 100%, and Pfizer is expected to grow by 250%. All of these companies are supposed to grow quite considerably and most of the growth of these companies is related to new cancer drugs. These cancer drugs come by enlarge from these three drug groups, which I have just described: tyrosine kinase inhibitors, checkpoint inhibitors and monoclonal antibodies treatments. In particular, checkpoint inhibitors will become the most expensive and the most quickly growing drug expenditure in the next couple of years.



(Min 44:30)

What does this mean to the consumer? This slide shows research by the Mayo Clinic, published in 2015. It states that: "In the USA, the average price of cancer drugs for about a year of therapy increased from $5,000 to $10,000 before 2000, to more than $100,000 by 2012." This shows a tenfold increase in fairly short period of time, of roughly speaking 10 years. At the same time, the average household income has decreased by about 8 percent in the past decade. "85 percent of basic cancer research is paid for by taxpayers' money. Americans with cancer already pay 50 to 100 percent more for the same patented drugs than patients in other countries." The situation in the U.S. is therefore to be described in the following way: while consumer income is stable or even declining, costs for cancer drugs are increasing rapidly; in 10 years by factor 10. They are also becoming more expensive in the American market than in other more regulated markets. I should point out that Germany is also one of the countries where cancer drugs are marketed above the price of the average European level. We are somewhere between the U.Ss and Europe when it comes to the cancer drug prices. All problems that we are now seeing in the U.S. we will see in Europe and many Latin American countries. To some degree the situation in Latin American countries will be even more comparable to the situation in the U.S. and in Europe. Cancer drugs are not fully provided by the health insurance system. If there is, for example, a major co-payment or cancer drugs are not available entirely by the coverage system, then the household has to pay for these cancer drugs. In the U.S. this is such an important issue, that by now, expenditure for health in catastrophic diseases, in particular cancer, is already the leading cause for the bankruptcy of individual households. Very often a household is not in a position to pay for the cancer drugs, being close to bankruptcy or being bankrupt. Major prejudice is occurring because often families have to decide how to get the money that is needed to get these very expensive drugs available to a patient, for example a child that needs the drugs if there is no full

coverage. In many Latin American countries, the situation can become quite similar if there is no regulation, which avoids these tragedies. I can ensure you that I know patients that have tried to get the drugs, and assume that they would get them, but then were not able to buy them. They suffer from cancer and at the same time from the problem that they need the drug, which is too expensive for their families. We are speaking about a major issue from the perspective of the families that are affected. This is an important topic to consider.



FIVE CHARGES AGAINST DRUG COMPANIES

(Min 48:53)

I will lay out five charges against drug companies. The good, news to begin with, is that we have better drugs currently with these three most modern drugs, which I have just pointed out to you. A lot of the research that is currently done by the drug companies is important, which should not be forgotten. Significative work is done in these labatories and it is clear that we need these drugs and that there is no alternative to them. On the other hand, there is still room for bringing forward a couple of charges against drug companies. Many of these charges have not only been developped by me, but also by leading oncologists in the U.S. and in Europe. This is not a flat industry critisism but a crisitism that comes from physicians, from cancer researchers and also from politics. It does not mean that profits are not accepted or that the issue is seen as a class fight issue. It is a more suttle topic. Drug companies take advantage of the fact that these drugs are desperatly needed by some patients, that they are very difficult to assess by doctors and that they can be marketed at very

high prices because the regulation that is in place is very difficult to maintain and very often does not work very well.

First of all, the price of the cancer drug does not correlate with the benefit. This is clearly the case. Many of these new drugs, that sell for a $100,000 or more per year, only increase the patient's life expectancy by a couple of months. There is others that are cheaper and have a longer life expectancy increase and the same results in improving quality of life. Research has clearly shown (the research list is available by office and my institute) that there is no correlation whatsoever, between the clinical benefits of a new cancer drug and the cost at which it comes to the market. There is no good cost-benefit relation for many of these drugs. Secondly, the drug industry often justifies the high prices to the governments or to consumers by saying that this money is needed to keep up the research and to pay for the costs of the research that has led to the drug development. For example, if a new checkpoint inhibitor comes to the market, and costs $100,000 or $150,000 per year, drug companies often argue that this price is high because of the development and research costs. This is clearly not the case. Research by economists at many universities, including Stanford University in the U.S., has shown that the costs of the research is typically much lower for the companies than they anounce. Most of the leading research of the development of a new drug is tax paid because it is very often university research which has led to the original resaerch results that make the drug development possible. For example, all of the major research on tyrosine kinase inhibitors and the most important checkpoint inhibitors was done by American universities and it was paid by American National Cancer Institute research money, the university money and public funding. As I pointed out previously, 85 percent of the major groundbreaking basic research of cancer drugs is funded by taxpayer money and a lot of it is done in the U.S. The U.S. is particularly successful in developing these groundbreaking research results. The U.K. is also very successful, as well as couple of European countries. Germany could be more successful when it comes to basic research in university settings, as I point out in my book. Yet, we are heading that way and we are currently making a major effort to have better results.

In summary, the high prices do not result from the research of the drug companies. The groundbreaking research by the drug companies is small and very often limited to only a couple of percent of the revenue that a drug achieves. Most of the price increases that we have seen in the last ten years go directly into the profit interest of the companies. They are not needed in order to do the research which leads to the drug.

FIVE CHARGES AGAINST DRUG COMPANIES

(Min 55:12)

Thirdly, the companies misuse their market power. As we have already seen, the number of companies in that particular market is small. There is not a lot of competition because it is difficult to develop these drugs from the patents, which are available. This is the case because, in order to do that, you need to invest into very expensive studies that lead to the admission of the drugs. Only if you get the admission of the drug to the market before someone else gets it, you will make a major profit. This is a market in which the drug company, which comes first to the market, gets most of the profit. Therefore, it is like a race to bring a patent to the market and to get an approval for the drug as soon as possible. The big companies that are in that market are specialized in that race. They have very good connections to the FDA, for example, or the European Medicine Agency, which is the leading European institution to proof drugs for the European market. They also need very good ties to university hospitals, in order to be able to patent the drug quickly and to have a compound. Then they get the studies done both in the laboratory but also with patients in order to get enough patients recruited to get to the admission. The drug companies have a unique access to the compounds, the patents, the patients and the researchers that are needed to complete the studies, which are required to get to the market quickly. Once they are on the market, they can then offer the drug at the price which they believe maximizes their profits since there is no, or very limited competition. A different drug will only be able to outsell the drug that came to the market if the new drug is better than the old drug. Yet, it is much more difficult to come to the market with a drug that is better in a particular way than a similar drug which is already on the market. In that type of market, speed is everything.

The big companies have the infrastructure to buy speed and, therefore, use their market power to increase their profits. Fourthly, the pharmaceutical drug companies often even obstruct research. They are very concerned with getting their drug to the market as quickly as possible, and with developing studies for drugs that are already on the market, in order to create additional indication. This obviously takes away attention and research capacity from basic research. Basic research is research, which opens completely new ways of treating cancer. The drug company research very often does not look at new ways to treat a cancer but only looks at studies that bring to the market the drugs that are already available and that have already been developed. The paradoxical situation that we currently observe in the U.S., is that the public and private funding for basic research in cancer is flat or even going down slightly, while there is an even higher expenditure for cancer drugs and rising profits. This is because too much money is going into research, which helps the companies to market drugs that they have on the market already and takes away research and money from the development of completely new drugs.

Fifthly, the drug companies are risking to burst the healthcare systems because the growth in prices is so substantial that in the long run, it is unclear if we can afford to keep up the solidarity principle. In Germany, for example, I have estimated that from now to 2030, within only 15 years, the current expenditure for cancer drugs will increase from about 6 billion Euros per year to possibly 40 billion Euros per year. Who is going to pay for these additional more than 30 billion Euros per year? It is completely unclear how our solidarity system will be able to cope with this cost. When we keep in mind that at the same time, while we see this major increases in drug expenditures both in Germany, in Europe, and in the USA on the other hand, the survival rate for cancer has not increased substantially. The drugs have not led to a major increase in survival of cancer. In most cases of an advanced cancer patients will die. They will have a somewhat better quality of life during the treatment. They will also have life expectancy gains. For example, for lung or kidney cancer we can expect a couple of months additional life expectancy in an advanced cancer. Some patients will gain much longer increases in life expectancy. But by enlarge, these major increases in cost and these major research gains, have not increased survival of cancer and quality of life to the same degree. We are therefore not speaking about wonder drugs, wonder pills or wonder infusions, but we are speaking about small yet very important changes. I should also admit that there are exceptions such as the drugs that I have mentioned before, like Imatinib. Imatinib is a major breakthrough for this rare leukemia, and almost a cure for the patient. Yet, this is far less than one in a hundred cancer cases.

It is also true that melanoma treatment advanced with checkpoint inhibitors. That is a revolution because many of these patients died very quickly. They now continue to live for long periods of time. They often live from five to eight years. These are major advances. Yet, for many tumors such as for lung cancer, advanced kidney cancer, advanced pancreatic or colon cancer, so far, we do not see major improvements in life expectancy. The cost effectiveness of these drugs is not particularly good, as far as we can currently judge from the research that has been done. In that sense we risk the ability to finance our health care system by paying for treatments which are good treatments but they are not 'super treatments'. We could get much bigger gains in terms of cancer survival if we were to successfully work on the prevention of cancer.

Despite the fact that I do not show a slide for cancer prevention, I will briefly point out that there is a lot that can be done with respect to cancer prevention, which would make a big difference to all of the countries that I have been talking about. The risk factors are reasonably well known, despite the fact that prevention does not work as perfect as it does for cardiovascular diseases.

I should underline that by far the most important risk factor for cancer is smoking. If we were to invest more in smoking prevention and cessation, we would basically do much more good for cancer patients than with all of the treatments that I have just mentioned. Smoking not only causes lung cancer but many types of cancer. Almost all solid cancers that people die from are influenced by smoking. Smoking affects all of the mechanisms of the hallmarks of cancer, as I have explained at the beginning of my presentation. Smoking is like a silver bullet for preventing cancer. In Germany, for example, we must expect that roughly speaking at least 25 percent of all cancer cases are due to smoking. The research has shown that in Latin American countries it is exactly the same, if not even a higher percentage. Smoking cessation and prevention should be our primary target if we want to avoid cancer deaths and also if we want to avoid an explosion of our health care costs. We will have a very hard time to finance smoking related cancers, if we treat them with the new and expensive drugs. With the same money we could easily be much more successful in smoking prevention.

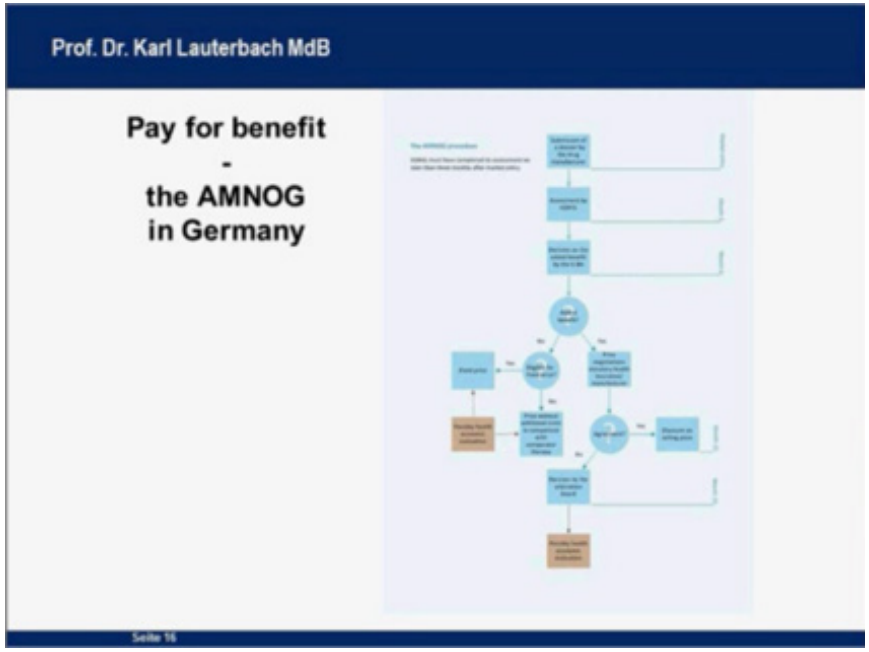
Secondly, obesity, which is known as a risk factor for diabetes, is also a major risk factor for cancer. We know that being overweight is a big risk factor for colon cancer and breast cancer. Indeed, many cancers depend on being obese. Fighting obesity is important because it reduces at the same time the risk of cardiovascular diseases, hypertension, strokes and heart attacks. It reduces the risk of diabetes and

cancer. In that sense it is particularly important to fight the obesity epidemic because in doing so we fight three of the leading killers of our times: heart disease, diabetes and also cancer.

Thirdly, people should keep moving. People who sit most of the day have a higher risk of developing colon cancer and some other cancers. Simply getting people to move around and exercise is already important for preventing cancer. We also know very well that a regular exercise, like running or biking, helps to prevent breast cancer.

Fourthly, we have to keep in mind that drinking too much alcohol is also a major risk factor, in particular for those who are also smokers. Interestingly, the risk of developing cancer caused by alcohol is much higher for smokers than for non-smokers. The reasons for that are also well understood, and I will not go into the research now, but I should point out that a simple way for us to reduce the risk for many patients is to get them stop smoking because at the same time it also reduces their risk to get a cancer which comes from drinking. Breast cancer and colon cancer are strongly related to drinking. Regarding colon cancer, drinking alcohol itself is a risk factor even for non-smokers, even if you drink only one glass of wine or beer a day. Therefore, alcohol is a risk factor that we have to take seriously and that we have underestimated in the past.

In summary the four main risk factors are: smoking, being overweight, lack of exercise, and alcohol. If we would control those, and would invest some of the money that we currently spend on the important, but often too expensive new cancer drugs, we would have a much bigger benefit for the same money.



PAY FOR BENEFIT – THE AMNOG IN GERMANY

(Min 1:10:38)

The pay for benefit system in Germany (AMNOG) is the way we determine drug pricing, also regarding cancer drugs. It is a system that works reasonably well. I am writing in detail about it in my book. It does have some weaknesses but also some strengths. I think, all factors considered, it is a good system and we will not abandon it in the future, but we will improve it. This is not the topic of my talk today but I will describe how the AMNOG works.

Basically, when a cancer drug comes to the German market it can only be reimbursed if the company provides information on how effective the drug is. The drug companies are under the obligation to provide all the information, which is available in terms of studies, to start the procedure. This procedure is initiated by a research institute, which is called the IQWIG Institute, which assess the studies provided by the companies in order to get a feeling on how good the drug is doing. First of all, in comparison to other drugs, which are on the market already, and secondly, in comparison to treatments, which are not drugs, including surgery, radiation therapy or hormone therapy etc. The IQWIG gets the complete information from the drug companies, analysis the information and then gives an assessment whether the drug provides a benefit or not. This is typically done in three groups: major additional benefit, minor additional benefit, or no proven additional benefit by the new drug. Most cancer drugs that fall into the three categories we discussed earlier (tyrosine kinase inhibitors, monoclonal antibodies, and checkpoint inhibitors), have either limited additional benefit or have no additional benefit. Some have major additional benefit but these are very few. Most of the cancer drugs that we currently speak about, fall into the middle ground of the AMNOG procedure. The assessment by the IQWIG is based on evidence-based criteria, using the information by the drug company and is forwarded to the G-BA. The G-BA is a joint committee by sickness funds, doctors, the hospital association, and also patients are included. The sickness funds, the hospital doctors and also the researchers and the physicians can vote in this procedure, within this joint committee on the drug. The patients can only get their voice heard but they are so far not allowed to vote. They are included in the procedure, which is very transparent, to bring in their point of view. In that sense, the decision is made by the sickness funds experts, the hospital experts and by independent members of the committee. There are three independent members that are also experts and they

vote on the drug. In order to vote, they use the dossier created by IQWIG and then provide an assessment in which category the new cancer drugs falls into (major additional benefit, minor additional benefit, or no proven additional benefit). Based on that assessment, meaning the level of recommendation (level A: major additional benefit, level B: minor additional benefit, level C: no proven additional benefit), the sickness fund starts to negotiate the drug price directly with the drug company that wants to market the drug in Germany. Then there is a bilateral negotiation with the association, which will represent all sickness funds on the one end, and the drug company on the other hand. The IQWIG reports at the negotiations in the G-BA joint committee. The entire process is transparent and open, but drug negotiations and price negotiations by the sickness funds, represented by the joint committee and the drug companies, are not public. These negotiations are done behind closed doors. The drug company can go two ways. They can try to get into a drug class, and then get a fixed price for the new drug on the market. This is what many drug companies do if their cancer drug gets no additional benefit. If a drug company has no additional benefit, as assessed by the G-BA, it is very unlikely that the price that is negotiated is higher than the price of the drugs that are on the market already. Then the company agrees on that price. That is what happens to most of new cancer drugs.

Many new cancer drugs go into a fixed price scheme so they fall into a group price which is determined in a fairly complicated way, by looking at what the average price in a particular group is. If the drug company does not want to accept the fixed price scheme and wants to achieve higher price, then they negotiate directly with insurance companies and with the sickness funds, until they reach an agreement or not. If they cannot reach an agreement, then the decision is taken by an arbitration board, which is composed by experts who hear both views, and then get an assessment of (...)

The benefits policy was mostly an implicit one but it had a little bit of explicitness to it. It is set to cover 95% of the disease conditions. In the law that was originally passed they actually listed what the benefits package would be, but only used very broad categories to describe what that included. The broadest categories in the law are three or five sub bullets for each one, which describe them in a little bit of more detail but nothing like a comprehensive, explicit list of benefits. The one thing that is most explicit is a list of exclusions and that includes things like high cost surgeries, HIV-Aids medicines are not included, because they are covered under the National Aids Program, dialysis, cosmetic surgery etc. Yet, it is a fairly limited list. That is what the current situation is. For the first ten to twelve years of NHIS

making adjustments to the benefits policy was simply off the table politically. No one wanted to talk about co-payments or restrictions to benefits. For a long period, it was politically untenable to talk about making adjustments to that unless you would promise more.

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