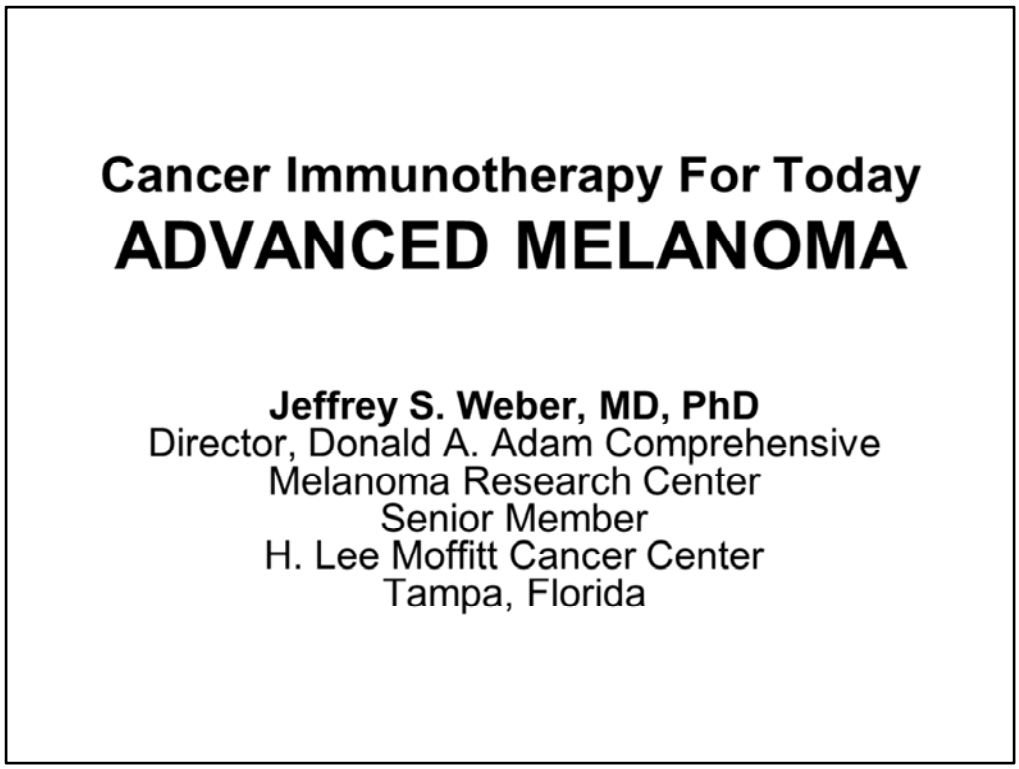
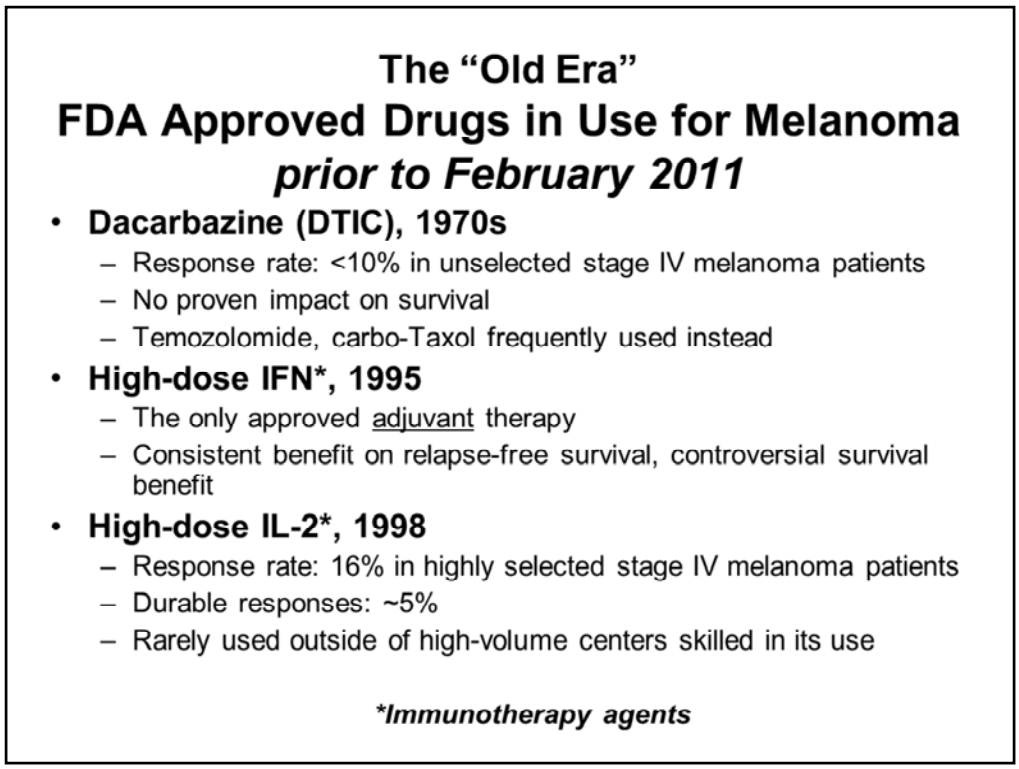
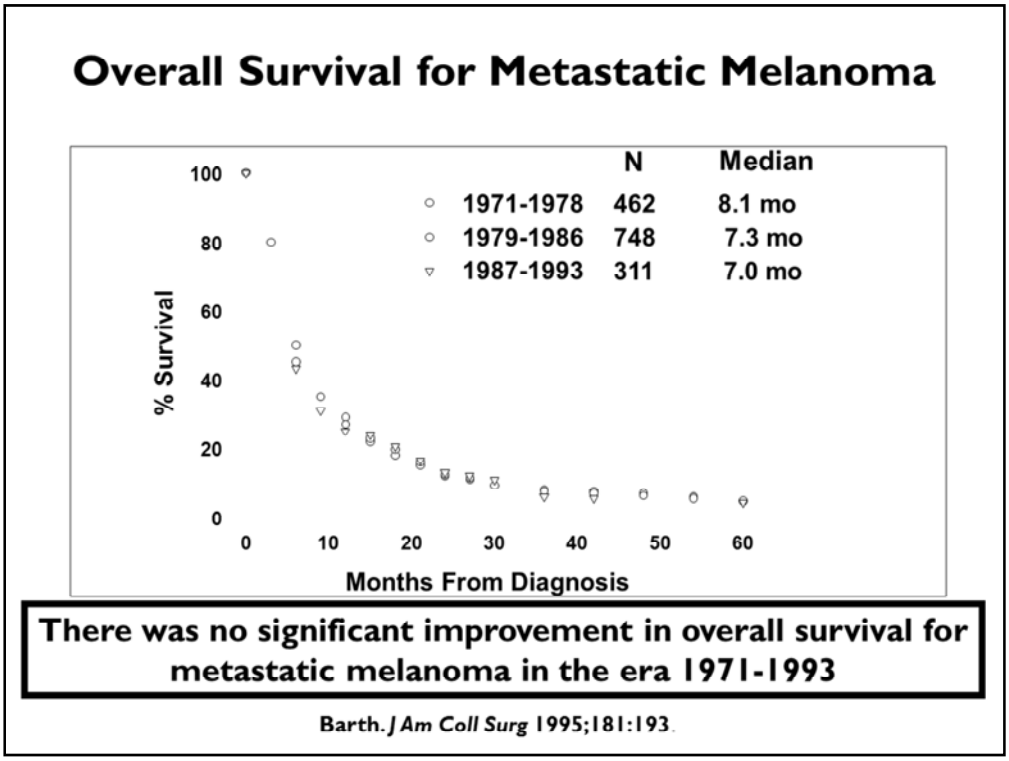


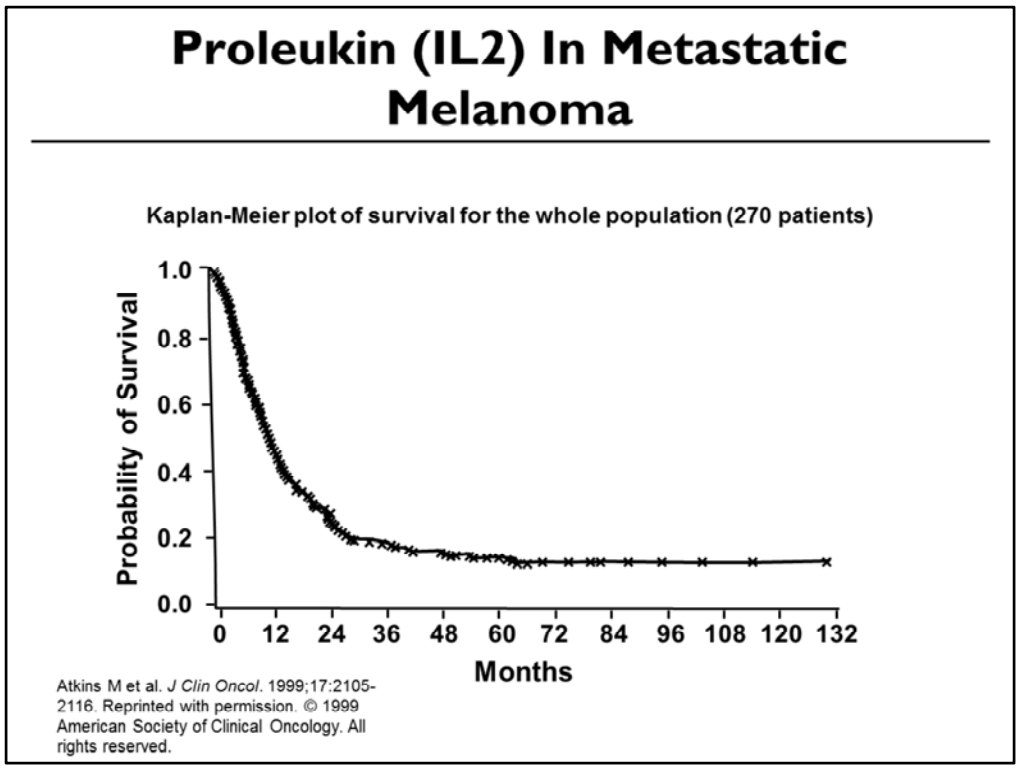
Dr. Weber: Okay, we are going to switch gears completely. We are going to talk about melanoma, and I should say one thing editorially. Whenever I give talks on melanoma immunotherapy, I always recall Rodney Dangerfield who is a comedian. Some of you may remember him, and his stock line was, "I don't get no respect," and immunotherapy never had respect in the past because it was always felt that it was a phenomenon confined to melanoma, and a lot of people would say in practice, well you know melanoma can respond to anything, but you just heard some data showing a lot of promise in bladder cancer and other malignancies. So, I think immunotherapy was the “breakthrough of the year 2013 in science,” and the reason is now it is broadly applicable to the non-small cell lung cancer and bladder cancer. There is activity in head and neck cancer. There is activity in ovarian cancer. There recently at ASH presented some fantastic data on Hodgkin and non-Hodgkin lymphoma with very high response rates in refractory patients. So, I think that is one of the reasons why we are here today because this is no longer just melanoma specific, but you need to hear about the melanoma data because this is where we really established that checkpoint protein inhibition would be important, and it was also the first tumor where a real immunotherapy like high-dose IL-2 had efficacy.



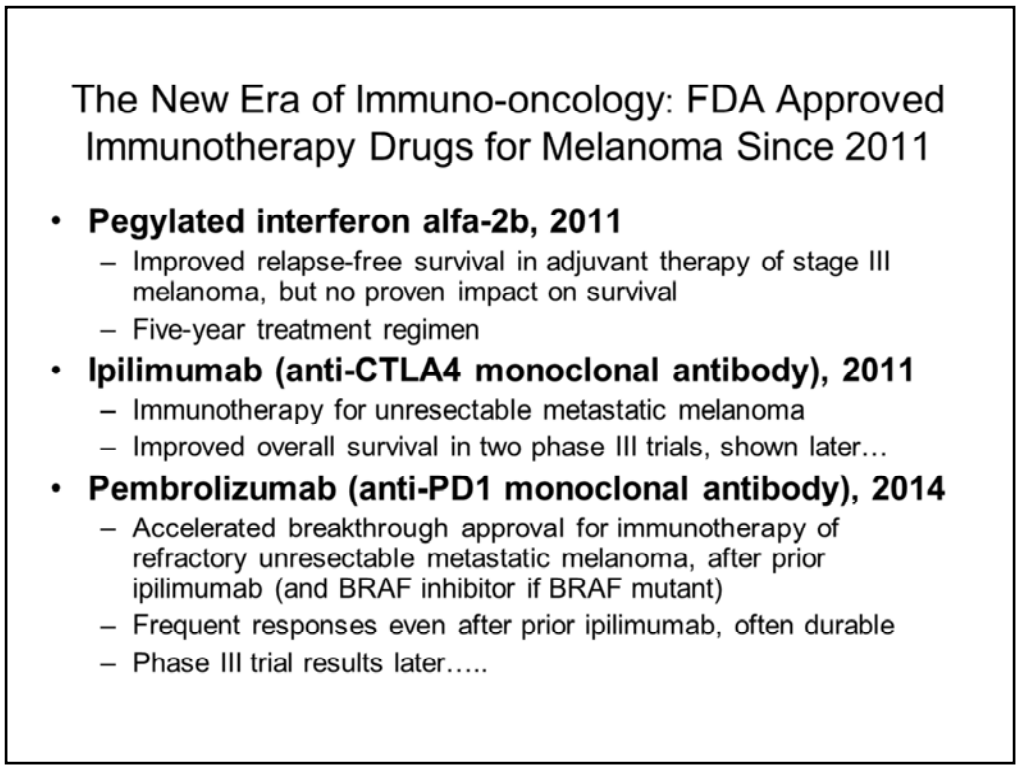
So, we are going to talk about melanoma today, and I am going to run through a sort of the history of immunotherapy and show you some seriously interesting and high-quality data on a number of randomized trials whose results were just presented at a melanoma meeting that was held in Zurich less than a month ago. So, these are sort of hot data right off the press. In the melanoma business 15 years ago or even 10 years ago, really all that we had were things like dacarbazine, which was an alkylating agent approved 35 years ago, and it had a 10% response rate, never was in a randomized trial. Today, it would never get approved by the FDA, and frankly, we do not use it much anymore. We use carboplatin and Taxol (paclitaxel) which interesting has never really been shown to benefit patients in a randomized trial, but it is probably got a 15% response rate, or we will use a single-agent temozolomide as a radiosensitizer when patients get whole brain radiation, or we will use it in the patients who are elderly and cannot tolerate other therapy as a third-line agent. High-dose interferon was approved only as an adjuvant and never was shown to have significant activity in metastatic disease. So, it is very unusual in the field of oncology to approve an adjuvant drug with no metastatic activity. It is the only approved adjuvant therapy today, a lot of side effects as you all may know. Many of you have used it in practice. It is not my favorite drug. However, we use it when we have no protocol options, and we use it when we have a young patient with resected high-risk melanoma. It definitely benefits people with RFS, and that is not a trivial issue. The overall survival advantage in meta-analysis is probably 2% or 3%, and that is what I will tell patients. High-dose IL-2, we have already discussed briefly was approved back in 1998 on the basis of a compilation of phase II studies. It has never been subjected to a phase III study. Today, it might still get approved, but it would be required to go through a phase III study and 16% response rate, durability 5%. Just as an example and anecdote, I have the patients that I treated back in 1988 at the NCI when I was a third-year fellow. She sends me a Jewish New Year card every year. She is now in her late 80s. She was then in her early 60s. She is still alive, free of disease. She had metastatic melanoma. She was a CR. So, it happens. Does it happen a lot? No, the durability is only about 5%, and as we discussed as all of my colleagues will concur, you need an experienced unit, nurses that know what they are doing, staff that are available at any time, and a pretty high level of expertise to make this work.



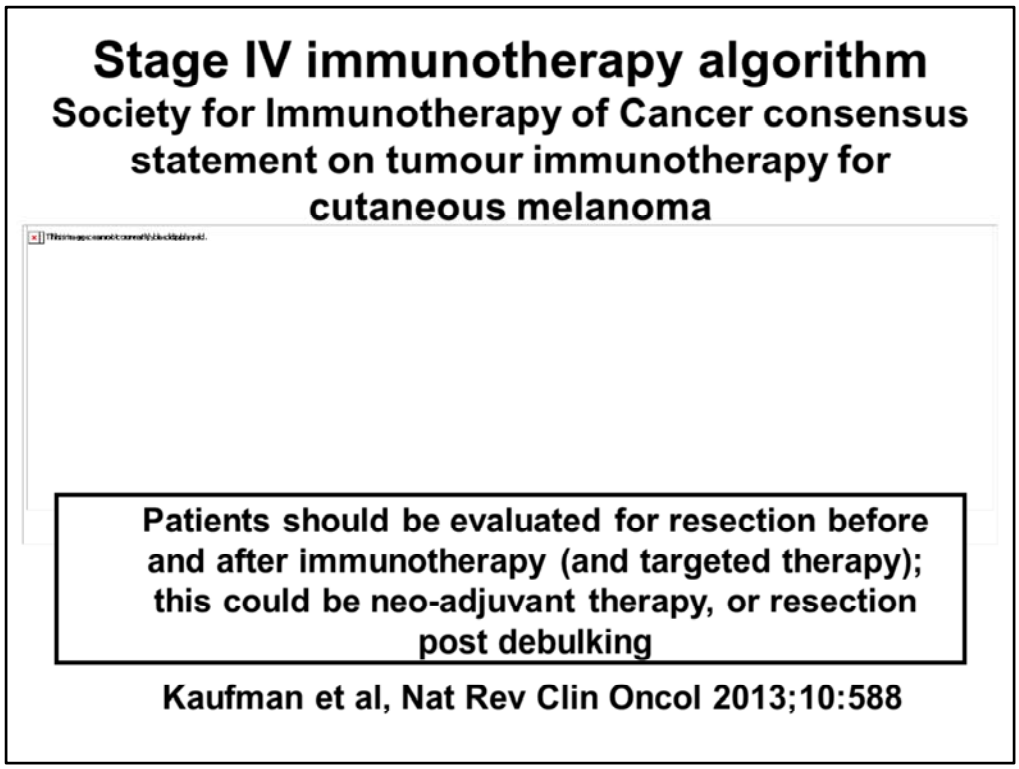
In the melanoma business, this is just an old slide. It shows that over the decades from the 70s to the 80s to the mid 90s, there was no difference in survival. That is not one curve. Those are all overlapping curves where if you look at the baseline here, these are mostly the patients with resected and resectable stage 4 disease. That is probably a baseline at about 5% of survival, and some of those people may well be cured but no more than 5%.



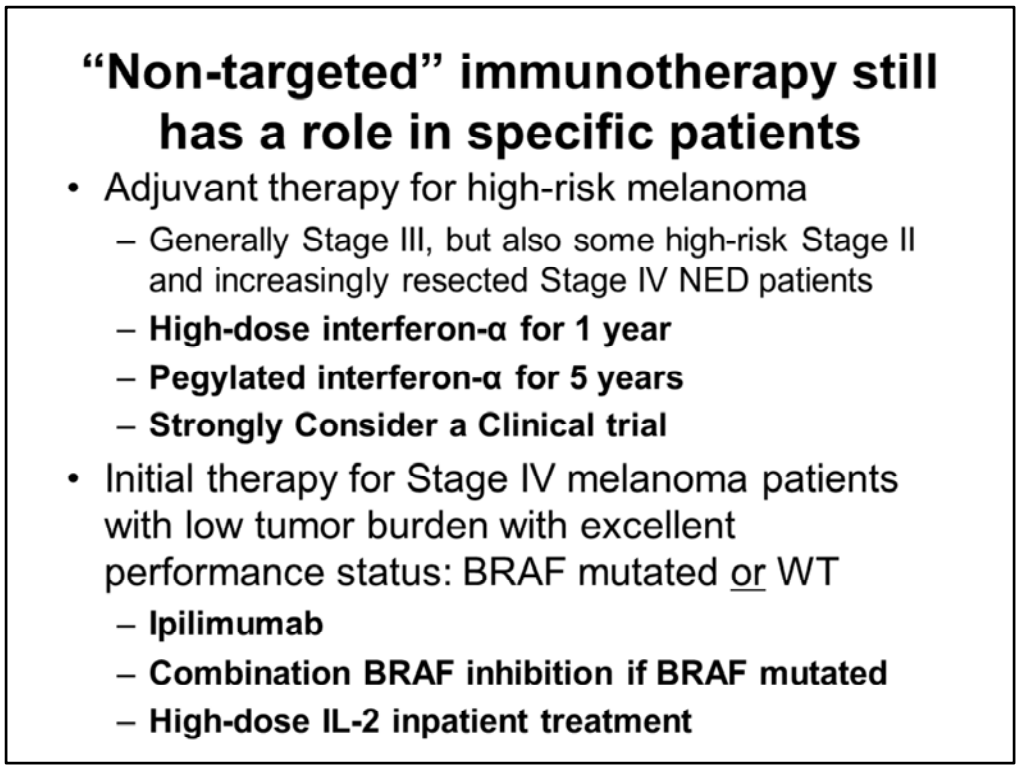
If you look at the IL-2 survival curve from the compilation of phase II studies, that baseline is undoubtedly higher. In the real world, if I had to say whether giving high-dose IL-2 clearly induced benefit in patients and cured some patients, I would say that baseline is probably between 10% and 15%.



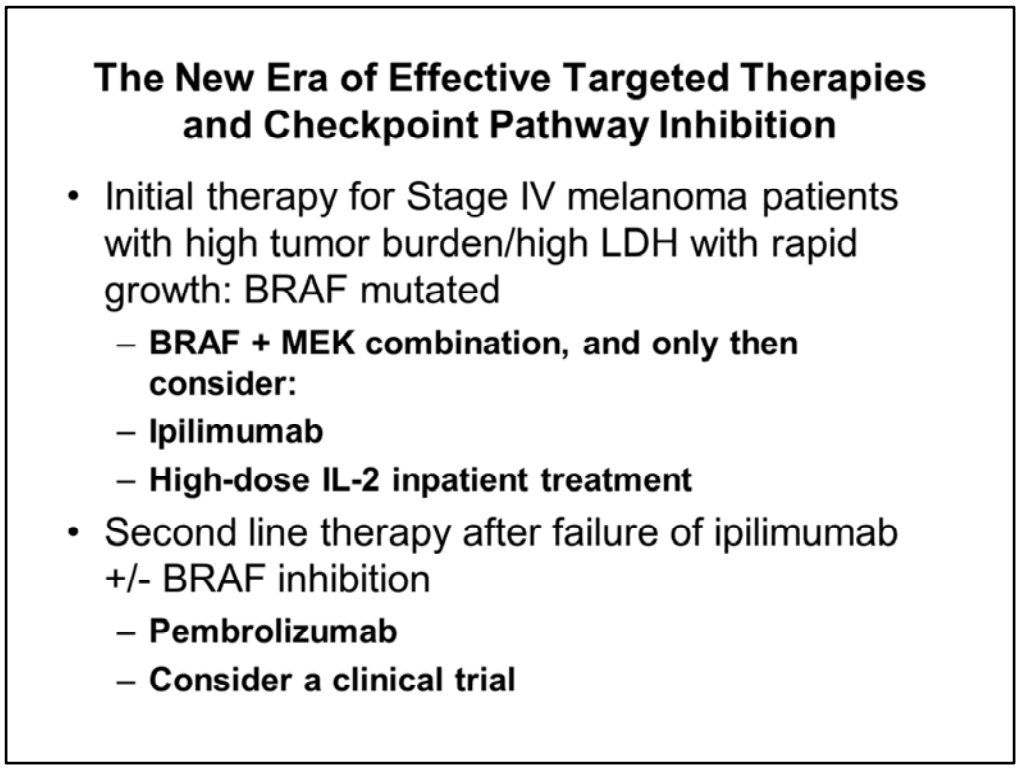
In the modern era, that 5% baseline is probably 10%. Today, if you gave high-dose IL-2, I think you would benefit about 5% of the patients. So, is there a real benefit? Absolutely. However, in the last decade, new drugs have come along. In fact, it is really only the last 5 years that things have really begun to progress in melanoma. First was a drug that was approved in 2011 which interestingly was based on a single phase III study done mostly in the Europe, and that was pegylated interferon alpha as an adjuvant drug for resected stage 3 melanoma, and it clearly had a relapse-free survival benefit; interestingly, no overall survival benefit. Yet RFS was the endpoint to the FDA, and that was acceptable, and interestingly, in those who had ulcerated primaries and sentinel node melanoma positive disease were the ones who benefited with survival. None of the other groups had any benefit, and these were predetermined analyses. So, in my practice, I will only treat someone with an ulcerated primary, which is a bad outcome, who had a positive sentinel node with microscopic disease. I will not treat people with bulk metastatic disease that is resected in the nodes with pegylated interferon, and it is also by the way, technically speaking, a 5-year regimen. I have yet to see a patient who can finish 5 years of therapy. However, the era really changed with the ipilimumab, which is now the CTLA-4 blocking antibody, and as you will see in the slide in a little while, CTLA-4 is one of the major brakes on the immune system. We heard from Dr. Luke that the immune system has many brakes and many accelerators, and is that a surprise? No, because if we did not have brakes on the immune system, everyone would die of autoimmunity as soon as you had a flu infection, you would have this vigorous anti-flu response in the lungs, and we would die of an overly vigorous immune system, so we need homeostatic mechanisms. Every organ in the body has an intense homeostatic mechanism. The immune system is no different. It has many brakes and many accelerators. Ipilimumab takes off the brakes, CTLA-4 is a major brake on the immune system, and it takes it off and allows you to have an unfettered immune response. As you will see ipilimumab has already been through multiple phase III studies in front line and second line, it clearly induces benefit in terms of survival and has a modest response rate in the range of 10% or 15%, but we will see those data later. The most recent approval was just a few months ago, and that was pembrolizumab which is a PD-1 blocking chimeric monoclonal antibody, and remember the IZ, so IZ was as Jason showed you, that is a chimeric antibody. So, this is a chimeric antibody with a few malsequences. It works very well. It is a nice drug. It got accelerated breakthrough approval by the FDA, which means they speed things up and they do not require a randomized trial for the initial approval. This was actually approved on the basis of 89 patients who received 2 mg/kg every 3 weeks in a phase II study. That was it. Now, that is not all. Obviously, the FDA requires that you then go on to do phase III studies. So, if your phase III studies do not work out, that approval might be rescinded, but in fact, as you will see, the data with this drug are very nice, excellent drug.



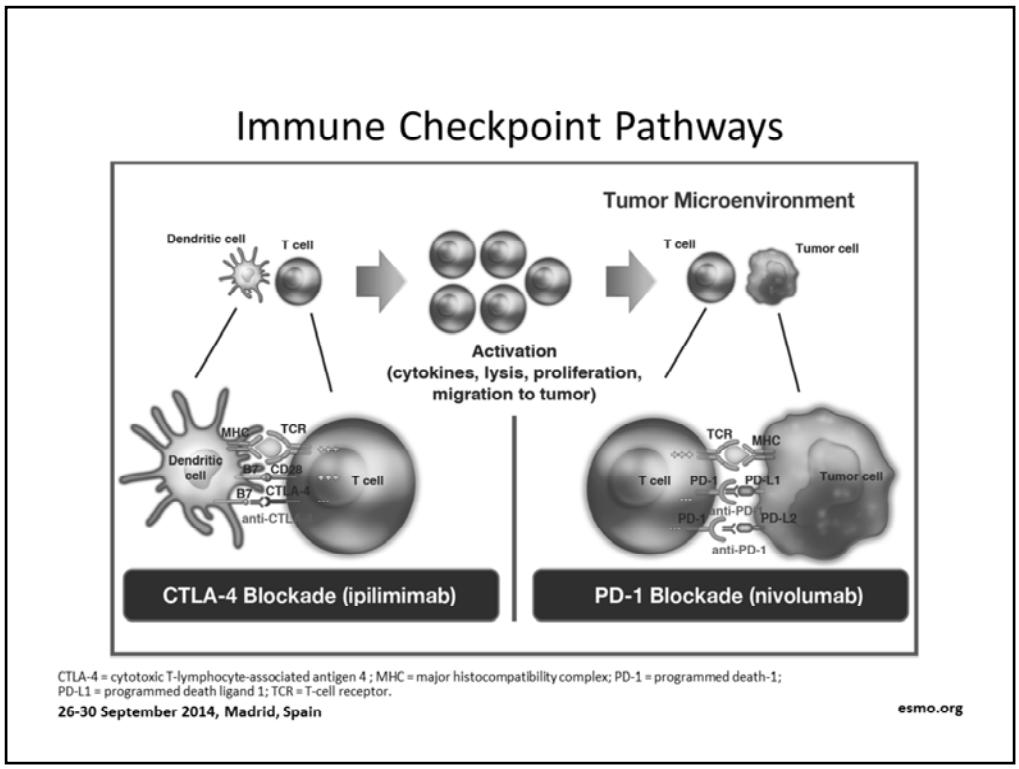
We had a meeting last year to talk about how should we manage melanoma in the new era, and I just think it is worth pointing this out for the practitioners in the audience, and we all agree that you should look at metastatic melanoma patients and high-risk resected patients in a multidisciplinary environment and talk it over. Everybody who has stage 3 or 4 disease in my institution gets molecular subtyping for BRAF and NRAS. In fact, now, we have a whole panel of 40 genes. They are not all actionable, although stay tuned, in the next year or so, you may see a lot of actionable genes being assessed in melanoma. So, we image everyone. We get LDH as a sort of a staging marker, and we genetically profile every single patient. So, if they have stage 3 resected disease, we will profile them because even though we do not do anything about it, let's say 6 months later, they relapse, they have metastatic disease, we do not have to wait 2 weeks to get the result back, we have an immediate knowledge of what their mutational profile is. And everybody should be thought of as a potential surgical candidate. In melanoma, and as you will see in colorectal and other tumors, if you can resect someone and render them free of disease, they are going to do better than if you cannot resect them. Now, is that cause and effect? Not exactly, but in melanoma, we will always seek to resect someone to render them free of disease to do a metastasectomy and then put them on an adjuvant trial, and I think those patients will do better, we will find out soon enough whether that is really true with randomized trials. And the problem in melanoma is as time goes on and the drugs get better, I think my colleagues would agree, we are going to see a lot more central nervous system disease, so when you make a diagnosis of metastatic disease, we always get an MRI of the brain, and I would advise that strongly because if they have brain metastases they are in different category. Now, they are N1c, bad outcome, and those patients are going to need to be stereotactically treated. Just as an aside, I do not know what Jason's attitude is, we hardly use whole brain radiation anymore, just too many side effects and it does not work. We will actually aggressively stereotactically treat people with multiple brain metastases with melanoma and perhaps that is true with other histologies. So, if someone is a surgical candidate, we will do a resection of a metastatic lesion or even oligometastatic disease that is confined to an organ, and then we will put them on an adjuvant trial. So again, I think we all agree if you can debulk someone with say a BRAF inhibitor or a clinical trial that has a high-response rate like ipilimumab and nivolumab and then operate on them, they are going to be better off in my personal view than if you cannot operate on them at all. So, we like the idea of debulking patients.



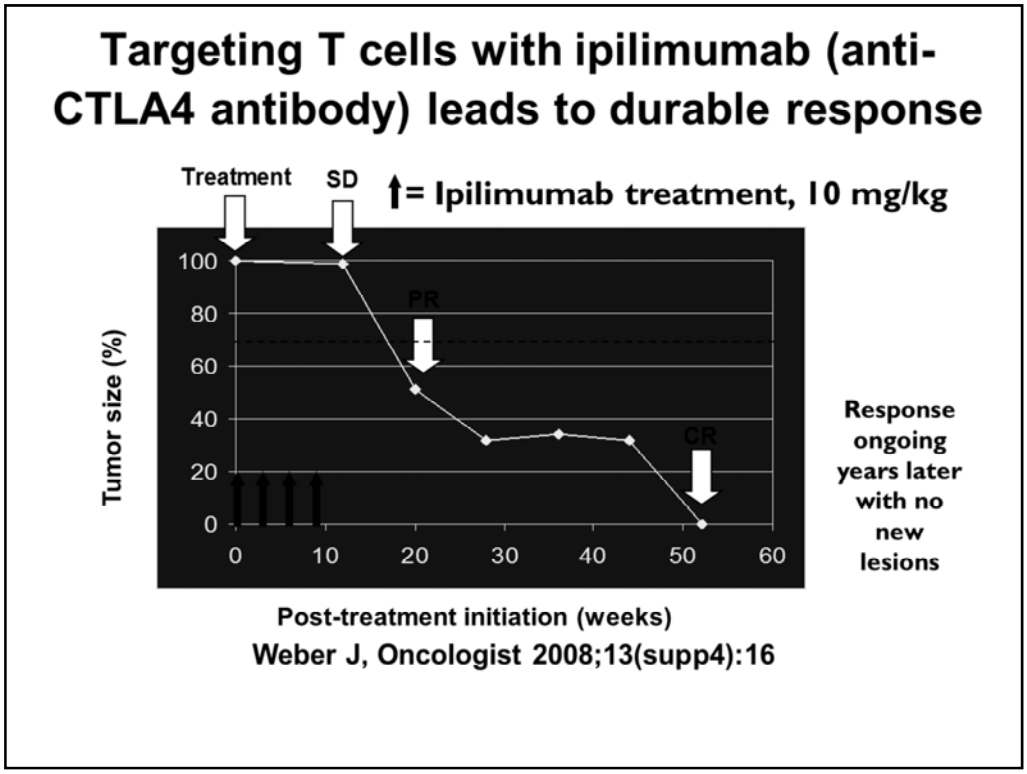
We all hear about targeted therapy, and melanoma is kind of the poster child for targeted therapy. We have now three targeted drugs approved for melanoma, two BRAF drugs and a MEK drug, but interestingly, there is still a huge role for non-targeted therapy because to tell you the truth, immunotherapy is not a targeted therapy. Technically, it is. We are targeting the immune system, but we think of targeted therapy as targeting a driver or a driver mutation in a cancer, and technically we are not doing that. So again, when we use adjuvant therapy, we are using high-dose interferon for a year and pegylated interferon for 5 years. That is not targeted therapy. It is standard therapy, but it is not targeted, and again, high-dose interferon is for one year, pegylated 5 years, and if I see an adjuvant patient with stage 3 BC disease, meaning bulk macroscopic lymph nodes, multiple lymph nodes, in transit metastasis, I am going to put them on a trial number 1, and actually that is fine with the FDA and with the NCI. If I cannot get him on an adjuvant trial, then they are going to be thinking about these drugs. If someone is 85 years old and has stage 3 melanoma, I am probably not going to put them on a toxic adjuvant regimen with a modest benefit, but if someone is 25 and I cannot get them on a trial, yeah, I am going to think about that. And again, in patients who have a low tumor burden, and again remember melanoma as I say falls into two categories, they even grow really fast, and they have high disease burden or they do not. Thank god the first category is probably less than 20% of patients. Most patients with melanoma have a relatively modest disease burden at diagnosis and have relatively slow growing disease. So, we almost always think about immunotherapy first, even if you are BRAF mutated or not BRAF mutated, which is about 40-60%, so 40% mutated and 60% not. Even in the 40% who are mutated with a low disease burden, I will propose to the patient to do immunotherapy first, and ipilimumab is the FDA-approved first-line treatment not on a protocol. If that does not work, we can think about either pembrolizumab, which is the PD-1 drug, or you can then move to your BRAF inhibitor if they are BRAF mutated. If they are BRAF wild type, obviously we are going to go to either pembrolizumab or high-dose interleukin-2, and if you go ipilimumab then pembrolizumab, IL-2 is a perfectly appropriate and reasonable second- or third-line option, but again, remember, it is in patient therapy, it is confined to certain centers. If you live in Georgia, you are going to see David Lawson in Atlanta or my colleague Raghu Katragadda, but it is going to be a very regional phenomenon and not every hospital will do it.



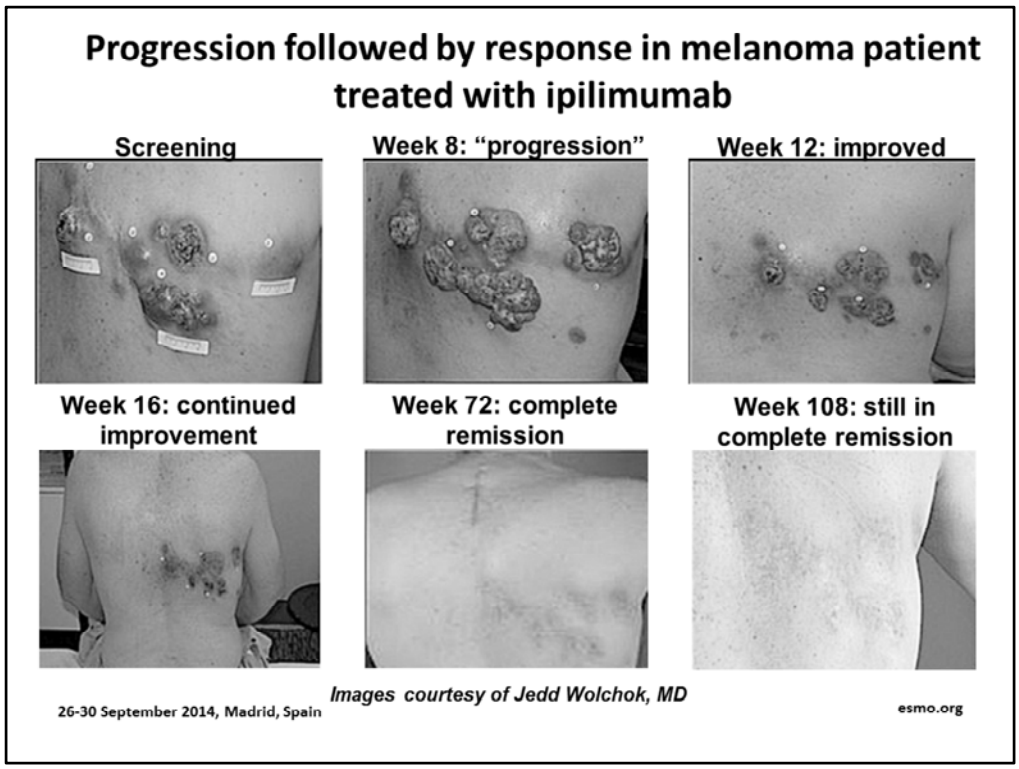
If you have high tumor burden, high LDH, rapidly progressive symptomatic disease and you are BRAF mutated, you are going on the FDA-approved BRAF-plus-MEK combination, and if that does not work, then and only then I would consider ipilimumab, and then if ipilimumab fails, you do pembrolizumab or high-dose interleukin-2. It gets very difficult to deliver high-dose IL-2 when you have a symptomatic rapidly progressive patient. The best patient for high-dose IL-2 is the patient who has subcutaneous nodal or lung disease only without the elevated LDH, without visceral bone mets, liver mets, brain mets, etc., and then if you fail ipilimumab, which is again we are talking off protocol, standard practice front-line therapy, and your BRAF mutated, obviously you think about BRAF inhibition, pembrolizumab would be your second choice because it is now FDA approved second line in those who have failed ipilimumab or ipilimumab and a BRAF drug by the way if you are BRAF mutated, and again, always consider a clinical trial, especially in second- or third-line patients.



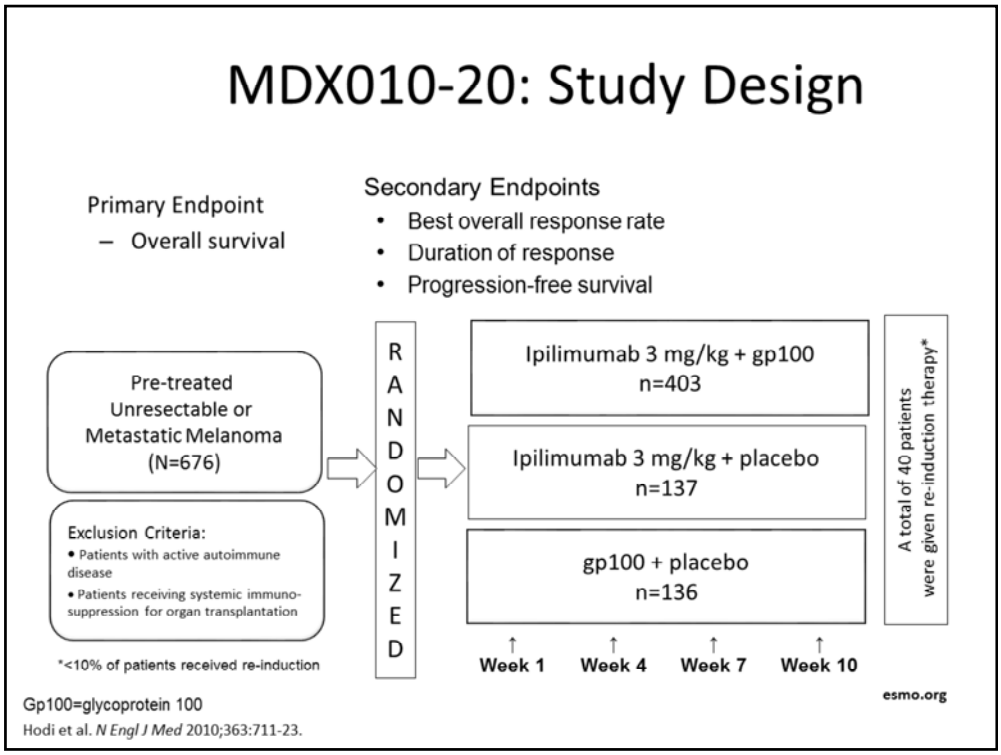
We talked about the brakes. Keep in mind there are many sets of brakes. It is as if you had a car with five or six different brakes, and in the afferent mode, meaning at the time you actually create or prime the immune response, CTLA-4 is the important brake, and that is here. The dendritic cell say in the lymph node where you generate the actual immune response, the CTLA-4 preferentially blocks the interactions that you need to stimulate the immunity as Jason Luke told you, giving antibody kills that interaction and allows the immune system to be primed in a unfettered manner. In the tumor microenvironment, that is the efferent mode, that means it is at the site of the effector activity of the immune cells, different situation. The tumor cell perversely enough is expressing PD-L1 which is the very ligand that binds the PD-1 on the T-cell and inhibits its activity. So, the tumors are very clever. They contain an active ability to suppress immunity, PD-L1. Almost every tumor known expresses PD-L1, not all of the cells do, but virtually all tumors, including hematologic malignancy, solid tumors, mesenchymal tumors, and ectodermal origin tumors express PD-L1. So in the tumor microenvironment, PD-1 and PD-L1 interacting is a huge break on immunity. If you can block it, you will allow the local immune response in the tumor microenvironment to proceed in an unfettered manner, and in practice, blocking these brakes works.



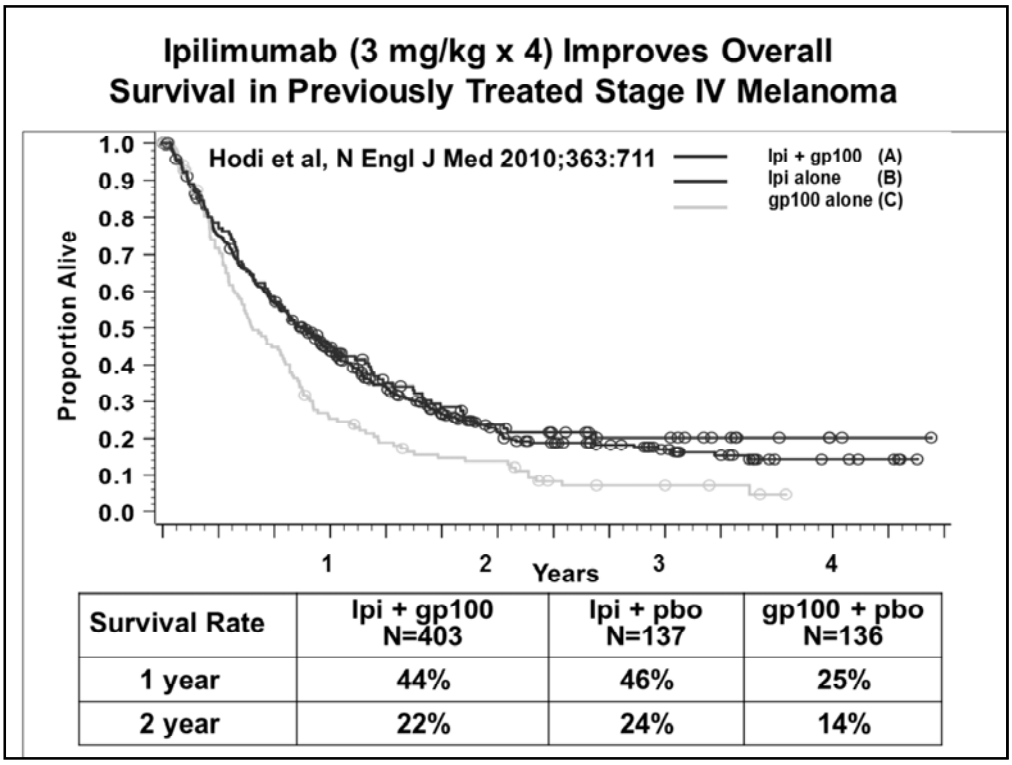
This is one of the early papers that summarize some of data with ipilimumab, the CTLA-4 blocking antibody, and it showed that at doses ranging anywhere from 3 mg/kg to 10 mg/kg, and here a 10 mg patient, you can take a patient, treat them, and you get this at the initial assessment a sort of stable disease, and then you get the slow response, keep in mind this is weeks, over time and then you sort of stabilize, and then you evaluate them again in a year and all of the sudden there is CR, and this is a patient by the way who went on to have a CR for a number of years, and it points out the unusual kinetics seen in early trials with this drug which had maybe a 10 or 15% response rate in phase II studies, but clearly, this was a different beast because you do not see this with chemotherapy. And again, I am not a big chemotherapy user anymore. It was early in my career, but correct me if I am wrong, this would not be almost ever seen in a chemotherapeutic response in a solid tumor, and you saw weird things like this, and again, this is one of several disgusting pictures from Jedd Wolchok, my good colleague from Memorial, he had a patient that was treated with ipilimumab, and again, the classic thing was checkpoint protein inhibitors like ipilimumab, pembrolizumab, and nivolumab is progression followed by regression. You do not see this with your grandmother's chemotherapy.



Here is the patient with these multiple ulcerated disgusting subcutaneous lesions on the flank and on the back, week 8 after starting ipilimumab, obviously, the patient is progressing, you can see that from across the room. But by the time the patient finishes four doses of ipilimumab, you get the feeling things are beginning to regress. The patient continues to get treated every 12 weeks with ipilimumab and slowly but surely slowly healing over. By week 72, it is gone, and you can see it is the patient's right upper back, and then 2 years into a complete remission, the patient stays there for years. This is a very unusual pattern, but this was perceived early on.

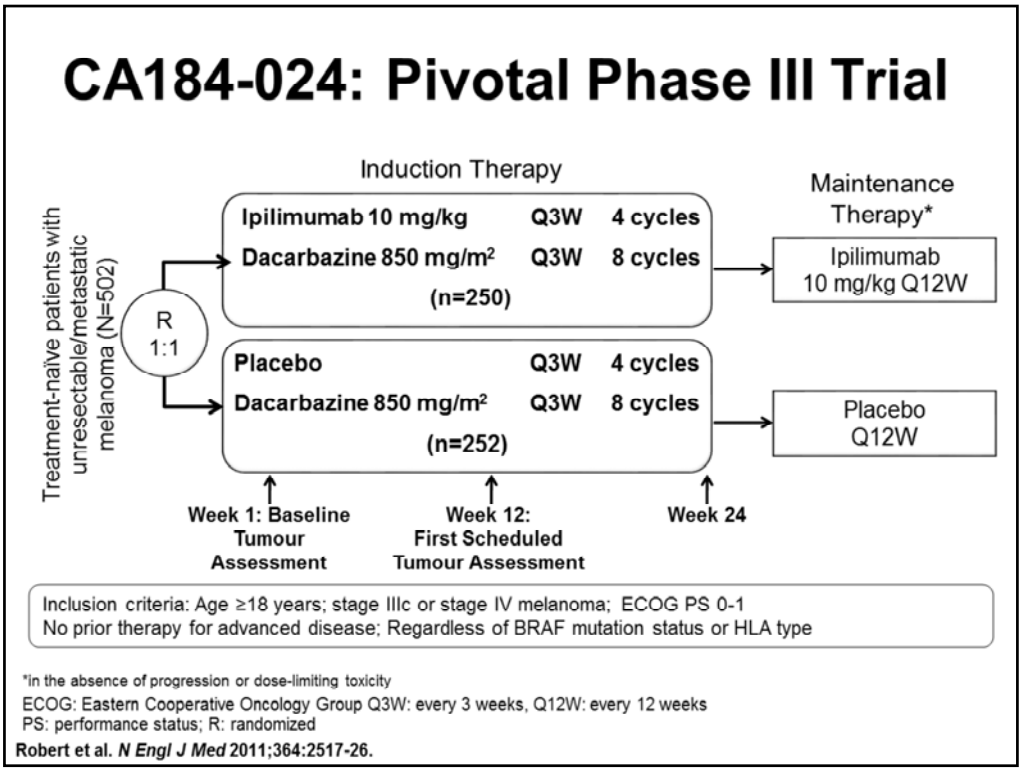


On the other hand, it said that this patient technically might not have been recorded as a responder initially. This patient would have been stable or even progressive I suppose. It said you have to start thinking about a different way of evaluating benefit. Benefit may not just be a PR or CR. Benefit could be a stable patient that stays that way for years and then becomes a CR two years later. So, obviously, the initial optimism about the activity of this novel drug led to multiple phase III studies, and back in 2008, 2009, and 2010 when these trials were designed, standard of care in melanoma in second line was none. So, based on data showing that giving this drug in animal models with a vaccine worked better than just giving the drug alone, a randomized phase III trial was devised. In retrospect, I think the logic was probably faulty, but it is easy to be a Monday morning quarterback. So, this was a trial with an imbalance randomization 3:1:1 because everybody figured the ipilimumab with this vaccine is going to be great. Since its contribution of components you need to have the main drug alone, so this was ipilimumab alone with placebo, and this was the vaccine alone as the control arm. Why vaccine stage 4 melanoma? In those days second-line therapy, no approved drugs. In fact, the only approved drug in those days was IL-2 which was a very limited type of drug. So, the FDA said, well, second-line treatment, this could be your control arm. And the reason for the imbalance randomization? If you were a melanoma patient, would you want a vaccine? I do not think so. So, the attraction for the patient was the imbalance randomization. You had a 4:1 chance of getting what was presumably the active drug compared to the control, and of course, there was no crossover. Survival was the ultimate endpoint here. Interestingly, relapse-free survival or PFS was the original endpoint, and the perception was we really need survival as the endpoint, and the FDA allowed that to change interestingly in midstream.

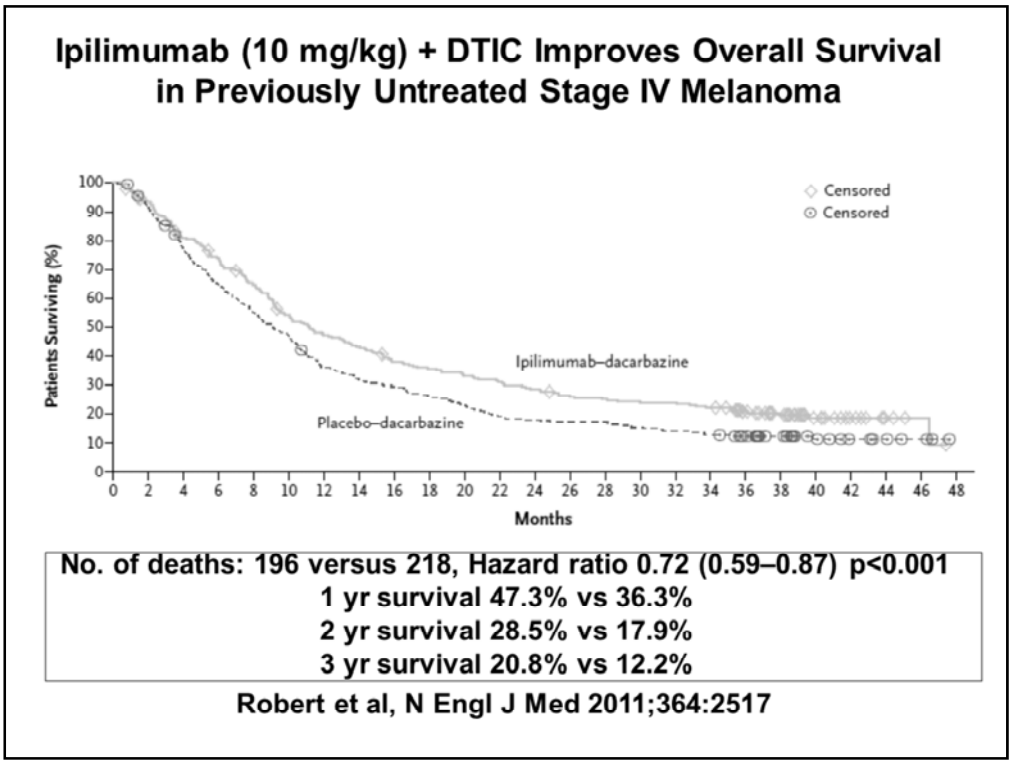


Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

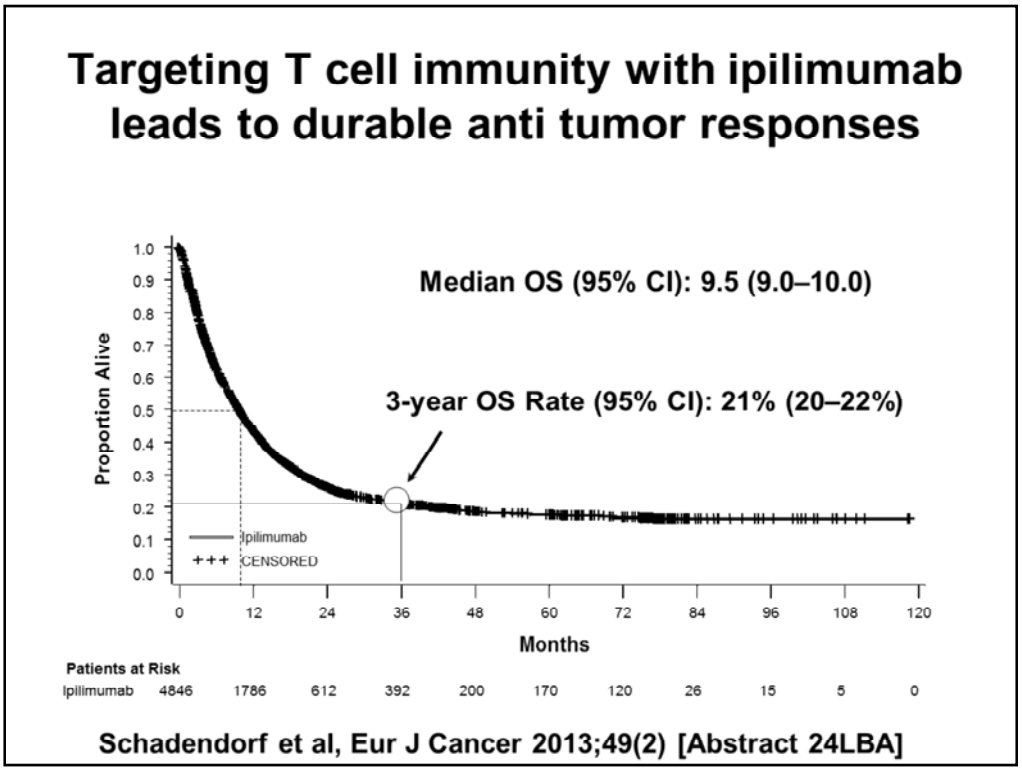
So, this was a randomized fair size trial, phase III study. Survival was the endpoint 3:1:1 randomization, CTLA-4 antibody, ipilimumab with vaccine versus ipilimumab alone versus vaccine alone. And no big surprise, guess what we saw? Whether you got ipilimumab with vaccine or not, you did better then if you got the vaccine, and this is essentially like getting a placebo. So, look at the red line, this is pretty much what you would see if you gave a stage 4 patient who failed a front-line therapy chemo IL-2 whatever a placebo, and the median survivals for the placebo-controlled patients were something like 6.4 months, and if you go back 20 years, that is the survival of patients who get ineffective chemotherapy for stage 4 melanoma, 10 to 10.6 months median survival, which again is a significant improvement, not a great number, but obviously from across the room, the *P*-values here were very significant. This was published in *The New England Journal of Medicine* in 2010. Whether you got ipilimumab or not, ipilimumab with vaccine or not, clearly benefited overall survival with prolonged median, and if you look at the landmarks 1 year and 2 years, clearly superior, and if you go out here, you probably have about a 20% plateau that I will show you in a minute where instead of 5% or 10% plateau for metastatic melanoma, you have now jacked it up by 10%; 10% is a real number, and there is definite benefit to the patients.



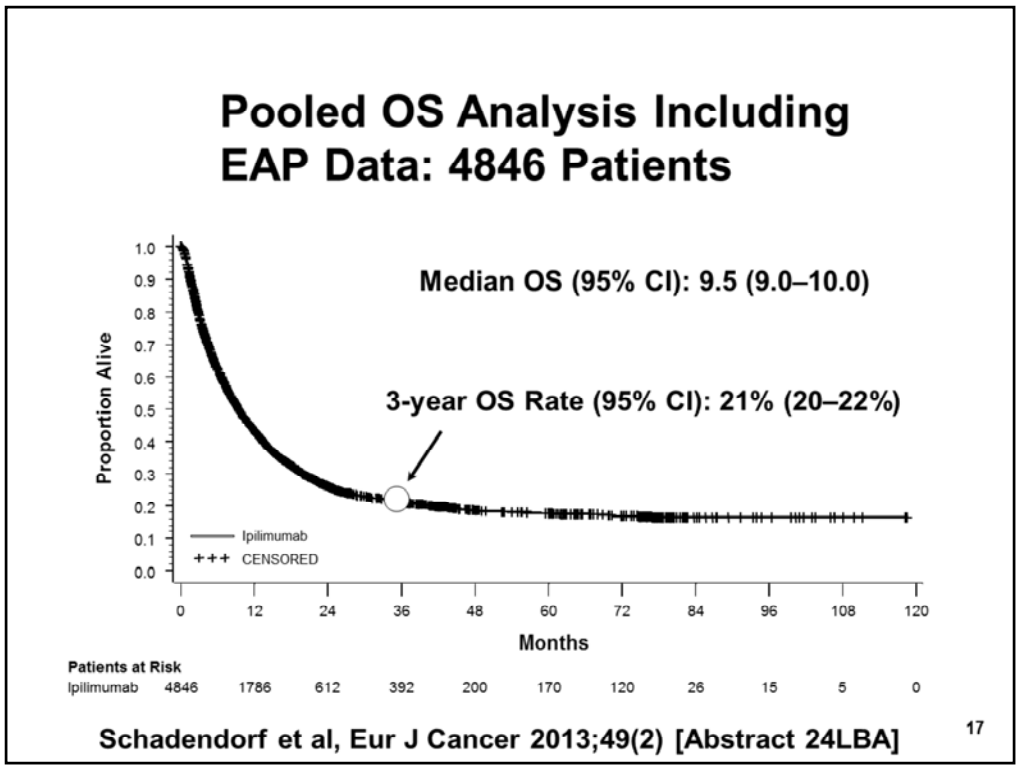
At the same time this was done, in fact in a staggered fashion, there was a phase III trial to look at front-line use of ipilimumab. Based on a phase II trial, which was a small trial that actually I was the PI on, it was decided that well this time let's jack up the dose of ipilimumab because it appears it works a little bit better. So instead of 3 mg/kg, it was 10 mg/kg, even though it had more toxicity, and it was ipilimumab with chemo versus chemo alone, chemo alone being the sort of the only approved drug in front-line therapy other than IL-2, and since IL-2 is regarded as of limited use, the FDA said yes, this is your control arm in front-line therapy. So, it was a head-to-head comparison, 502 patients, and again, the endpoint was overall survival. Of course, PFS responses were looked at, and you did therapy for 12 weeks and then you went on to maintenance ipilimumab every 12 weeks, and so a little bit of a different regimen than what I showed you before where all that you got was four doses of ipilimumab, done. Here, you continue to be maintained every 12 weeks after those initial four doses.



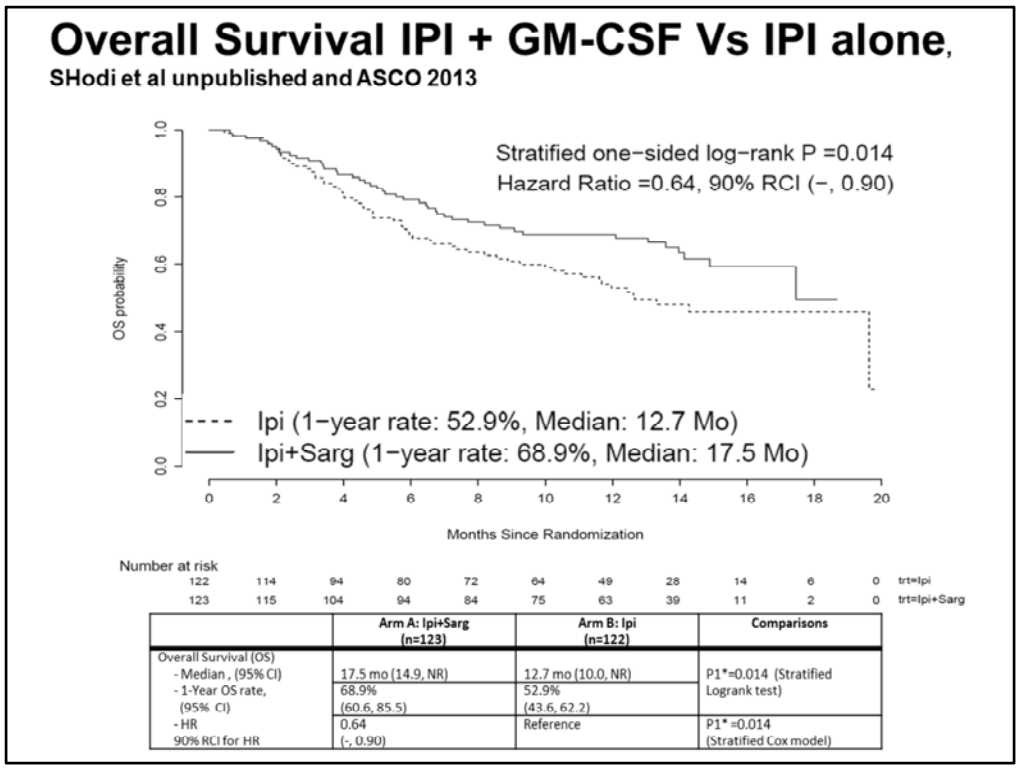
So, here is the result, and again, from across the room it is pretty obvious that the ipilimumab plus dacarbazine group are better than dacarbazine alone group, and again, if you look at the plateau, you are probably talking about 20-25% plateau at 3, 4, and 5 years, and the curve flattens.



So, again remember, I showed you that old curve of about 5-10%? So, with dacarbazine alone, you are probably in the 5-10% plateau. You are 10 points above that with the use of ipilimumab with dacarbazine. To be honest, dacarbazine probably adds nothing to the ipilimumab, but it does not matter, the FDA required if you have a control arm, it was appropriate that you combined the control group with the ipilimumab as your other alternative regimen. Look at the 1, 2, and 3 year survivals, it is about a 10% difference across the board, and ultimately, at 5 years, it stabilizes. So, you probably plateau and some of these patients may be cured, and I will show you a slide later suggesting that is indeed the case.



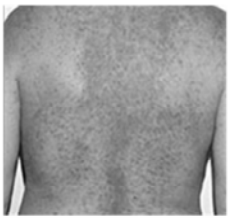
So, we talked about a plateau. The evidence for the plateau is further reinforced by an expanded access trial that was done by BMS prior to the approval of ipilimumab in 2011. Between 2010 and 2011, we had finished those studies. The drug was not approved, and that is when you do a "expanded access protocol." This got a little bit out of hand because it ended up having almost 5,000 patients, which would have to be the biggest trial I have ever participated in, but what it did was it gave you a real-world experience with ipilimumab, mostly second- and third-line patients, and if you look at 3, 4, and 5 years, the data that were collected were pretty much survival and toxicity, but it gave you a feel for what the long-term survival was with ipilimumab. And the suggestion is if you get to 3 years, you are going to stay there for a long time, and the implication is there is a 20% plateau. There is a "tail on the curve," and the difference compared to a control of chemo would be about 10%. So, for every 10 patients you treat, one of them is probably going to be out there, probably cured, and I dare to use the C word with melanoma, but indeed, I think you would agree that if you expect in the alternative treatment, the plateau to be here, a 10% change, would mean one additional patient out of 10 would probably be cured because the 3, 4, or 5 year survival rates are identical, they are all at 20%, and that has been shown.



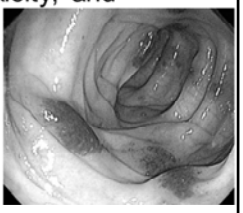
We have had a lot of other trials where there have been piloted clinical protocols of adding things to ipilimumab, and I have been responsible for adding dacarbazine, carboplatin and Taxol (paclitaxel), a whole bunch of different agents. And none of them really were promising, but this is one very interesting study that will be followed up on, which is a relatively small study. It was only about 250 patients. So, it was a randomized phase II study not definitively powered to show a difference in survival, but if you look at the survival curves, it is pretty interesting. It looks like a lot better to get ipilimumab plus GM-CSF versus ipilimumab alone. Why GM-CSF? Well, GM-CSF may have some immunologic activity, and it is based on the fact that in animal models if you gave a GM-CSF vaccine with ipilimumab, it works a lot better than just giving ipilimumab alone to the animals. So the investigators thought, well, why not to give them GM-CSF? We do not have a GM vaccine that is easily useable, just give GM. And amazingly it worked and bizarrely enough it decreased the side effects to some degree, and there is some theoretical reasons why that might happen, but it was a very interesting study, very surprising, and the question is, look at the hazard ratio of 0.64. The *P*-value, and this is stated as a one-sided, it really should be a two-sided *P*-value, that would be 0.02 kind of borderline, I mean you want to see 0.1 or better, but still with short followup, it is only a year, those curves look significantly different to me, and the *P*-value looks real, so this will eventually get followed up on with a larger trial. But there has been some reticence, and I think this just actually got published.

Ipilimumab treatment and immune related adverse events (irAEs)

- Blockade of CTLA-4 frequently leads to the development of irAEs, due to T cells losing tolerance to self-antigens
- Common autoimmune adverse events include
  - Dermatitis
  - Hepatitis
  - Endocrinopathies/pituitary dysfunction
  - Enterocolitis

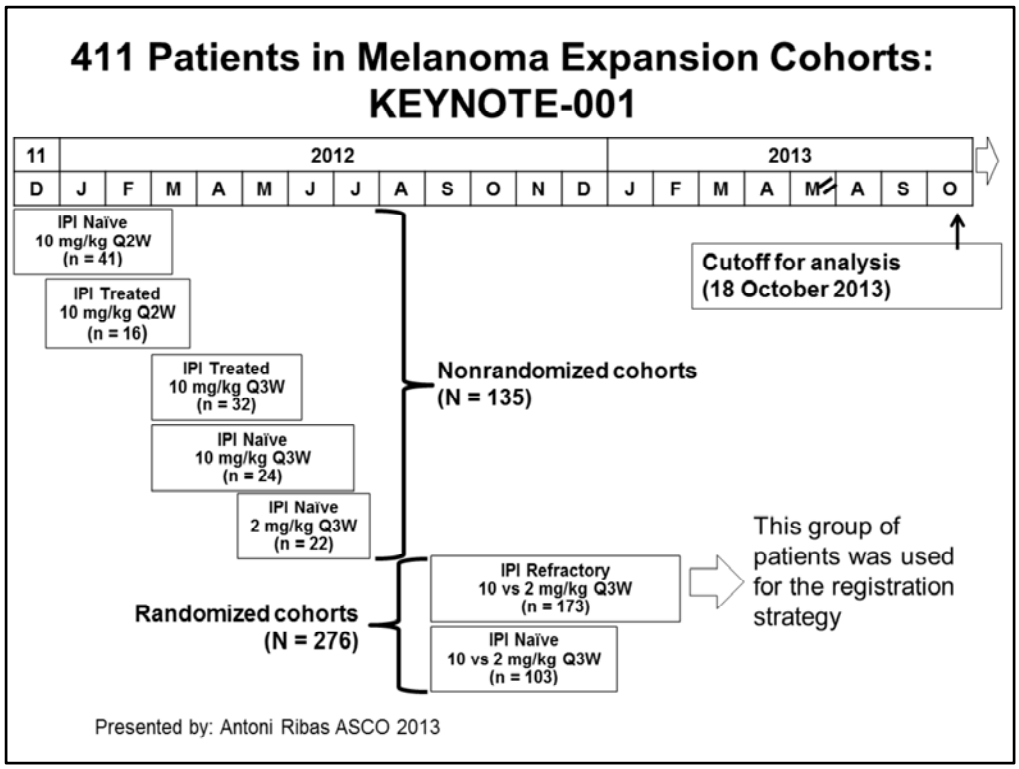


- Diarrhea is often the first manifestation of autoimmune toxicity, and requires prompt and aggressive treatment
  - Antidiarrheal agents (loperamide or diphenoxylate/atropine
  - Intravenous and/or oral corticosteroids
  - Oral budesonide
  - Infliximab (anti-TNFα antibody)
  - Surgery in extreme cases (<1%)

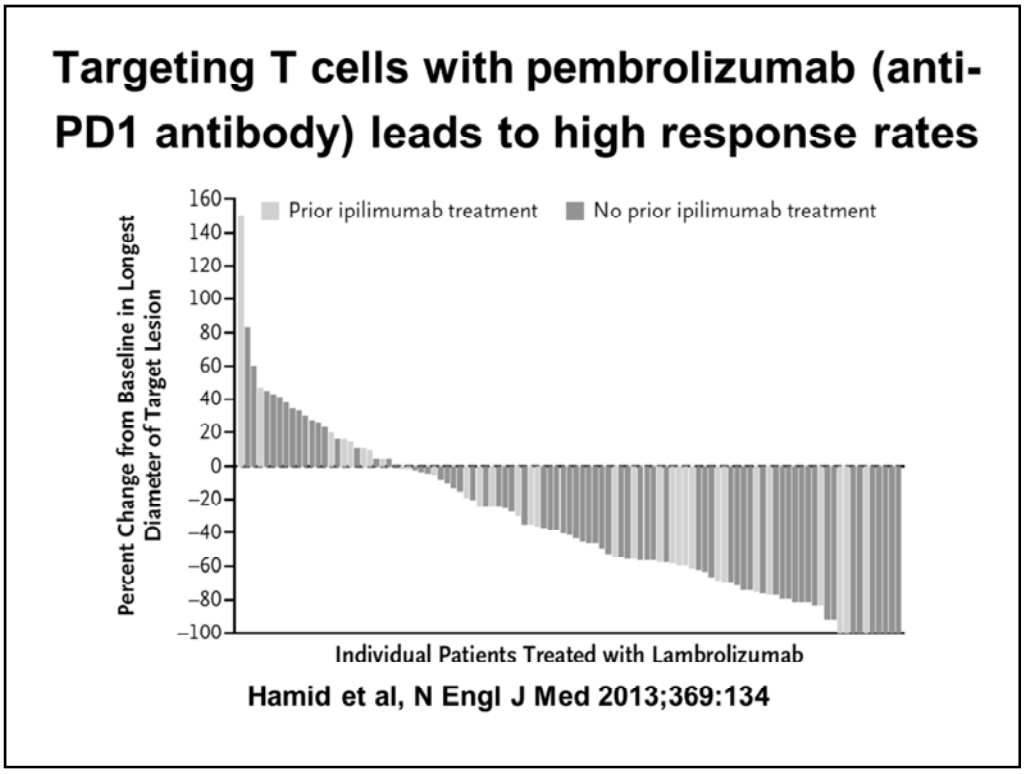


- Toxicity does not equal response, but there appears to be an association

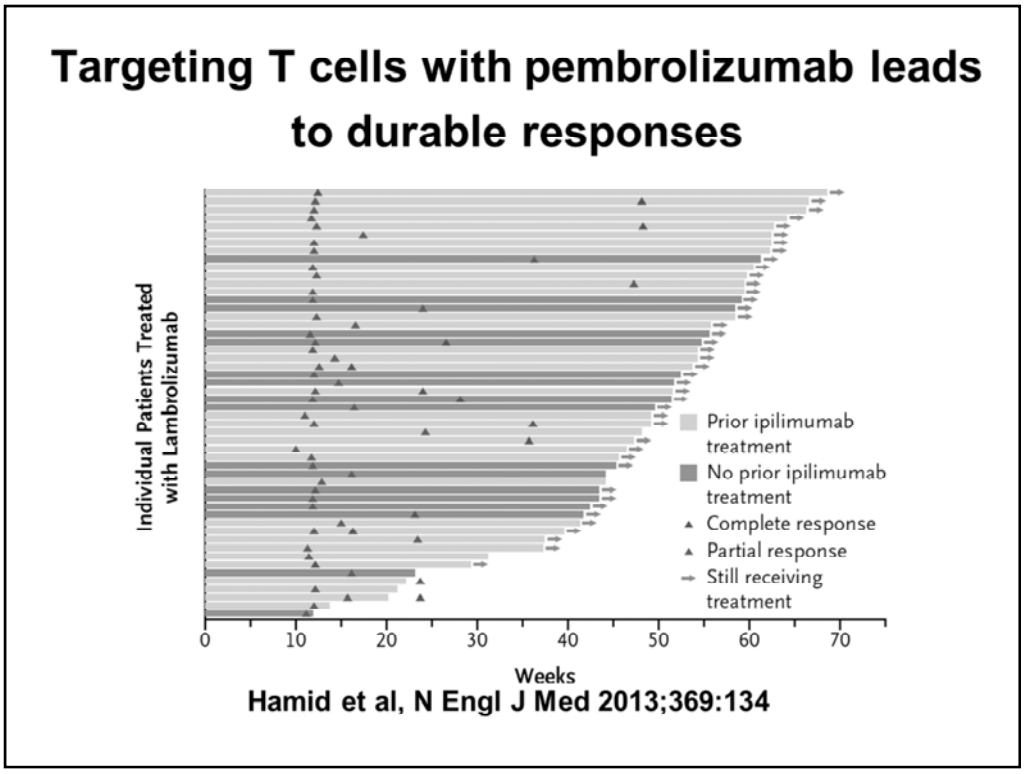
So, those are good pieces of news about ipilimumab, but the bad news is the drug has some toxicity, and it does not just have toxicity, it has unique toxicities that as of the first time I used the drug, which I guess would have been the end of 2001 beginning of 2002, so it was a long time ago, was perceived as being unique and very different than anything I had ever seen with chemotherapy IL-2 vaccines, you name it. And these are so-called immune-related adverse events, and they are directly related to the physical activity of the drug as a stimulator of immunity, and as I tell patients, as you can imagine if you are giving an immunostimulant that takes the brakes off immunity, your main side effects are going to be overstimulation of the immune system, and that is just what this was, and these immune-related or auto-inflammatory events were skin, liver, endocrinopathies, and pituitary dysfunction; 15 years ago, if you had seen autoimmune hypophysitis, inflammation of the pituitary, that would have been publishable. If any of you in the room in your practice observed, you probably sent in a letter to *General Clinical Oncology*, and they published it. Well, it turns out that about 2% of all ipilimumab patients get hypophysitis, so it is not so uncommon, and it is very common and keeps the endocrinologist very busy; 10 years ago, I thought of the endocrinologist as like the Maytag repairman. Remember the guy who would sit around waiting for phone call?" I mean unless they were treating diabetes, they had nothing to do. Our endocrinologists have 50 to 80 patients in their practices with hypophysitis, low thyroid, and low cortisol, and they actively manage them for us and participate in their care. You can also see enterocolitis which with ipilimumab about 6-7% of the time can be severe at grade 3, and that is a very ugly looking ulcerated yucky sigmoid colon, and that is a serious side effect that we take very seriously. You can see some impressive eruptions, and again, you can always say well nobody ever died of a rash, but early on the development of ipilimumab there were two patients who died of toxic epidermal necrolysis. So, you have to be very careful about the rashes, easily treatable, as is the colitis, but you have to be on the lookout for it, you have to know how to handle it. Diarrhea is often the first manifestation of autoimmune toxicity, obviously colitis, and you got a jump on it, and you got use antidiarrheal agents, you got to keep them hydrated, and if someone gets grade 3 colitis, which means it is severe colitis, abdominal pain potential obstruction or more than seven diarrheas in a day, 24 hours above baseline, that is grade 3 and they are going on oral corticosteroids or you are going to give them a shot of Solu-Medrol, admit them, hydrate them, and then put them on an oral taper. The first patient I have ever saw with colitis, I gave a 20-day taper, that was a big mistake. That was back in 2002. You give long tapers, 30 to 45, days because there will be a recrudescence of the symptoms. I often use oral budesonide to treat symptoms, although in a trial we did to test it as a prophylactic measure to prevent diarrhea did not work, but it can be therapeutic, and if steroids do not work and the patients are really sick, you give them infliximab, which is the TNF antibody used by our rheumatology colleagues for Crohn's, colitis, pediatric Crohn's, psoriatic arthritis, and rheumatoid arthritis, and you can take the patient, and Jason has probably seen this, you can take a patient with 10 diarrheas a day in the hospital, grade 3 colitis, bloody diarrhea, give them a shot of infliximab because the steroids did not make them better after 72 hours, and in the next day, the patient will say, "Doctor, I feel wonderful. This is a miracle. I have not had a diarrhea all day." It is an amazing drug, and we will soon be writing a trial to test whether giving infliximab upfront is better than just giving steroids in the beginning. And finally, it is very rare to ever use surgery in someone who gets colitis. I have seen may be two cases in 550 patients, but if you cannot put the bowel to rest any other way, you do a diverting ileostomy, and I guarantee that will put the colon to rest if you have severe colitis resistant to everything, and the old saw about toxicity equaling response is not true. Plenty of patients who have no toxicity whatsoever have great responses. You can have toxicity and do very poorly. The association is very, very weak.



So, that was ipilimumab. While that drug had been approved. We were developing other agents that blocked as you heard PD-1 or PD-L1. Now, CTLA-4 is one break. Ipilimumab blocks that. The other break more important in the tumor microenvironment is PD-1 on the T-cell. So, how do you block it? You have an antibody, and one of the antibodies that first got to a definitive trial was pembrolizumab, and it was called the KEYNOTE study, and this was a very messy study that started out as a phase I study. In ipilimumab-naive patients, they were using 2 mg/kg every 2 weeks, 10 mg every 2 weeks, and with an antibody, you generally do not need to go above 10/kg, but look how many different cohorts there were. There were ipilimumab-naive patients, ipilimumab pretreated, 10 every 3, 2 every 3, 3 every 2, it was just a mess. It ended up being a 411 patient study, and one of the cohorts was a randomized cohort of 89 patients at 2 mg/kg every 3 weeks, which ultimately led to the approval of the drug, but the trend in oncologic development today is not that you do a phase I study, but you just keep going and extend the phase I into a gigantic phase II. And this was technically a phase I/II study,

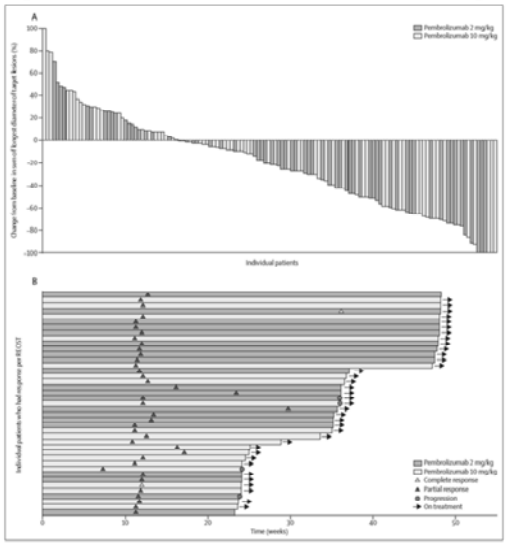


but look at the waterfall plot, this was for a subset of patients, in fact its original name was lambrolizumab, it is now pembrolizumab. That is a pretty damn impressive waterfall plot, and this is an immunologic agent with overall a 40% response rate whether in ipilimumab refractory or ipilimumab-naive patients, and that is a fantastic waterfall plot. Now, over time with more experience, this being a subset of 135 patients of the original phase I/II study, the ipilimumab refractory patients do not do as well as the ipilimumab-naive patients, no big surprise, but look at the swim plot,



again this is duration of treatment. At the point when this was published the average patient was out about a year, but nonetheless, look at all the arrowheads, something like 90% of the patients had a maintained response over time, so look at the sustained responses, all those arrowheads, this a response that is ongoing. So again, very impressive, published last year in *The New England Journal of Medicine* suggesting that not only did you have a high response rate in the 40% range, but they were durable responses.

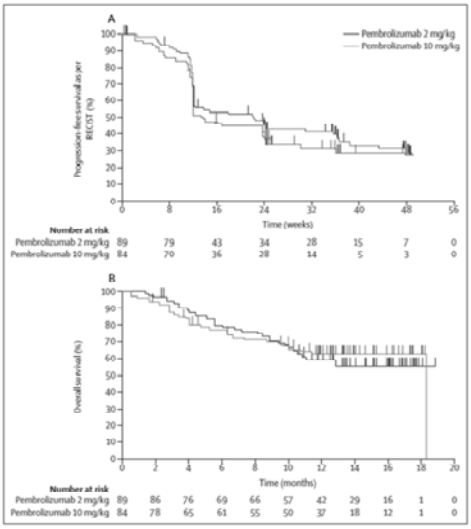
Targeting T cells with pembrolizumab leads to frequent and durable responses



Robert et al, Lancet 2014;384:1109

Since then, we have gone onto see other trials of pembrolizumab. This was just published in *The New England Journal of Medicine*. It was presented at our society for Melanoma Research Meeting a couple of weeks ago, and it was a randomized trial of different doses of pembrolizumab versus dacarbazine in second-line therapy, and if you look at the plots, very impressive, again very nice waterfall plots, and again, the same thing, you have a 90% plus rate of durable remissions, meaning patients continue to get treated, even though the followup is short, they continue to get treated, stay in remission. We are probably talking that 2-year plus duration of response which is fantastic,

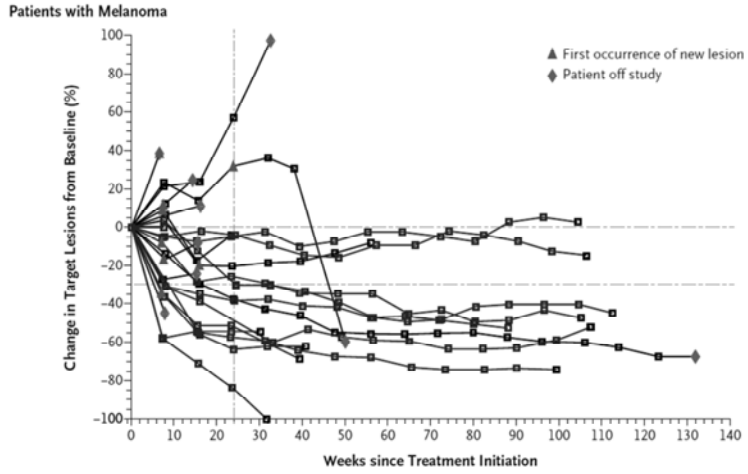
Targeting T cells with pembrolizumab leads to prolonged progression-free and overall survival



Robert et al, Lancet 2014;384:1109

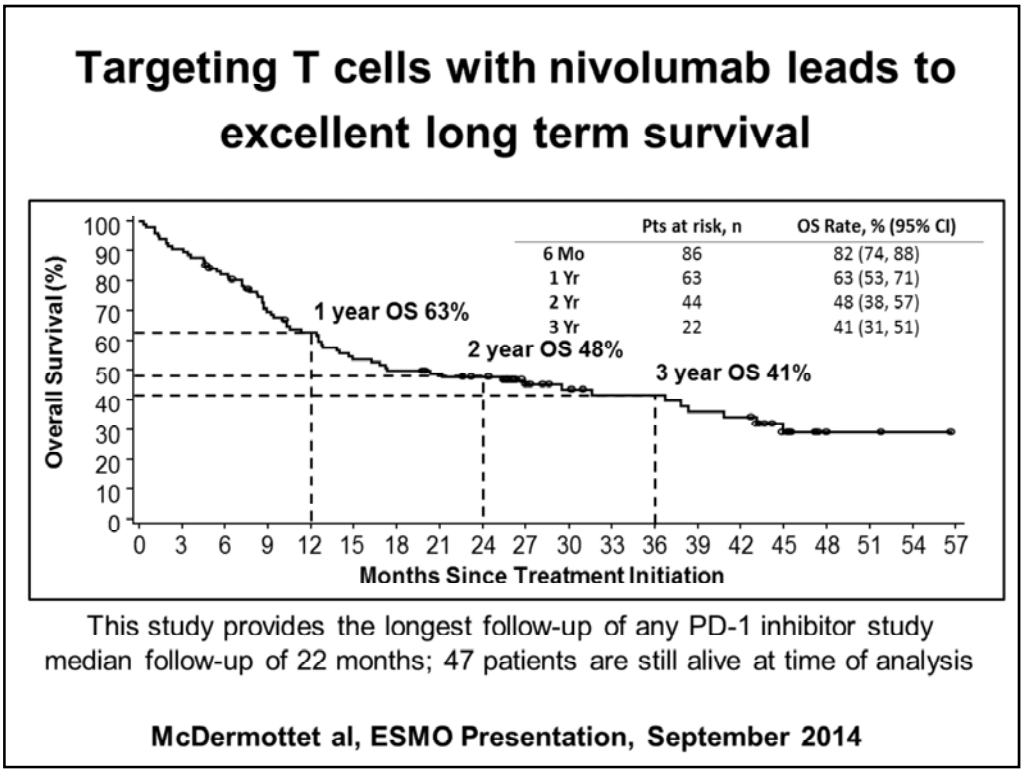
and if you look at the data, again this was published in *Lancet*, and if you look at the data in this randomized trial, this is 2 every 3 versus 10 every 3; if you look at the progression-free survival, actually pretty much the same. So, it does not matter if you jack up the dose; overall survival, not bad. If you look at, even though the followup is short, if you look where the median is, you have not reached the median yet, and again, the survivals as well as the PFS do not change with the dose, so pretty much they overlap, which is why 2 mg/kg every 3 weeks was taken to the FDA for approval. The company feeling 'why to use a higher dose with potential for higher toxicity when you can use a lower dose and get just as good an outcome?' So, these were interestingly the data that ultimately led to the approval. So, if you look at the red line, that was 2 mg/kg every 3 weeks. These were the data that led to the approval. This was the ultimate publication which was in *Lancet*.

Targeting T cells with nivolumab (anti-PD1 antibody) leads to durable responses

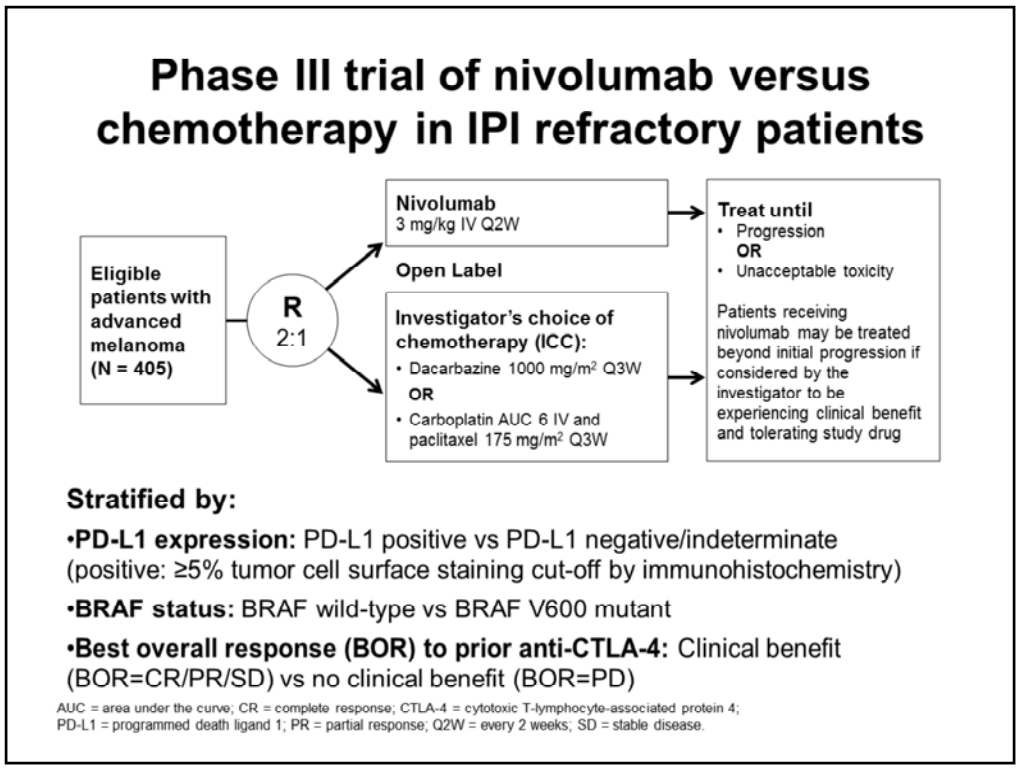


Topalian et al, N Engl J Med 2012;366:2455

Nivolumab is the other PD-1 antibody, interestingly which developed earlier. It was used perhaps a year or so earlier and has been developed in many other histologies than melanoma, non-small cell, bladder, and renal, but these were the original spider plots suggesting that you had very nice looking responses of long duration. So again, the concept with PD-1 is you respond, you stay in remission, you have long durations, this is weeks, because these are responses that are way out there 2 years, and most of the responders who stopped treatment at 96 weeks on this trial stayed in remission, and just parenthetically, I have done my own investigator sponsored trial of that drug at Moffitt. We treated 125 patients. It is a pretty big single institution study. The study is done. It is being written up, of the 13 patients who finished 2-1/2 years of treatment which was what was called for in my protocol, or stopped treatment because of toxicity and was in a stable PR-CR, everybody stays there. So, we have patients out 3-1/2 and 4 years now who have stayed in remission after stopping drug, whether 2-1/2 year's completion or they could have gone off after 24 weeks because they had dose-limiting toxicity but had a response and we just follow them.



So, that is pretty impressive, and this is a followup of the original 107 patients in a phase I study of nivolumab in melanoma showing that 3-year survival of 41% is pretty good. This is probably a plateau as I will show you in a little while, and I would say a 3-year survival of 40% melanoma is pretty darn good,



impressive data which then led to a phase III trial, and I presented these phase III data at ESMO a couple of months ago, and again to get this drugs to approval, the path chosen was not phase II breakthrough designation. It was a classic approach with phase III studies in front- and second-line melanoma. So, this was the second-line melanoma trial, and it was either the PD-1 antibody nivolumab 3 mg/kg every 2 weeks or investigator choice chemotherapy, dacarbazine second-line typically used in the Europe. In the US, we tend to use carboplatin which I think is probably a slightly better drug, and this was stratified by whether you are PD-1 positive because we heard that PD-1 positivity may favor a response, whether you are BRAF mutated or not because we did not know whether the BRAF mutated the patients would do well, and prior response to ipilimumab because this is a second-line study, these were all patients who had failed ipilimumab. So, this is once again the second-line trial, in Europe and in the US, ipilimumab is the front-line FDA-approved treatment most commonly used.

Targeting T cells with nivolumab leads to higher response rate versus chemotherapy

Treatment	N	CR+PR	ORR[a], % (95% CI)	Best Overall Response[a], %				
				CR	PR	SD	PD	UNK
Central review[b]								
Nivolumab	120	38 (4 CR)	32 (24–41)	3	28	23	35	10
ICC	47	5 (0 CR)	11 (4–23)	0	11	34	32	23
Investigator assessed								
Nivolumab	120	31 (2 CR)	26 (18–35)	2	24	27	46	2
ICC	47	5 (0 CR)	11 (4–23)	0	11	23	62	4

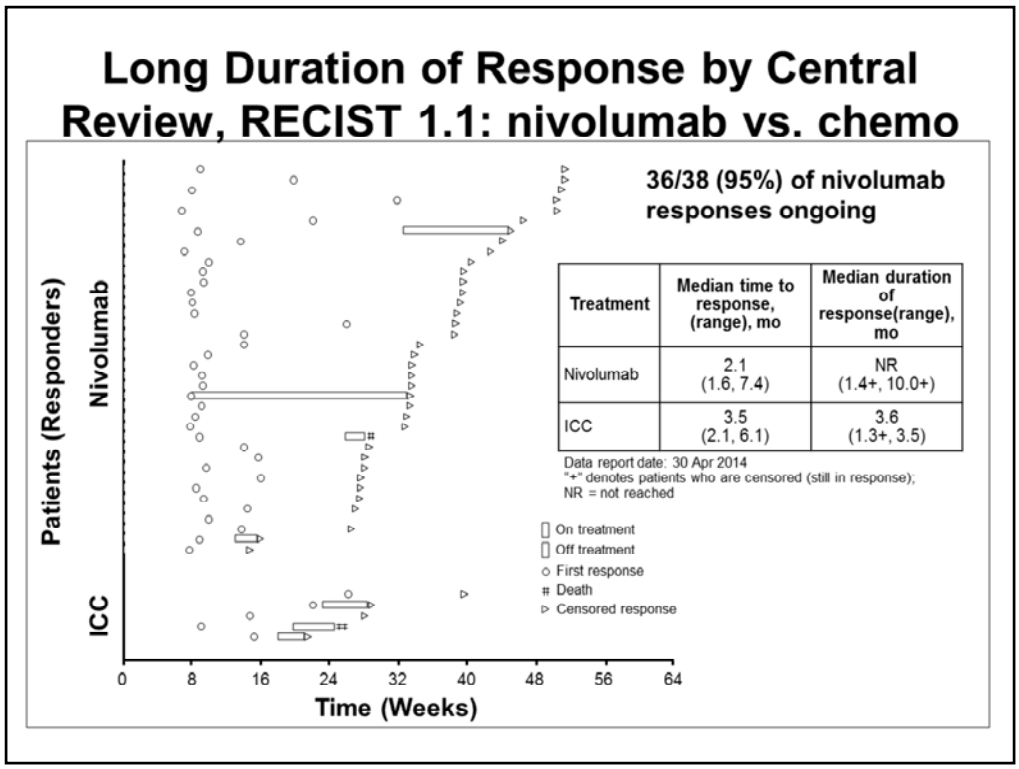
ICC=investigators choice of chemotherapy (DTIC or carboplatin/paclitaxel)

[a] Confirmed response

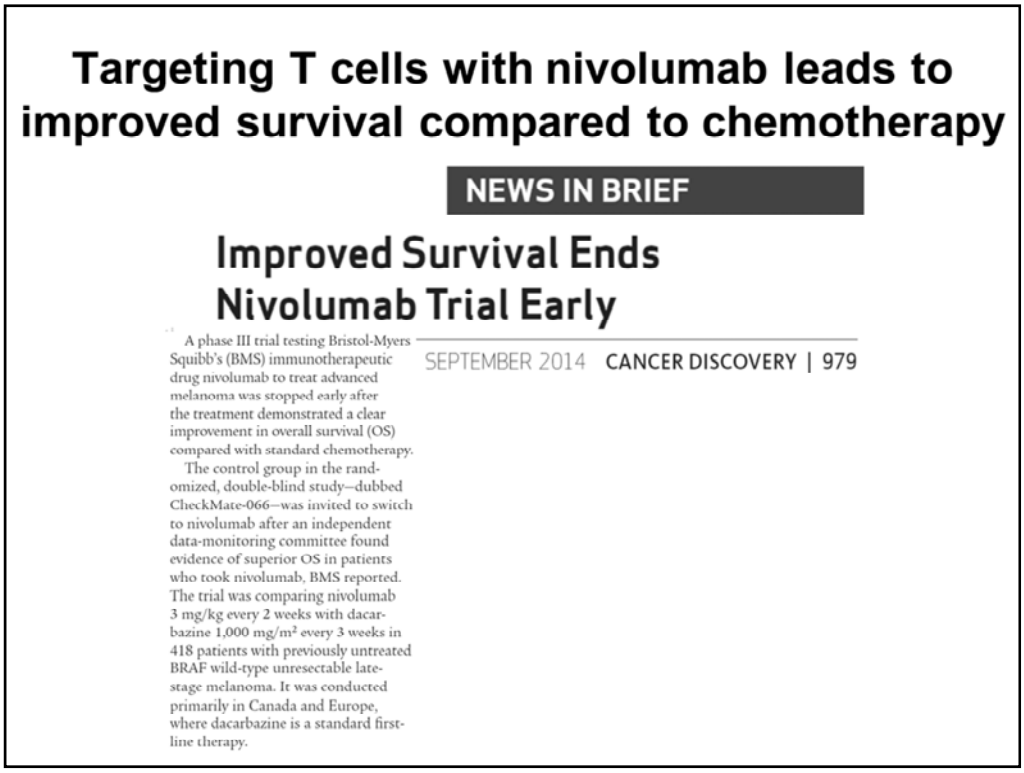
[b] Independent radiology review committee (IRRC) based on RECIST 1.1

Weber al, ESMO Presentation, September 2014

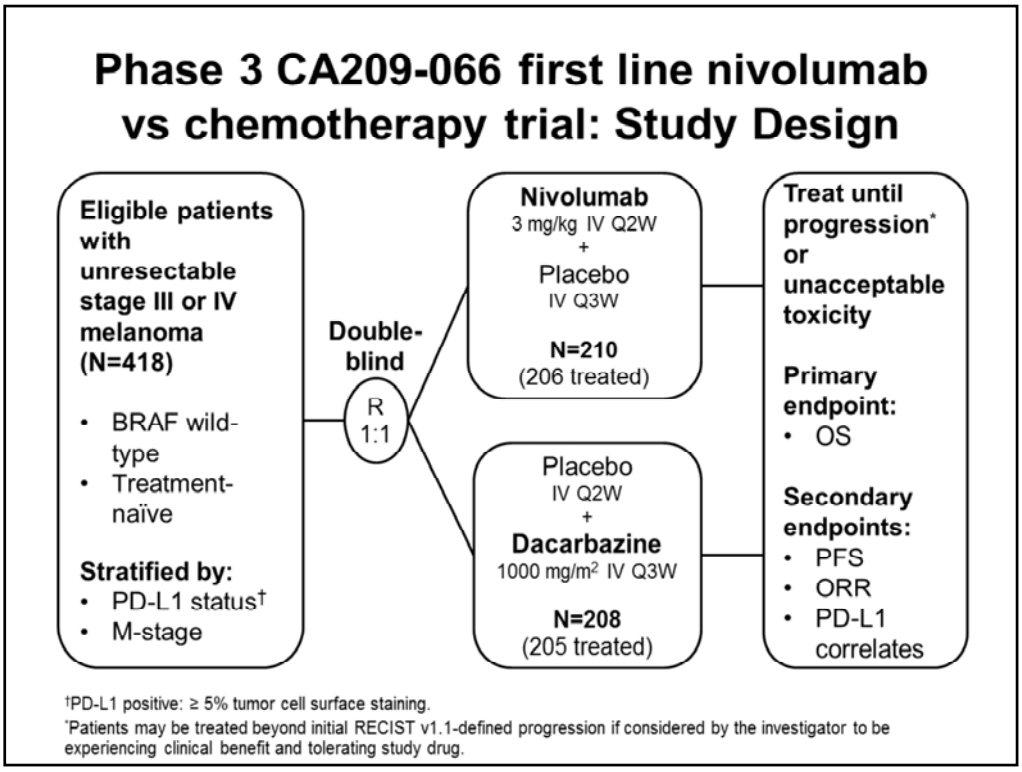
So big randomized study, 2:1 randomization, and here is the data that were the initial data because the endpoints were response with a preliminary assessment after about 120 patients saw nivolumab, and 60 patients had seen chemotherapy, so 2:1 imbalance randomization and 32% response rate versus 11, and this is centrally called. So, this is anonymized centrally called and analyzed response so sort of the gold standard. Interestingly, the investigators were more conservative, 26 to 11, but I think you would agree those numbers are very different,



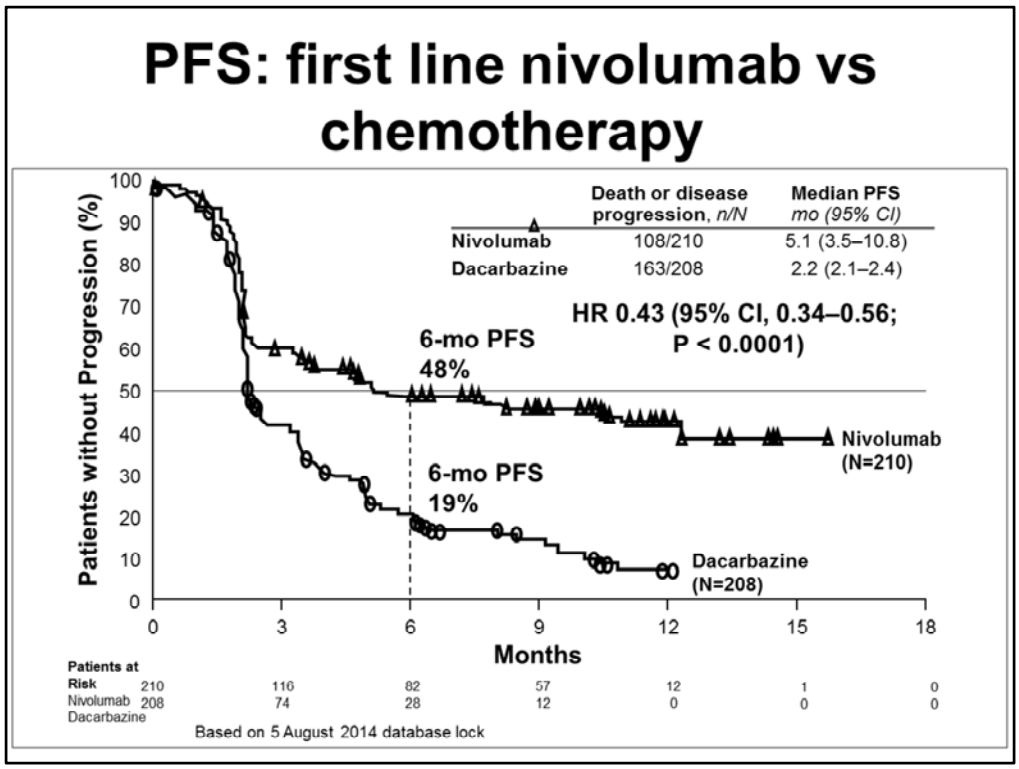
and again, if you look at the swim plot, 95% of the responses to nivolumab have stayed there. All the arrowheads are the patients who stay in remission, and if you look at other things like time to response, it is pretty quick, it is 2 months, for the chemotherapy, longer, no big surprise, and if you look at duration of response it is pretty short for chemo, but it is not reached for the nivolumab, and it is probably going to be beyond 2 years. So, at the end of the day, I think you are going to agree the 24 months is a lot different than 3.6 months. The survival data are not mature, so the way this trial was done was response was regarded by the FDA as the primary endpoint. They also wanted to continue the trial, no crossover allowed so that you could look at survival, and survival data will be out probably by January. Looking at this compared to this with the chemotherapy, I think it is a pretty safe bet that the survival is going to be very impressive. Predictions, and I do not know the data, prediction is we are going to have 10- to 11-month survival with dacarbazine or carbo-Taxol, and you are going to have a 20-month survival here. So, you will essentially double the survival, but we will see maybe I am wrong.



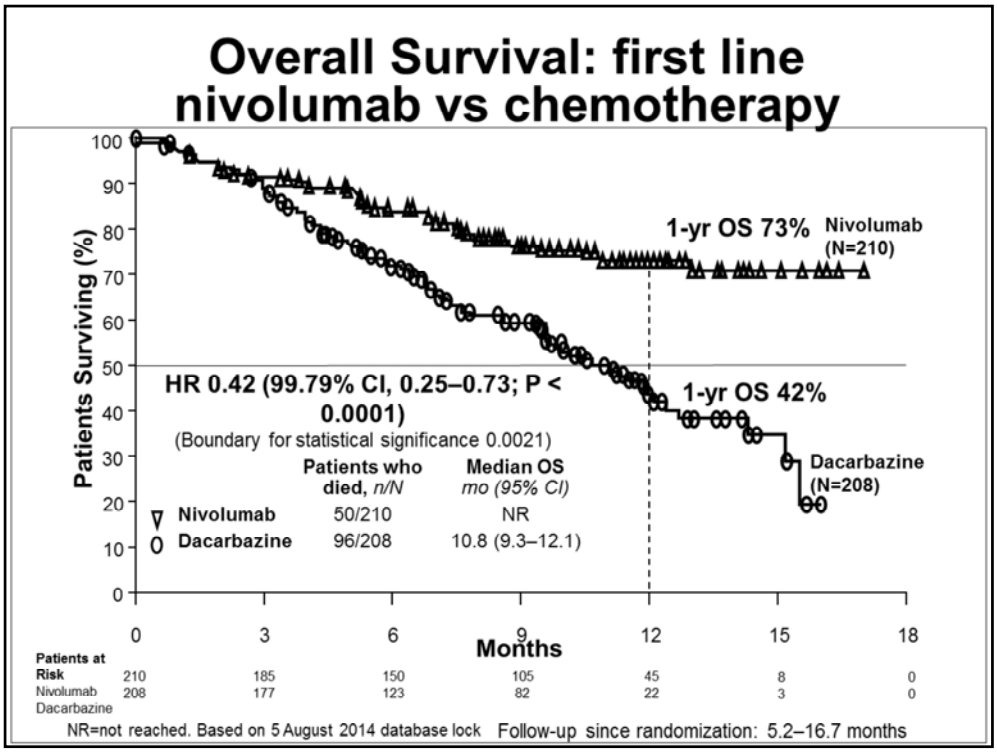
So, came along another trial in front-line, and that led to this, so this was a trial that was stopped early, another phase III trial whose data I will show you in a moment. This was a trial done only in Europe. It was front-line nivolumab versus dacarbazine. In the US, we do not use dacarbazine anymore. In fact, I have not used dacarbazine single agent in probably 5 or 6 years. In Europe, in the era of 2011 to 2012 when this trial was done, dacarbazine was still the front-line favorite. In 2012 I think in Europe, ipilimumab was approved front line, and nobody used dacarbazine anymore.



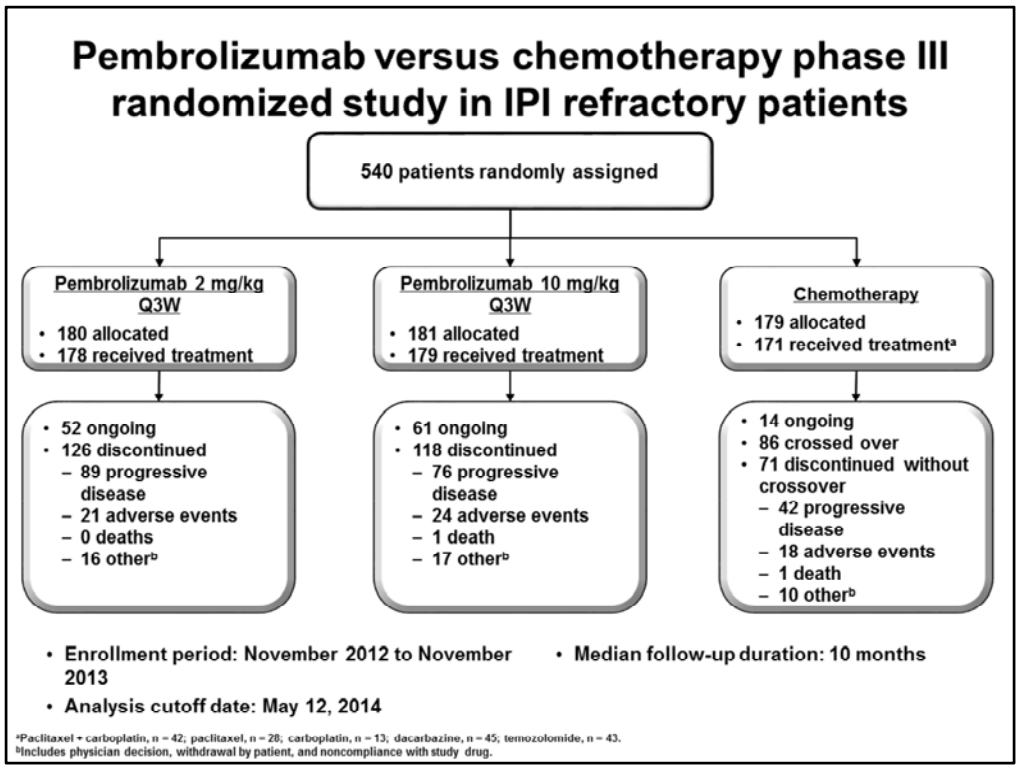
So, this trial was done a couple of years ago, and it was a pretty straightforward trial, head-to-head one-to-one, randomization of nivolumab with placebo versus placebo plus dacarbazine, and again one-to-one randomization, and the primary endpoint was survival and of course the usual secondary progression-free survival and overall response rates.



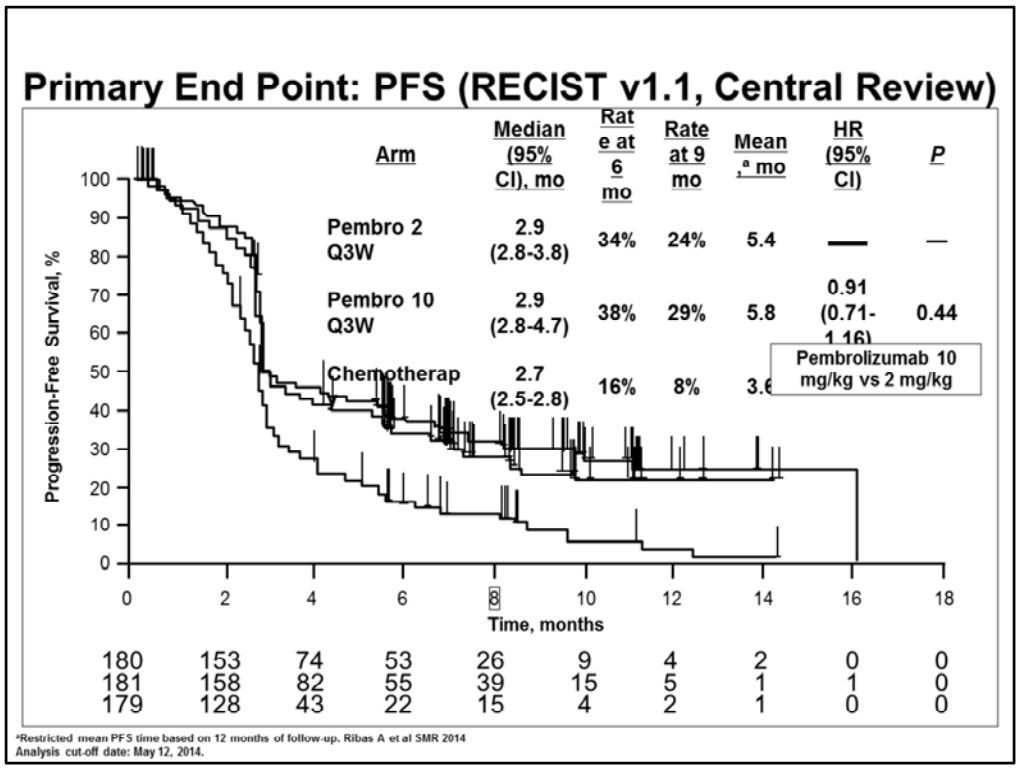
In my view, this was a trial that was a no-brainer, I mean it was stopped early because at the first interim analysis, I mean look at the PFS, I mean it is pretty obvious that this is a very positive trial. Look at the hazard ratio and the *P*-value, it is very impressive in terms of progression-free survival,



and if you look at the overall survival, 1-year survival 73% and it looks as if you are plateauing way above 50%. I mean obviously the dacarbazine survival curve is going to come down almost to the abscissa. That is very impressive, and this is why the trial was stopped early. The hazard ratio is very impressive. I think they were looking for a hazard ratio of 0.5. A hazard ratio of 0.2 is fantastic. The *P*-value is .0001, and again, the median survival has just been reached because 10 months, and the first- or second-line it is probably going to be about the same, for about 10 months, if you project out on the back of napkin the median survival in front line, it is going to be more than 24 months. That is a very impressive difference. These data are available to the FDA as are the data I just showed you from the second-line trial. The approval for nivolumab is pending. They are either going to approve in second-line for ipilimumab failures, and if you are BRAF mutated, BRAF failures, or they can approve it for any line based on this result. So, we will see how that plays out.

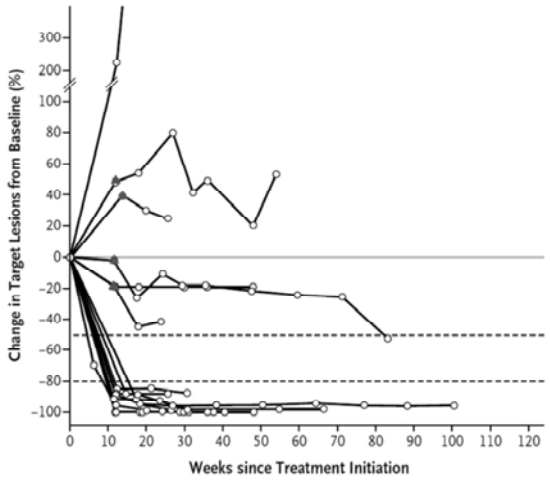


Meanwhile, pembrolizumab has had another phase III trial. This is a different sort of trial design. This was a scenario where the patients were treated in second-line, but it was a crossover study. So, they either got pembrolizumab in the study or they got chemotherapy, and you had two doses of pembrolizumab.



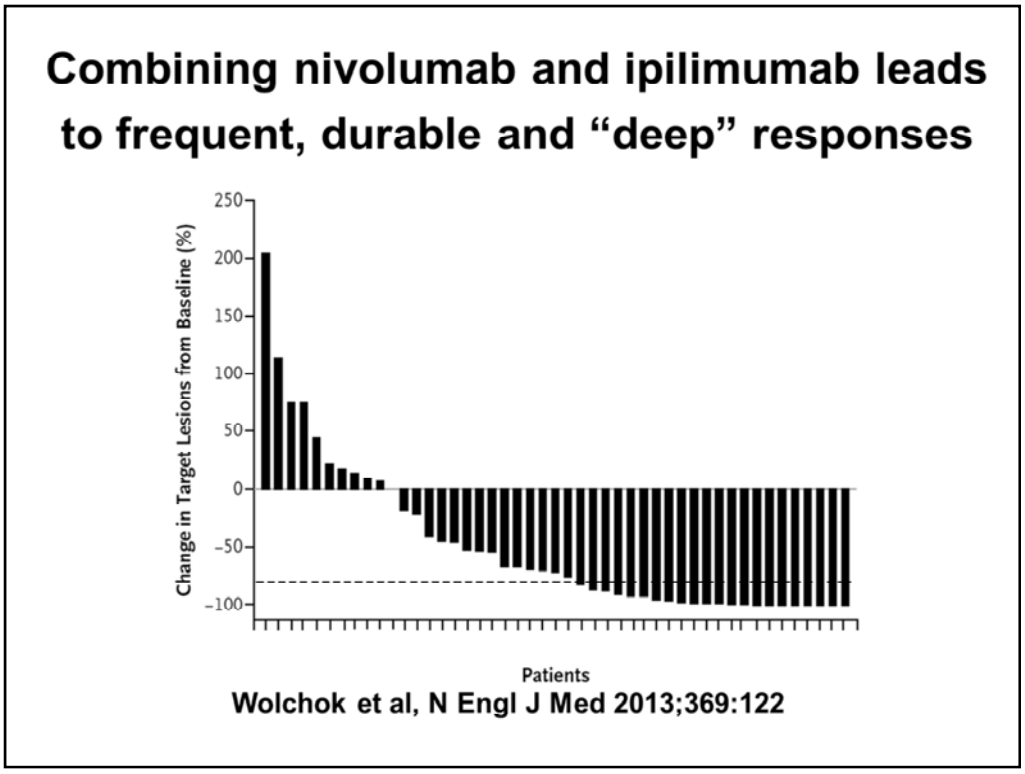
It was 10 or 2, and this is the PFS curve because in this trial, there is a crossover. PFS was the endpoint, and that was acceptable to the FDA because they had a high response rate that led to breakthrough. The FDA wanted to see some more information in a randomized trial. So, looking at 10 or 2 every 3 weeks, no real difference; PFS curves look identical; chemotherapy arm, no big surprise, significant difference, very impressive hazard ratio, and I think it is pretty obvious that there is clear benefit to giving pembrolizumab, the other PD-1 antibody, to the patient in second-line melanoma. You are not going to get a survival curve of any significance. A, it is too early. B, there is a crossover.

Combining nivolumab and ipilimumab leads to frequent, durable and "deep" responses

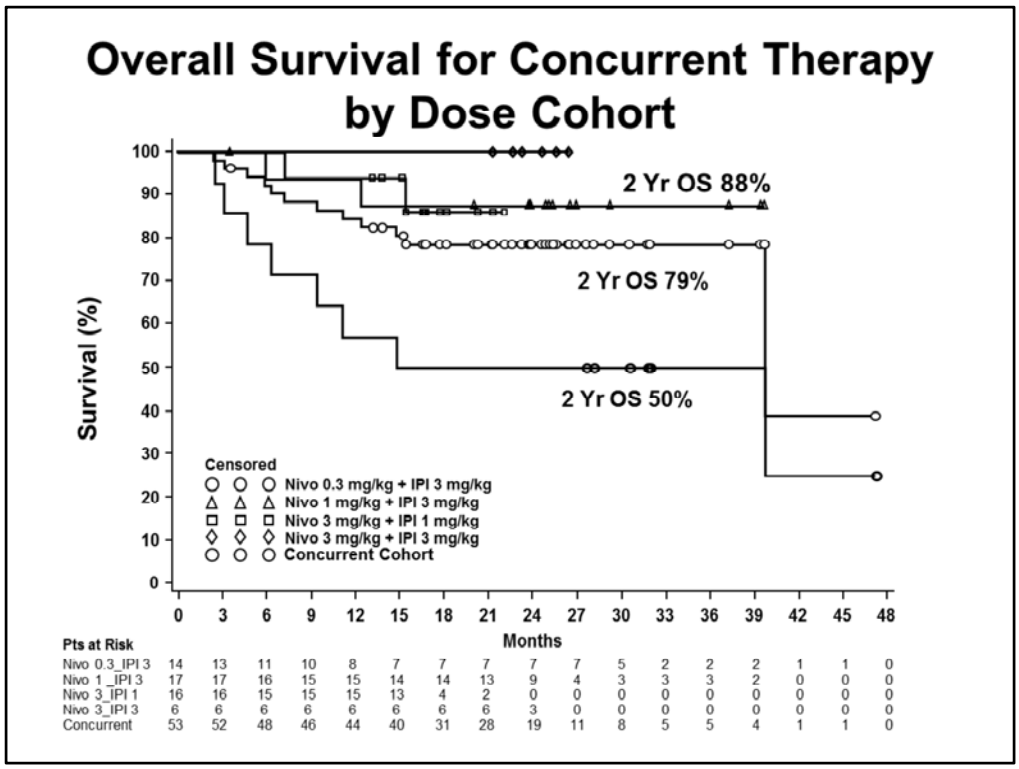


Wolchok et al, N Engl J Med 2013;369:122

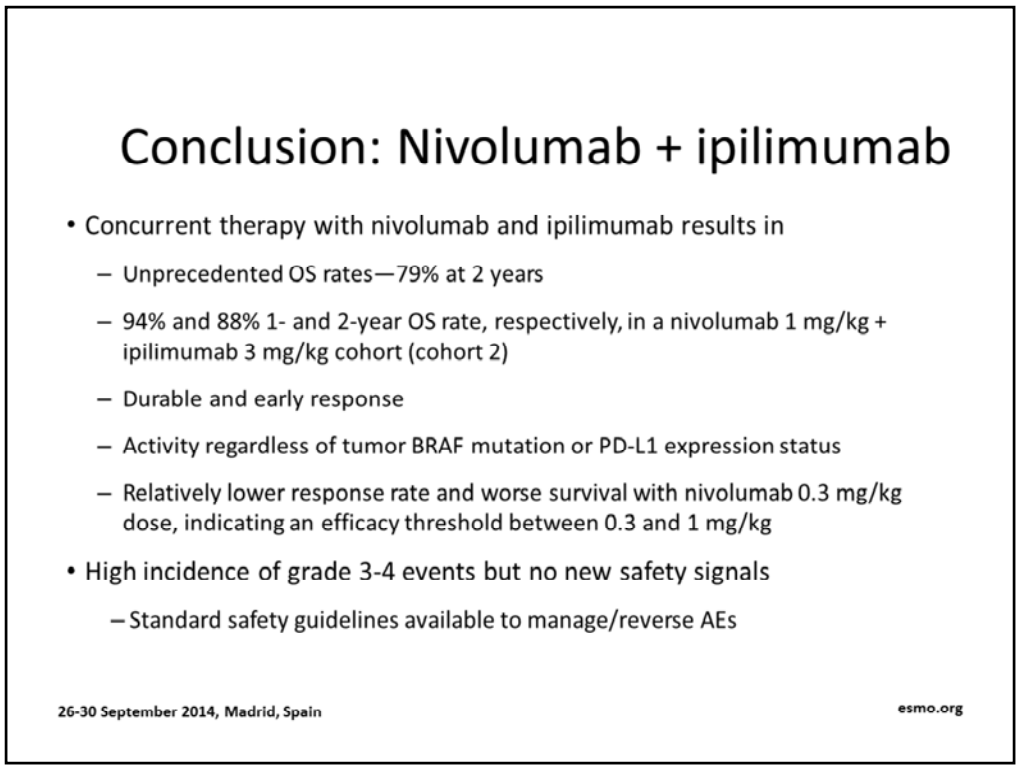
Now finally, what we are going to do now? We have some very nice drugs, pembrolizumab is approved, and nivolumab will probably get approved in the next month, second line. The FDA could be very generous and approve it both first- and second-line, but Jedd Wolchok and Mario Sznol have pushed the idea that you should be combining the drugs. Well, nivolumab toxicity by the way is very modest. It is may be a 5% rate of dose-limiting toxicity, 10% rate of grade 3-4 toxicity overall. It has got half the side effects of ipilimumab, and it has got triple the response rate, so how can you go wrong? But if you put the drugs together, you might have additive or even synergistic toxicity. On the other hand, this is a spider plot of an initial trial of a modest number of the patients, 30 or some odd, who got concurrent ipilimumab and nivolumab, and that is pretty impressive. If you looked at a spider plot of just one drug or the other, you would see a fairly descent spider plot, but it would take a bit of time to see the response. The ipilimumab responses, I showed you were very slow. These are not slow responses. These are rapid responses where the majority of the patients had very impressive plots like this.



This is what you would see with BRAF inhibition. This is an amazing waterfall plot, and this is again published by Jedd in *The New England Journal of Medicine* last year showing something like a 45% response rate, 80% of the patients had evidence of tumor aggression, and in those who responded, the depth of the response, meaning the amount of tumor regression that constituted the response, was 80% and more in the most of the folks,

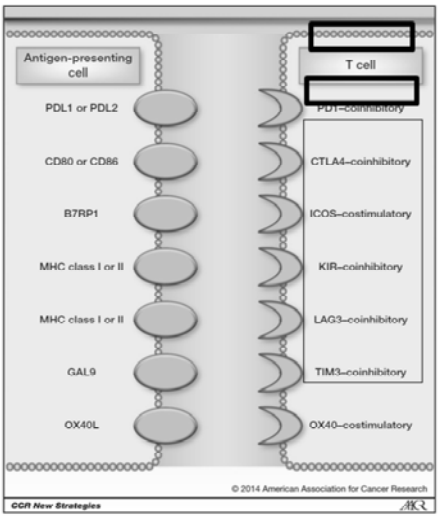


and if you add together the survival of everybody who got concurrent ipilimumab and nivolumab, 2-year survival of 79% in melanoma is the best you have ever seen. That is really phenomenal. On the flip side, the grade 3-4 irAE rate is 62%, and that is not additive, that is sort of synergistic because it is about a 14% rate with ipilimumab. It is about 10% with nivolumab. If you added them that is about 25%, 25% is not 62%. So, this is a very toxic regimen, although many of toxicities are biochemical, but very impressive survival data.



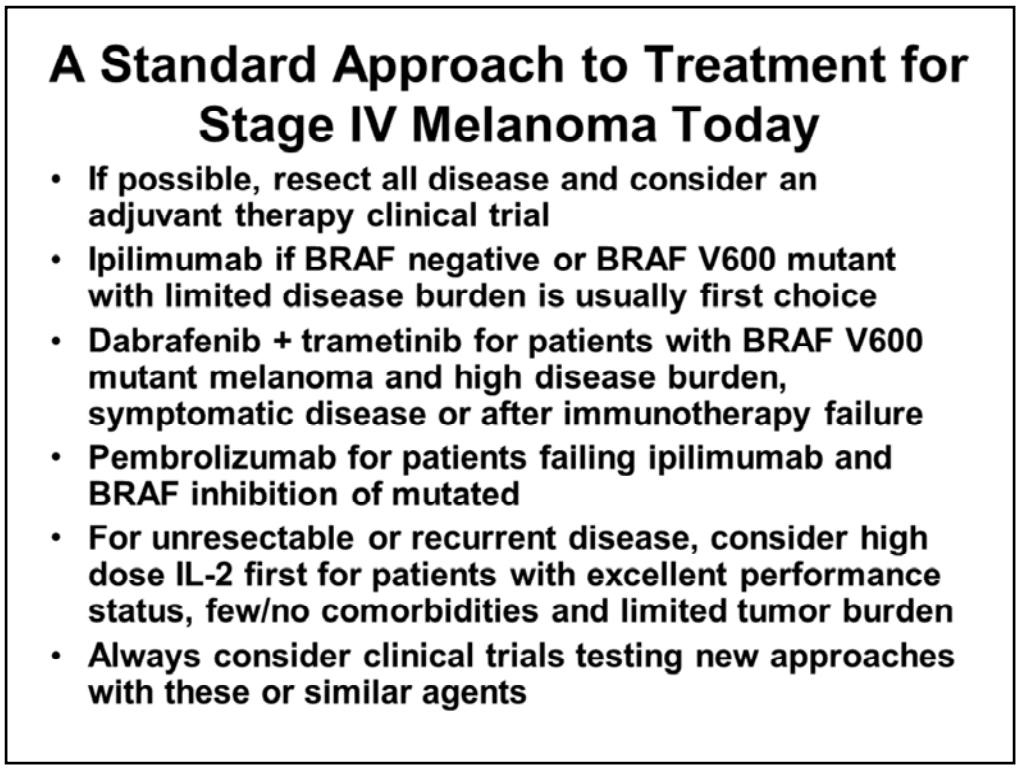
So conclusions on the combination which I think in some ways is the future because we are not just going to use single-agent checkpoint inhibitors anymore, we are going to try to combine them. I agree this is an unprecedented survival rate, 2-year 80%, that is fantastic. The 1-year survivals are also very impressive, and by the way, it is probably just as good if you add pembrolizumab to ipilimumab. So whatever PD-1 or PD-L1 antibody you add to ipilimumab it is probably going to look good. They are durable responses, they happen early which is different than ipilimumab alone, and PD-L1 positive, PD-L1 negative does not matter; BRAF mutated or not does not matter; all these patients have great responses. So, on the flip side, there are no new safety signals but the absolute rate of grade 3-4 toxicities is pretty high, and you can manage them. A lot of patients bizarrely enough have asymptomatic amylase and lipase elevations and feel perfectly fine with an amylase of 1,000, and actually these days, when we get amylase that goes up to grade 3, we just treat through it and have no problems.

PD1 and CTLA4 are not the only targets! The future is bright for immunotherapy



Forde et al, Clin Cancer Res 2014;20:1067

So, just to end up, it is not just going to be about PD-1 and CTLA-4, as you saw, you have seen a couple of slides, there are all these receptor-ligand interactions on T cells between the T cell and the tumor that hit the brakes. You probably have 15 different sets of brakes on the immune system, and it turns out that many of them are overactivated in the malignant state, and we may need to start combining antibodies, that is what next up the road. We have now a LAG-3 trial. It will be a TIM-3 trial. It will be VISTA trial. So, all these antibodies that block the breaks and combining them is probably going to be better than anyone alone.



So, again to conclude, when you are managing stage 4 melanoma, try to resect all disease if you can and then try to put them on an adjuvant treatment or trial. If you are BRAF wild type, ipilimumab is the front-line approved therapy, and pembrolizumab is the second-line therapy. Soon it is going to be nivolumab in the next month. If you are a BRAF mutated with limited disease, I would go the immunologic route, and that will be up to the patient and that is discussion between you and the patient. If you have V600 mutant melanoma that has got high-disease burden and rapid growth put them on dabrafenib-trametinib, Tafinlar, Mekinist, that is I think the way to go. If you fail ipilimumab, pembrolizumab is the next step. You can do it if they are BRAF mutated or not. They do well either way. If you have unresectable or recurrent disease and you fail those two treatments, high-dose IL-2 should be considered in the right kind of patient, meaning someone under the age of 70 who if they are over 50 can pass a stress test and who tends to have relatively low disease burden. Someone with 50 liver metastases, bone metastases, and a performance status of two is not going to get high-dose IL-2, and again always think of clinical trials.