What's Hot & What's Not in Immuno-Oncology Licensing

Based on Two Web Panel Discussions
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1 Linda Pullan: What is immuno-oncology, and why is it so hot right now?

Axel Hoos:

Immuno-oncology (I-O) is a rapidly evolving field that focuses on the immune system in the fight against cancer. Immuno-oncology strives to find new ways to stop cancer from evading the immune system, thereby restoring the body's natural ability to recognize and eliminate cancer. Cancer is a disease that arises from the body's own tissue. In response, the immune system tries to create some kind of a balance so there is not a destructive response against its own tissue. So, there's a huge opportunity to use the immune system to fight cancer. Obviously this can be done in many different ways. The idea is actually a century old, however, until recently we haven't had the tools to understand the mechanisms of the immune system well enough to develop any mechanism-based drugs.

It's early, but with a better understanding of immune mechanisms and the development of new tools like monoclonal antibodies to target immune mechanisms things are changing quite dramatically. In the last twenty years we've seen many approaches, mostly cancer vaccine-like approaches, toward immune manipulation, but those were largely unsuccessful because we did not fully appreciate the immuno-suppressive side of the immune response. You can stimulate the immune response, but it can also be suppressed. The immune system usually tries to create a balance between stimulatory and suppressive mechanisms.

With a better understanding of checkpoint blockades as the mechanisms that control immune response, we are now more successfully manipulating immune responses and achieving real clinical benefits. Immuno-oncology is very young, but it's moving along at an extremely rapid pace. We've already seen three generations of cancer immunotherapies. The first was in 2011 when the CTLA4 antibody, Yervoy (ipilimumab), was launched generating a lot of interest in cancer immuno-therapy across the community. The second generation was the expansion of immuno-oncology into the PD-1 and PDL-1 axis of checkpoint modulation. We are now entering the third generation where we are seeing a variety of new approaches to modulate the immune system. So, the door is now being opened to a very wide playing field.

2 Linda Pullan: What does the early data tell us about how promising I-O therapies might be? Could this just be a frenzy or a tulip craze? How is this different from many of the other trends that have come before?

Jeff Bockman:

The answer to that is quite simple—I-O therapies are not just qualitatively different, but quantitatively different from anything we've seen before. Historically, we've focused on targeting variant nodes within cancer, or more recently using targeted agents to go after alleged key, if not driver, mutations. The problem with the majority of those approaches

is that in some cases you may have high response rates, but you have poor durability. We see resistance emerging very rapidly. What's very different with these new immuno-oncology agents, in particular with checkpoint inhibitors, is not just the high response rates, but the outcomes and durability. We're not sure of the ultimate impact, but the fact that we are seeing impressive successes with monotherapies in previously quite problematic settings like melanoma or later stages of lung cancer speaks to the fact that these agents are doing something very different from other types of cancer agents.

Also, the immune system is unique. By definition the immune system is flexible and adaptable, so in many ways it's the best match for cancer, which has always been considered so problematic because of its plasticity.

Nate Sanburn:

It's important to note that as we see response rates and efficacy develop within this space we're also seeing a correlating increase of new opportunities. The mechanisms and the interactions and the modulations of the immune system currently seem vast. The ability to tweak the immune system to attack cancer cells also opens the door to the possibility that there may be a more broadly efficacious medicine developed that may not need to be as targeted as it has been in the past. Understanding the multiple approaches creates new biology and new opportunities for tweaking the immune system in a certain interactive way that then creates opportunities to explore and pursue those opportunities further.

Jeff:

In addition to responses and durability of response, what also makes I-O hot right now is this multiplicity of targets and approaches. Immuno-oncology is not a monolithic entity; it includes many different approaches—antibodies, checkpoint inhibitors, vaccines—and beyond that there's a whole range of targets, not just on T-cells, but on targeting T-Regs (immunosuppressive T-cells) and other regulatory components as well as innate immunity. Even within one category, such as vaccines, there are a vast array of approaches. So this is a great opportunity for companies, not to mention patients. Many of these approaches will be combinable and will at least have some type of additivity.

3 Linda: How does I-O fit strategically? Will every company that sells cancer drugs have to be in immuno-oncology?

Axel:

In the long term, in order to have a viable business model, at least every large pharma companny with an emphasis on oncology needs to be in immuno-oncology. As immuno-oncology matures, we are already seeing it replacing standards of care, such as with some of the checkpoint modulator Phase 3 programs that have emerged. Chemotherapy is being pushed aside. Over time, we will see combinations and we will see additional monotherapy approaches where standards of care will

at least be challenged, if not replaced. In the long term, immunotherapy will probably dominate oncology. Therefore, for every serious company that wants to develop oncology drugs, it becomes an unavoidable component of their portfolio.

Nate:

I agree. It's early and somatic mutations and other types of tumor-based genetic mechanisms will remain on the horizon, but a company won't be able to survive with only those tumor targeted approaches without having a complement in an I-O space.

4 Linda: How much of your efforts are focused on immuno-oncology licensing?

Axel:

At GSK, our focus is strongly on immuno-oncology. That, in part, is due to the unique situation that GSK finds itself in. GSK had a strategic transaction with Novartis that was executed in early 2015 where we divested our marketed oncology drugs to Novartis. What we retained was the R&D pipeline. We've now focused that pipeline to focus primarily on immuno-oncology, epigenetics and cancer stem cells. Our goal is to be a leading player in immuno-oncology.

Ferran Prat:

Right now almost 90% of our activity is focused on immuno-oncology. All of the large transactions we've done lately have been in immuno-oncology. And this is a very unbiased example because MD Anderson does not have a particular strategy; we go where the science tells us to go and this is where the science is telling us to go. It's just astounding the weight of immuno-oncology today within the field of cancer.

Nate:

At Lilly we're putting a large portion of research, licensing, and collaboration efforts into the I-O space. We've been quite successful over the last eighteen months with regards to both licensing and clinical collaborations. And, while we haven't had a PD-1 or PDL-1 that is out front, we do feel that we have very solid combinations. We've done licensing reviews for clinical phase programs as well as early phase programs and we're really getting at the biology and novel approaches that are immunologically-based.

5 Linda: If someone comes to you with an ADC or another targeted approach, in order to be interested, do you require them to demonstrate combinations with immunotherapies?

Nate:

The data has to drive that decision. We always evaluate opportunities (targeted or otherwise) based on what we believe the combinability is. I wouldn't say that we always require the combination data upfront as a standard, but eventually it will be required.

Axel:

At GSK, the data drive the decision. Our strategic focus at the moment is on immuno-oncology, but we do look at other things, just a lot less commonly so. In addition, we do look at the immunological characteristics of a non-immunotherapy agent. From a licensing perspective, but also within our own portfolio, we have retained a few assets that are not immuno-oncology agents. We've done that particularly because they have immunological features that lend themselves to combination therapy. We understand a lot more about what a systemically administered agent can do to the immune system, even if it was designed mechanistically to address pathways in tumor cells. It is given to the whole body and the immune system will be exposed. An understanding of that can make it more useful for subsequent combination therapy development.

Jeff:

People realize now that many of the traditional agents that have been utilized have an immunologic component of their activity and efficacy driven by that ability of the immune system to be modulated by application of those traditional agents. They've always been there, but in the past no one was looking. A good example is the interesting data coming out now about the role of targeting VEGF in the tumor microenvironment and the interaction there with the immune system. Historically this has not been an I-O area.

6 Linda: I see most companies now focusing on I-O. What doesn't fit with I-O?

Jeff:

If you're a small biotech today the answer is, very little.

7 Linda: Do you see things that specifically increase the presentation of tumor antigens?

Nate:

From a licensing perspective, increasing antigen presentation as a general mechanism is not high on our list. It's not as specific as what we'd like to see. General chemotherapies can increase antigen presentation, and you will see that in various forms throughout the types of treatments within the immunity cycle. But as far as general antigen presentation, not as much. As we consider tumor infiltrating lymphocytes and what some of the specific antigens could be, either within the T-cell or within the tumor itself which are unique, those are approaches that we think will have the long-term possibility of having the biology play out and make sense.

Ferran:

At MD Anderson we have a different view. We believe there is a limited reach to current approaches of checkpoint blockades. If we consider breast cancer, or colorectal cancer, immuno-oncology is an absolute must. On the one hand, a lot of things cause neoantigens to be

displayed. On the other hand, it hasn't been proven to benefit patients. Our view is that whoever gets there first with proof of the benefit of increasing antigen presentation will gain tremendous advantage. Other people will come right after them, but still, when you look at melanoma or lung cancer, even though there are other PD-1's in clinical development, the PD-1's from Merck and Bristol-Myers Squibb are expected to do exceedingly well with a first-mover advantage. This may not be so in other cancers, where other PD-1's may arrive first. We believe the major cancers—breast, colorectal, prostate—will be tackled in great part by antigen presentation. When considering pancreatic cancer, for example, it's much more likely a matter of increasing T-cell infiltration.

Axel:

Antigen presentation plays into the space of cancer vaccines. At GSK we have a long history of investigating cancer vaccines, which includes a lot of unsuccessful approaches, which is not to say that antigen presentation or providing antigens to the system to stimulate immune responses is not important; it's a matter of finding its place and we haven't found that place yet. Neoantigens are becoming quite interesting because they are focusing the immune response on potentially more relevant targets. That may help, but it may also require other modalities to maximize the effect and that may mean that the checkpoint modulatory approach that we're currently pursuing with so much success could become useful combination agents. Investigating vaccines together with checkpoint modulatory agents is something that still hasn't been done systematically. There have been bits and pieces, but it hasn't been very systematic. We will need to understand that better before we can really say what the role of antigen presentation in itself will be.

8 Linda: What kind of data would be necessary to gain licensing interest on a vaccine or antigen presentation approach in cancer? Would they need to do that systemic exploration or would you be excited if they had some particularly great data in combination with a PD-1?

Nate:

Again, data drives that decision. It's important to be able to take the biology and validate it through animal models, but also through immune system models. We need to be able to demonstrate the cause and effect that leads to both immune stimulation and also the impact on the tumor. So, when we evaluate immuno-oncology agents for licensing, we evaluate whether the data connects with the biology, the animal models and the validation. Does that require clinical validation? That's a question that can be somewhat case-by-case dependent. But from a Lilly perspective as we evaluate data, we want to ensure that the immunology data, stimulation or the checkpoint impact is lined up with the biology that was expected in the tumor in the microenvironment and then leads to the anti-tumor activity in a model that is validated.

Jeff:

It's still relatively nascent and certainly hasn't been explored systematically nor comprehensively, however, if you look at clinicaltrails.gov, for example, and use that as a surrogate of activity and look at the number of combination studies being done with checkpoint inhibitors, a very solid proportion of those are combinations of checkpoints with vaccines. These vaccines still constitute a pretty large majority of the pipeline of I-O agents, because so many started long before the current age of immuno-oncology as defined by Opdivo and Keytruda, but that is just a function of the limited time that we've had some of these key tools to do those combinations.

The ability to systematically and comprehensively study them is starting to occur. It will take a couple of years, but there are deals that are being done by companies trying to study combinations. Some are the collaborative model that we've seen a lot of with I-O in vaccine approaches with people who own checkpoint. Some are creating the combinations, by licensing or acquisitions, driven either by the vaccine companies, such as Aduro, who just acquired BioNovian in order to access their checkpoint inhibitors to control their own, or by other companies that are reaching out to the smaller vaccine companies such as Immatics or Bavarian Nordic, etc. It's going to be a large and burgeoning area.

The question becomes how relevant the vaccine antigen is to the tumor—many of these vaccines are still based on defined choices of tumor associated antigens, which is in contrast to neoantigens, which really are unique and a one-off from patient to patient. So, those are two very different ideas—on the one hand, preparing some off-the-shelf antigen or antigen-defined targeted vaccine approach, versus the highly personalized immunome analysis that might lead to a personalized neoantigen-driven vaccine that would be combined with some type of checkpoint inhibitor.

Nate:

Increased antigen presentation is not very specific. Specific antigen presentation and how that gets placed within the tumor microenvironment and within the immune system is very key.

Axel:

We've spent a lot of energy in the genomic era to identify mutations and new targets for cancer intervention. That work now has the potential to play nicely into utilizing some of these mutations as neoantigen targets for vaccine approaches. We're currently just scratching the surface, but next-generation sequencing is maturing, which will help us very quickly identify the fingerprint of a tumor in terms of mutation status, not just mutation load, but also very unique and specific targets for that specific tumor, which could be created as personalized vaccines or even personalized T-cells through a TCR or CAR T approach.

9 Linda: Let's talk about approaches such as brakes and checkpoints. Why is this area so hot? What makes PD-1 a backbone therapeutic?

Nate:

As a backbone therapeutic, it's not necessarily the tumor target expression versus the immune approach. It's not specific to just one tumor type, but can potentially be broadly applicable. PD-1 can become a backbone based on the fact that it does tweak the immune system, reducing immunosuppression. It's one of the leading agents, both from a safety and efficacy perspective. There are also a number of other combinations already in development that have the potential to be important and relevant. So, as a backbone, PD-1 is an important agent that can tweak the immune system, while other agents might hit another part of the microenvironment, or the tumor. The combination approach is going to be key, so it's an emerging backbone that will be important across a number of tumor types.

Axel:

Almost all of the clinical promise that we currently see in cancer immunotherapy originates from checkpoint modulation. That's where most of the strong clinical data comes from. That, in part, is because it's a universal mechanism and isn't tied to any specific tumor histology or specific mutations. The modulation of the immune system or the immune response is broad. Also, this can be accomplished through a variety of pathways that are all checkpoints. So, because they are universal targets, they lend themselves well to be backbones. We see that with CTLA-4, which has already been overtaken by PD-1 or PDL-1 approaches. Very soon we will see PD-1 blocking or PDL-1 blocking antibodies become backbone therapies because of the time in which they were introduced. And, as we learn more about other checkpoints, the next generation will fill a lot of gaps that these early checkpoints have created and may provide other backbones.

10 Linda: What kind of gaps have the early checkpoints created?

Axel:

When I say "gaps" I mean that not every patient benefits. So, even though the response rates are high with some of the PD-1s or PDL-1s, not every patient has a response, not every patient has benefit; even with these agents there can be relapse. There are still a lot of open spots for providing patient benefit beyond the first wave of checkpoint modulators.

11 Linda: And you see other checkpoints as able to deliver that?

Axel:

Well, they will contribute. We don't know the full story yet. But immunologically speaking, many of the pathways of the immune system have not been addressed yet and may play a role where PD-1 or

PDL-1 don't provide benefit. We are also seeing combinations that can make a difference. These combinations have to be tested and we have to immune profile patients to identify the right patients for the right drug. We're really just beginning to do that. PDL-1 status in the tumor is the very first step in identifying who will respond to PD-1. It's not a perfect marker, but it provides some important information. There are other biomarkers coming. You will see a variety of approaches to dissect the paths—biomarkers for the immune status of the patient and biomarkers to predict response.

Ferran:

I'm really curious to see how all of this is going to pan out. Here at MD Anderson we are working on a best-in-class PD-1. If you look at the interactions of PD-1 with PDL-1, PDL-2, B7H4, it's not a clean one-to-one binding. It's actually extremely complex. I believe there is a role for a best-in-class PD-1, which will evolve over time. If that's the case, what's going to happen to the other twenty PD-1s that are in development?

Jeff:

That's a good point. The checkpoint inhibitors that are currently defined by the PD-1 or PDL-1 agents are not unlike how things have been historically. They were the foundational, chemo cytotoxic backbone combined with many other cytotoxics across many different tumor types and multiple lines of therapy. So, in a similar way the checkpoint inhibitors are now the new generation that will fulfill that role where everyone will want to combine on top of those. But that also raises the question of whether there will be a best-in-class.

The challenge in oncology is that it's very unclear what that means. The precedence for best-in-class is limited. What often happens is that the first-in-class becomes by default best-in-class because the accumulated data and evidence so entrenches that player that to be displaced something would have to come along that was dramatically different as opposed to just carving out an adjacent spot, or displacing the leader with a modest difference.

I'm not saying that there couldn't be a best-in-class PD agent, but while that is being pursued there's a vast array of next-generation targets that may become the best-in-class checkpoint, as opposed to just the best-in-class PD-1 agent. Not to mention the co-stimulatory agonist and the combinations thereof. There's a great need here for precision. We need to determine which tumors, in which patients, considering their own immune background and the specifics of their cancer, will benefit from which particular combinations and agents. Therefore the more agents we have, the better. There's still a lot of learning to do, but certainly there's a need for a range of mixing and matching of different types of modalities to get to where we ultimately want to get.

In doing so, we will move the bar from twenty to forty or even eighty percent or more of patients in many of these tumor types that will have long, durable remissions that may even be called a cure. They may still need intermittent therapy—that also is a wild card that remains to be determined in how we use these agents.

Axel:

The concept of best-in-class comes from a time when we had the luxury to add incremental benefits on top of existing incremental benefits that the first-in-class, and later, a best-in-class could provide. We will not see that same thing in exactly that form again with these checkpoint modulators. They are already providing massive benefit. The trial to prove the benefit of a slightly better PD-1 when there is already an efficacious PD-1 is a study that no one is willing to do for the benefit that it will add. It's probably more effective to look for other impact on the same pathway, like blocking PD-1 and PDL-1 at the same time through a combination approach. That might be more beneficial than slightly improving a PD-1 alone. Combinations with other checkpoint targets such as OX40 might show more benefit than trying to slightly improve the impact of a single checkpoint blocker. The field is moving so fast, and there's such a wealth of new opportunity—new targets and new molecules—that I don't think we have the time or luxury of conducting replacement trials of PD-1s.

12 Linda: What about co-stimulatory agonists? What are some of the exciting targets and how crowded is this space?

Axel:

It's an interesting question because we have spent most of the time so far on checkpoint blocking antibodies, which have been quite successful. We are seeing a shift now toward agonists or checkpoint stimulating targets. OX40 is the first. There are already four of them in the clinic, one of them from GSK. And, there are others emerging. There's absolutely no reason to believe that agonist antibodies will not make major impact on cancer.

Ferran:

We all know that the clinical development of these agonists is a little bit more complicated, but at MD Anderson we have great faith that they may be as important as checkpoint blockade. That's why we out-licensed OX40 to GSK.

13 Linda: What about the approaches of providing killer cells such as NK and CAR T?

Axel:

The field started with T-cells. Almost all of the approaches that we're taking right now, almost everything we've discussed, is actually strongly focused on modulating T-cell immunity. There are two other parts of the immune system that we should consider. The first one is innate immunity, which we are just now touching on. NK cells are at the forefront, but macrophages belong there, as well as a variety of other cell types that could be modulated, just using different targets. NK cells can be relevant and could be supplementary to what T-cells can deliver. This is the next frontier in the third generation of the immuno-oncology age.

The third arm of the immune system is B-cell immunity. We haven't even gone there yet—trying to stimulate antibodies to provide a supplementary effect to what T-cells can deliver. We know that antibody responses work very well from a prophylactic perspective when we make prophylactic vaccines. They are probably one of the most successful tools we have created in modern medicine. The B-cell itself can be used for therapeutic approaches. There is untapped potential here and it's going to be the next wave after we have broadened our activities in T-cells and NK cells in innate immunity. This will not necessarily be a personalization, but just a broadening of the mechanisms that we have at our disposal.

Ferran:

NK cells are going to be the next frontier. There are challenges, but I see strides being made in that field because now we have a template on what happened on T-cells and, more importantly, people realize that it matters. In the past NK cells were fairly obscure, but now they are getting a lot of attention and there's tremendous progress being made.

Axel:

When we stay with the T-cell story—CAR Ts, TCR-Ts (T-cell receptor transduced T-cells)—the focus has been on CD-19, because it's such an exquisite target and has delivered very good clinical data. But it's only scratching the surface. We have just seen in a first clinical trial that NY-ESO-1 and a TCR approach delivered a 50% response rate in ten patients with sarcoma. So, it can be done. It will require significant adjustments in terms of supply chain and manufacturing optimization, but this is a very attractive approach.

We are basically engineering an army of T-cells to fight the tumor. In the long run, the complexity and the many technology components needed to apply this approach widely across many different tumor types will probably dictate that it ends up being a large pharma platform. It will take a lot of time and resources to make this approach work broadly. Novartis has taken a first step. GSK is now building a large platform of technology around cell and gene therapies, having filed the first regulatory submission for approval of a cell and gene therapy, not in cancer, but in rare diseases. We're pushing towards making this a platform approach and having a long-term view on it. In the future, cells will be medicines. The question is how quickly we can translate this into a solution for a large number of patients.

Jeff:

All of this progress on next generation adoptive cell therapy approaches, whether allogeneic or autologous, or dual targeting to address some of the specificity issues of going after solid tumors, as well as the various suicide genes designed to incorporate some safety features and ways to increase activity, is ongoing in parallel with antibody T-cell engagers (in contrast to cell therapy) as well as many other approaches that are out there. So, at the end of the day it's a very powerful and unique idea to proceed with these cell approaches, but it remains to be seen how well they will perform and at what price point. We don't yet know what the cell therapy outcomes will be for patients in comparison to alternatives that have similar effects, maybe in a much more facile way.

14 Linda: What about the business model for CAR T cells?

Nate:

From a business model perspective and from a CAR T approach, it's likely a big pharma platform. It takes a lot of investment to commercialize a personalized approach. It's not a one-off opportunity. The manufacturing of CAR Ts and the application to the patient is complex. Does it expand into solid tumors? Does it need to? When we identify ways to use T-cells within the body versus being manipulated ex vivo we see tremendous opportunity. The biology and opportunities in this space are all unique licensing opportunities. We believe that T-cells are very intriguing, and we're watching the development of NK cells and innate immunity. But undoubtedly, CAR Ts does require a platform approach, because it gets quite complex very quickly.

15 Linda: What about combinations? What does it take to show a combination is important and what are some of the challenges in combination development?

Ferran:

We're seeing a lot of alliances right now, mainly for two reasons: First, it's just what the companies have on the shelf. And secondly, it's because the CEOs of the two companies know each other. I think companies can and should be a lot more thoughtful about those alliances, especially in this particular field where window of opportunity studies allow you to take advantage of assessing how the immune system evolves. For example, what's happening to T-cells? What's being expressed or not expressed in a variety of ways? We do have the tools that can guide combinations, but we don't see that companies are taking advantage of those tools.

Axel:

One of the things that is driving combination therapy is life-cycle management. If there is a successful drug already in a given space, you usually add onto that drug or position it versus a new drug in order to maximize benefit for patients, but also to remain competitive. That, in part, is driving how combinations are done and is very much the way oncology drug development has been done in the past. Now, there are new components becoming available, but it's going to take time to build on those opportunities. Remember, as a successful area, immuno-oncology is four years old. And, it's moving so fast that it's not entirely possible to capitalize on all the science while remaining competitive. There are combinations that are driven primarily by life-cycle management considerations. And then there are scientific approaches emerging.

16 Linda: Will regulators allow combination trials with two non-approved drugs when there is an approved agent such as a PD-1 out there?

Nate:

From a regulatory perspective, trying to suggest what would happen probably isn't a wise thing to do. As we look at development of novel agents, they need to be in patient populations that make sense. When we consider combinations and other approaches, the consideration has to be about what's going to be most beneficial for the patient.

The approaches that we are taking when we think about standards of care that may be combined with an up and coming immuno-oncology agent, or when we think about novel approaches that could be combined, we have to consider what's going to be the best benefit/risk ratio for the patient. That's what we continue to try to look at as we approach this. We have some biomarkers that help us address which combinations might be best. But patient selection is going to be key to how we apply these medicines. It's not just about having the lead PD-1 or the best-in-class, we think that patient selection is also going to be critical as we look down the road to both combination approaches as well as which ones are going to be the most effective.

17 Linda: Why does the market see CAR T as big, and why are pharma and providers so cautious?

Jeff:

This is a very interesting space that's evolving. Why is it so big? In large part because these immuno-oncology agents are demonstrating results that seem to be very different both qualitatively and quantitatively from anything we've seen with other anti-cancer agents. Just look at the results presented by Novartis at ASH this year with CAR T CD-19 in acute lymphoblastic leukemia (ALL) patients. After three years, the ongoing follow up demonstrated a 94% complete response (CR), without using aggressive chemotherapies.

That degree of success is what has continued to fan the flames of the intense interest in not just CAR T cells, but also more broadly the adoptive cell therapy world. The ability to expand that success into other areas, just like the ability to expand the success of the checkpoint inhibitors from melanoma, into lung, bladder, renal and other areas is meeting with varying degrees of success. So, although these adoptive cell therapies, particularly CAR Ts, are not necessarily demonstrating, as of yet, the broad utility that many will hope they will ultimately achieve, they are nevertheless starting to show signals, certainly in other hematologic malignancies, in NHL, and myeloma. Looking at the pipeline, we're seeing that mid- to late-stage activity is more or less comparable between hematologic tumors, but the early clinical pipeline of cell therapies is heavily skewed toward solid tumors because that's where everyone realizes this needs to go

in order to have that significant impact that at least large biopharma will be looking for. But, of course, that's a very different and challenging world. The solid tumor world is very different in terms of the tumor suppressive microenvironment than in hematologic malignancy.

The second part of the equation, which can be argued both ways, is the role of large biopharma in the space. On the one hand, pharma might say they have to be in it, and should be in it because they have the wherewithal to do the level of clinical development and regulatory science to broaden the utility. On the other hand, and rightfully so, many biotechs can easily push back and say that, at the moment, as long as it's autologous it's really a process-based system, a cell-based therapy system. Big pharma doesn't necessarily have the history, or even the interest historically in pursuing that. It's plausible therefore, that small, well-funded biotechs could bring these forth on their own. Right now both things are happening. Large biotech is getting into it and making deals and some small biotechs are moving forward on their own.

18 Linda: What is the business model here? How does it fit for big pharma?

Axel:

Cell and gene therapy are extremely exciting. The CD-19 CAR Ts offer great promise and in their own right are a phenomenal medical advance. However, so far we're merely looking at the tip of the iceberg because these CAR Ts serve relatively small patient populations. There's a lot more research and development to be done before a broader spectrum of therapies can reach patients. A lot of different types of technologies will need to be co-developed with the first generation of CAR Ts or TCRTs in order for a broader spectrum of medicines to emerge. This will undoubtedly be a big pharma play. It's not a biotech play, even though biotechs provide value in terms of bringing new technologies to the table. But what is often the case is that they bring one technology and that technology then gets integrated with others. It takes time and it takes a lot of resources to make these integrated medicines accessible to patients. There's a lot more to be done before the whole field of cell and gene therapy becomes a broad success. This is about making cells into medicines. In the past we made antibodies into medicines; we made small molecules into medicines. Now we're at a new frontier. This is more complex than anything we've done before. At the end of the day, most of the resources and the integration of technologies that will have to be committed to this appear to be a big pharma play.

19 Linda: What about from a provider perspective? Does it fit?

Ferran:

People underestimate the amount of effort that is required to get the oncology community to adopt something new, something that is a new modality. There is a constant underestimation of how oncologists prescribe what they feel comfortable with. And it's not just being uncomfortable with how it is administered, but it's a level of discomfort about how to handle the side effects and how to handle the situation when things go wrong. When we talk about CAR T cells, especially when we're moving toward solid tumors, there are quite a few things that can go wrong. It's something that oncologists are going to take a long time to feel comfortable with. From a provider perspective, it's going to take longer than what most people imagine.

Jeff:

That's a good point. The science here is moving very quickly. Immuno-modulatory factors could ultimately be engineered to have both checkpoint co-stimulatory factors and suicide switches to add that safety factor that would make oncologists more comfortable. The field is growing so dramatically that we're seeing attempts to get beyond the cell handling or autologous side of this. Cellectis is perhaps the most well-known in the news for their potentially allogeneic off-the-shelf cell therapies, but there are others working in this space, and that's just the evolution of CAR Ts and other adoptive cell therapies that potentially become off-the-shelf products and therefore more akin to the antibodies. But at the same time, other technologies are potentially competing with the adoptive cell therapies, whether they're T-cell engagers, bispecific types of approaches or artificial types of cell systems that do some of the presenting. There are also co-stimulatory and checkpoint blockades being utilized by these cell therapies, so science is marching on at a rapid pace. There's also the grand hope, and right now it's purely speculative as to where the actual gene editing may go, that the low-hanging fruit will be applied to ex-vivo cells or in-vivo in monogenetic disorders. One might be able to envision a world where some of what is being done with these antibodies or cell therapies may be able to be done within the patient through the CRISPR/CAS9 editing systems.

Nate:

I think that's exactly right on. It is a continuum. Twenty years ago, CAR T, with regard to gene transfer, saw us trying to figure out what genes to put in in order to elicit the effects that we're now seeing. The technology has been there for some time. How we use that technology in a way that implements strong and durable responses is the key. As we think about the autologous approach, and eventually getting into allogeneic, it's important to get the process worked out so that it's an easier process. Perhaps an allogeneic approach where the origin of the cells may not necessarily be limited to the treated patient. As a therapy, that would be interesting.

The goal will be to work out how to

allow the body to attack cancer with an exogenous drug-like application—a small molecule, a bispecific, or an antibody—that would elicit the response that we're seeing with the CAR T approaches. Long term we'd like to be able to think that there are ways to get at that. It would be a universal approach versus an ex-vivo manipulation that gets to the end product. We are still not there, but that's where large pharma can play a key role in helping to bring these various technologies that already exist to what will be the next step in therapies.

Axel:

The complexity and timelines of this approach are so different from what we've done in large pharma before. CAR Ts around the initial target of CD19 produced a lot of excitement in cell and gene therapy, but they're really just the beginning and really just the first generation of cell and gene therapies in oncology. There are multiple generations to follow and we've seen the very first steps towards that by introducing gene editing into the manufacturing of those CAR T cells. Just at ASH 2015 we saw the first gene editing produced CAR Ts infused into a patient with clinical success. That's a technology for generation two. While generation one is an autologous T-cell transduced with a CAR through a viral vector transduction mechanism and an ex-vivo expansion of cells. There are still a lot of pieces that are not yet addressed, such as the introduction of the gene through other mechanisms like gene editing or the use of suicide switches or managing toxicity. These will come to play at some point in different contexts. The choice of the targets we will use, beyond CD19, will influence, in all likelihood, what kind of second-generation mechanisms we might need. For example, CD19 is a clean target in hematological malignancies that is very abundantly expressed in some diseases. So, you can target it well and you don't have too much healthy tissue expression. In solid tumors we have a few clean targets like NYESO-1, but they are rare. So, if we go to other targets that are more common, we end up in a situation where we have healthy tissue expression that will require potentially switching off those cells when you see toxicity. Suicide switches might play a role. Having these multiple technologies at our disposal while we're building our repertoire of cell and gene therapies will be quite relevant. At the moment we're using effector T-cells. We could also use memory T-cells, which is just a small departure from the original approach, or we could go to other cell types like NK cells, which are already being tested. We will see that the second or even third generation will expand further beyond just technologies, but also toward the use of different carriers or cells. It's a great opportunity, but there's also great complexity that will take a lot of navigation.

20 Linda: Do you all believe that there will be success in solid tumors, that cytokine release syndrome and on-target off-tumor effects will be overcome with choice of cells, with gene editing and dose fractionation and other approaches?

Axel:

I think so. At GSK we've recently done a partnership around a T-cell receptor transduction approach for autologous T-cells, which is primarily focused on solid tumors. And, we've shown in the first series of patients with synovial sarcoma expressing NY-ESO-1 a 50% response rate. This is early data in a small sampling of patients. Broadening this approach into other diseases will be complex, but the possibilities for addressing solid tumors are real.

Ferran:

At MD Anderson we have no doubt either. We are employing the technology of CytomX where the antibody binds to the target and is protected by a cap and that cap is released when the T-cell or the NK cell is close to the tumor microenvironment. That way you reduce toxicity when the NK cell is elsewhere. We know that that's just one approach, but there are many other approaches and we are confident that this is going to succeed.

Jeff:

Because of the degree of engineering and the speed with which that engineering can now be done, whether it's the gene-edited CAR Ts that came out of Carl June's lab that were presented at ASH, or the CytomX approach that has started using antibodies and now adoptive cell therapies, we can now envision multivalent antigens that provide the specificity beyond the limited number of tumor-specific or tumor-associated antigens. We can also envision a combination or multivalency where there are both positive and negative signals that are required in order to allow the cells to act and to recognize the appropriate antigen and not recognize some other antigen. So, there are lots of things we can do just on antigen specificity, which is very important. And then there's all the other engineering that may build into these cells, the checkpoint antagonists and the other immuno-modulatory stimulatory elements, whether it's co-stimulatory or other elements. So, ultimately it becomes an engineering question. Can we quickly bypass some of those inherent challenges to solid tumors, whether the nature of the targets or the nature of the microenvironment?

Nate:

I absolutely believe the applications will be transferrable to solid tumors. Do I think that will happen using an ex-vivo manipulated cell? That's not clear right now. There are multiple ways we can get at this. But undoubtedly, what we're currently learning is going to be applied to solid tumors in one way or another.

21 Linda: What about more classical approaches? What do you think about immune cell recruitment to the tumor environment? Are chemokines and interferons back? What other approaches can drive the right tumor microenvironment?

Axel:

Chemokines and cytokines have not yet delivered on their promise, which probably has to do with the unspecific approach they represent. They activate many pathways and influence many cells and it's a bit hard to focus them and to manage the toxicities that may come with their use. Examples are high-dose IL-2 or interferon treatment. Nevertheless, the other cytokines and chemokines that are now being studied will probably make a contribution to the overall picture. At the moment, I still have my doubts that there will be monotherapies with great impact. They will likely be a part of treatment regimens. Obviously we need much more data to understand fully how that will play out.

22 Linda: What about IDO and adenosine and the small molecule approaches that are currently being explored?

Nate:

We've all been watching and anticipating data on small molecules that have efficacy within the immune system and efficacy with anti-cancer agents, and for good reason. IDO is out in the lead and there are some good data in regard to melanoma. Data in other tumor types continue to mature, but it does look promising in that space. Just a year and a half ago there weren't that many programs that from a licensing perspective looked attractive. But more of those are coming into the public domain. Clearly there were some very big deals in this space earlier in 2015 around IDO inhibition. I think adenosine is a target that continues to mature as well. From a biology perspective, it's not just within cancer, but within other spaces as well. And, the biology continues to be explored within the microenvironment. This is an interesting target. It's hard to say right now how this is going to play out, but from a licensing perspective at Lilly we're looking at any of the small molecules that can demonstrate immune cell and microenvironment impact.

Axel:

At GSK we recently summarized the landscape of small molecules and targets that exist in the immuno-oncology space. That yielded a few interesting messages. IDO has been one of the first targets that has really been purposed for immuno-oncology applications. It is probably the small molecule target that is in the lead. Of course it had immediate followers, and some big ticket deals have been done.

Then there is innovation on other targets. Most of these are tumor microenvironment focused. They basically prime the tumor microenvironment to be more friendly for T-cells to act against tumor cells. For

example, the immuno-suppressive tumor microenvironment will become less immuno-suppressive by reducing the level of immuno-suppressive metabolites. That's one key mechanism, and there are multiple targets around it. Other small molecule druggable targets are more in the conventional signaling cascades. For decades we have made molecules against enzymes that activate pathways. Kinase inhibitors, for example, are such small molecules. Mostly these are developed to hit tumor signaling pathways, however we can also focus them on immunological pathways because they exist in lymphocytes and then the molecules can be specifically designed to hit only one part of the pathway—pi3k is an example—and focus this on the signaling cascade in lymphocytes. This represents a repurposing of tumor signaling pathways toward immuno-oncology. A lot of this is going to be relevant in the future, but it will also be relevant as supplementary to modulating immune suppression outside the tumor through checkpoint modulators. There's a lot of opportunity to bring mechanisms together to get the best results.

23 Linda: Ninety percent of the industry's general pipeline is small molecules, and yet there's such a dominance in this space of biologics, antibodies or cells. Why do you think that's true?

Ferran:

There are several very good reasons. When oncology people think of intracellular mechanisms of action they think they're either too dirty, or not specific enough. In immuno-oncology, that would most likely indeed be the case. If we are thinking about small molecules as a mimic for an antibody—something that has broad interaction between PD-1 and PDL-1—then you have other types of challenges. An antibody gives you enough specificity. A small molecule would be very unlikely to give you that type of specificity. So, there are many reasons why an antibody is still probably the best tool for the job.

Axel:

The field has tried to make small molecules against certain popular antibody targets, so far with very limited success.

Jeff:

I think it will be interesting to see. We say these things can't be done then the rapid advance of science and technology takes us by surprise. Someone comes up with interesting fragment-based approaches to try to address protein/protein interfaces and all of a sudden we're able to do something with specificity that was once thought to be only in the realm of antibody. I'm not saying it's easy, and there's not a lot of activity there that's public, but I think it is possible that one might see a world where some of those start to arise.

24 Linda: Biomarkers haven't been a big subject of success yet, but clearly everyone is looking. What measures are there to track the immune recognition, suppression and response?

Axel:

The biomarker space in immuno-oncology has exploded. We did a lot of tinkering prior to 2011, but the resources in the space were limited; people mostly focused on technologies instead of associated biomarkers. Now we have technologies and we need biomarkers to focus those technologies in the right patient populations, or understand immune responses. So, a lot of resources go into the biomarker space. PDL-1 was the tip of the iceberg. It was just the first to emerge because it's so closely related to the heavily investigated PD-1, PDL-1 pathway. There are others that we have studied that also relate to checkpoints. Some of the new checkpoint targets actually emerged as biomarkers and then got repurposed as drug targets.

An example would be ICOS, an inducible co-stimulator that was described as a prognostic marker within the ipilimumab program. It was associated with better survival and higher response rates in patients who overexpressed ICOS, which is actually inducible by either PD-1 or CTLA-4. That could be the target for an ICOS agonistic antibody. Knowing a lot about ipilimumab we focused on that at GSK and we're going to bring the first ICOS antibody that is an agonist to the clinic early in 2016. There will be others that will follow us. I expect there will be other targets, with similar origins or philosophies.

We can go beyond that and look at other areas, for example, repurposing small molecules. Not immuno-oncology molecules, per se, but ones that have immunological effects. They come with their own biomarkers. Then, in terms of activating the immune response, we can look at T-cell receptor diversity, which is becoming a big thing, or just at the markers of immune activation. Not only at single markers, but clusters of markers that would enable us to understand the phenotype of the cells infiltrating the tumor microenvironment. That will help address one pathway versus another, patient specific. Therefore we can hopefully combine assets more effectively and have greater effects for patients. I see a lot of value in the biomarker space. They will help us focus a plethora of different immuno-oncology agents that are being investigated.

25 Linda: What about genotyping? Is that playing a role in immuno-oncology?

Ferran:

I'm very pessimistic about genotyping. There's too much variety and too much at play. When you have targeted therapies (e.g., kras for EGFR inhibitors, braf mutation status), following the signal is almost binomial, and it's relatively simple to develop a companion diagnostic alongside it. But in immuno-oncology, it's a lot more complex. If PD-1 expression could have been used as a tool for basic selection, then it would have worked. But if it's not something as simple as assessing the level of expression of the target by IHC then the development of that biomarker is a tough endeavor. Pharmaceutical companies dabble at it, but they're not the experts. And diagnostic companies, who are the experts at it, don't have the incentive for developing those tools, or they don't have the risk appetite to do it. They don't have the appetite to perform those types of interventional trials that will actually change the standard of care. So, I see a lot of people dabbling in it, but I see very few, if any, conducting the type of studies that will actually get it implemented and change the standard of care.

26 Linda: In other oncology programs it has become almost the norm for licensors to require that a biomarker comes with the program. Is that not true with immuno-oncology?

Nate:

The answer to that might depend on whom you ask within the organization. When you ask the payers and the reimbursement specialists if a biomarker is required then you get one answer and when you ask the scientists who know that science evolves as more data are generated then you get a different answer. I think we could require a biomarker for licensing, but I don't think we'd actually license that many programs. If we're talking about licensing from a business development perspective, we need to look at the data in a program in aggregate. Biomarkers are important to consider, but right now in the I-O space it's a bit more challenging. There's a lot of biology that's going on. It is not as simple as a BCR-abl translocation identification and therefore knowing your patient population; the IO space doesn't give you as clear cut of an answer. So, I don't think we can say that requiring biomarkers for licensing is full stop. For a number of checkpoint inhibitors, early development is often the only time when a lot of these I-O programs are actually available for licensing. Requiring a biomarker is a hurdle that can rarely be jumped over. At Lilly we continue to look at the data in aggregate and how the biology relates to models and validated approaches, both in cancer and the immunological correlates.

Axel:

Let me just remind us all that it's only been four years since the immuno-oncology field took off. In those four years we have seen an enormous uptake in the investigation of biomarkers and we've made enormous progress. I expect something will emerge from this. Biomarkers will absolutely play a role.

Nate:

I agree with that. As a research organization, biomarkers are obviously at the forefront of a lot of what we're doing. Understanding how small molecules and antibodies are impacting pathways and cancer is extremely important. But from a licensing perspective, requiring biomarkers might be a hurdle that's unrealistic.

27 Linda: One of the issues that often arises in immuno-oncology is that there's less clarity of mechanism than for classic oncology approaches. How important is mechanism, and the clarity of mechanism, versus results in immuno-oncology licensing?

Nate:

The mechanism is important. The industry has had a lot of history with vaccines in the immune space and other approachess where the mechanism was not as clear. As some of the checkpoint inhibitors have come forward and we've seen the follow-ons, we're seeing that the mechanism is important and if we can see a biomarker around that mechanism, so much the better. We continue to work toward having data that tells a story. It's not necessarily just the results and how you get there, because there are some serendipitous discoveries that have happened, but we would prefer to build a data package that is based on a mechanism. That's not to say we don't chase results. When you find something that you didn't expect, you continue to move forward as well. When we talk to biotechs and other companies and we're trying to correlate biology and response, mechanism is clearly important.

28 Linda: Understanding mechanism is challenging in many of these cases because the immune system components are species specific. How much of a problem is lack of species cross reactivity and must an agent have activity as a monotherapy?

Jeff:

There may be that challenge of not only whether a specific target exists or not, or perhaps more relevantly, are the pathways of regulation the same in an experimental model versus a human? In some cases, they clearly are not. Also, the industry and academia have historically focused on immuno-deficient mice or xenotransplant. That has been the flavor for decades, though work in syngeneic models existed even further back. Those are coming back into vogue now, so you can do some of these experiments in the presence of an intact immune system, but that being said, there still remains

the usual caveats and skepticism about how far such data in experimental model systems will take you in the human system. While that has always been a great caveat and confounder for clinical trials and success and failures of drugs that cured many a mouse, it's only amplified when talking about the immune system. So, heterogeneity and diversity certainly come to the fore, which is why we see comments being attributed to Ira Melman who sees the need for these grand human experiments. That may be in part behind many of the collaborative kind of deals that we're seeing, whether those include riders for actual options that are publicly disclosed or not. It is not necessarily clear if x should be combined with y. Or, if there is evidence from animal models, it may not be definitive enough for someone who wants to pull the trigger right then and there for one of those big outsized early licensing type deals that we're seeing in I-O. Therefore, being able to do these collaborative types of relationships to see in the real world of the patient how these combinations play out becomes increasingly important. That being said, there is an increased push in funding in investigation, trying to improve those models in terms of mimicking the exact immune system.

On the single-agent activity, certainly what we see and hear and what we like to tell our clients is that you can't have a one-model system; you have to have multiple models or multiple tumor types to show that your mechanism has a sufficient robustness, even at the preclinical stage. And then, if you don't have strong single-agent activity, what does that mean? From our perspective, that constraint of requiring single agent activity for interest has certainly loosened a bit. There was a time when if you didn't have strong, or any, single-agent activity, it was more or less dead in the water. However, there are many immune approaches that have very minimal single-agent activity on their own, but clearly enhance the activity of an antibody or ADC, affect cell functions or rev up NK cells. So, there is more flexibility for agents that may have minimal single-agent activity.

Axel:

After 2011 the level of interest in immuno-oncology agents changed in large pharma, from near zero to very high. Many deals were possible because there was a lot of catch up to be done. Now that things are settling a little bit, prices will decline and we will get more differentiated about what kind of assets we're willing to spend money on. And mechanism will matter because we ultimately try to have specific effects either in combination with assets we already have access to, or we look to combinational effects complimentary to what's already licensed and available to patients. This is the trend. We will see it happen in increments. Then the immuno-oncology space will become a big component of oncology at large.

Nate:

There's no doubt that this trend will continue because understanding is increasing and the anxiety around missing out on a deal is diminishing. New approaches are emerging which will continue to drive good data and good deals. That's good from the perspective of large pharma. At the same time there is currently more of a steady progress

forward compared to that first wave of agents.

Jeff:

We're seeing a tremendous upsurge in early-stage deal making, at preclinical and research. A lot of large biopharma companies have entities that have been set up over the last couple of years in order to facilitate academic collaborations. That access and the need for that novelty and innovation will continue to be snatched up and nurtured by industry and academia.

29 Linda: What are the limitations of animal models to replicate human immune systems? Are you interested in licensing new complex models?

Nate:

Licensing new complex models is not necessarily a high priority for Lilly. The application of the models and new ways to look at agents and the impact is. Traditionally we've not been in the business of trying to bring all the models in house as much as we attempt to utilize them with the folks who are running them themselves.

30 Linda: There's been a flurry of activity in collaborative deals in the I-O space for the last couple of years. Why is it heating up so much?

Nate:

The deals we've done at Lilly have spanned the continuum from late-phase combination approaches, to clinical collaborations, to preclinical deals. We've been focusing on how we get at both new targets as well as some validated targets with new approaches. We're also focused on the academic approaches. Sometimes it's an asset we've developed that we're looking to collaborate with academics on. Sometimes it's an asset developed within academics that we see the potential to combine with one of our pipeline assets. These are things we're excited about from a business development perspective, but also from just a purely development perspective. These are BD transactions, but they really help move programs forward in a development area by defining which patient, for which treatment, at what time. Those are clearly important for us.

31 Linda: Sometimes combination deals don't have financial ties to the other drug in the combination. Are these kind of deals particularly challenging to set up, or is the motivation equal on both sides?

Nate:

In the past, it was much more difficult. Today I would say it is less so. Usually both sides understand the value that they are gaining by having a collaboration. There are factors to be considered in these type of deals. Is it a marketed product? Or is it an investigational agent? These things can impact this type of collaborative agreement. Drug supply, data sharing and the usage of that data can also be important factors. And lastly, strategic priority. One company may have a program that they want to combine with another company, but it has to fit strategically for both companies.

32 Linda: Let's address prices. Are they getting out of hand?

Axel:

Prices, initially, have been inflated. There's certainly been a bubble. It's been a bubble with substance, but still a bubble. Today, prices are decreasing, but valuations are still high. It depends on how conservative an organization is going to be. The sentiment right now amongst several large drug companies is that we are not going to massively overspend on deals. We expect to see a projection of actual value that's going to be delivered at the end of the day. At GSK we will continue to do deals, but the science has to drive the incentive. In some instances, you can make a molecule in-house more efficiently then you can by buying it. As more companies begin to pursue in-house discovery, things will begin to balance out. There will be a lot of biotech influence, but there will also be in-house work.

33 Linda: That balance does seem to be shifting and the IPO market seems to be softening. Has that shifted the balance of power in negotiations for out-licensing?

Ferran:

That's not my perception. The dynamic in immuno-oncology is still such that what's freaking out a company like Bristol-Myers is not that if they don't do a deal with a biotech company, that biotech company may go public instead, but rather that the deal will end up getting done with Merck or somebody else. What I do see, and this is having a chilling effect, is the talk around drug prices. It's a recurring theme and it's a real worry. It's not just a negotiating ploy to get better terms, but it's actually something, especially when we're talking about combinations or complex therapies, that is a genuine concern.

Jeff:

In terms of the science and the issue of combinations, the deal making that's

happening and the pricing issues all converge because, from the outside, the ability of someone to control multiple assets that they ideally would like to and expect to combine gives them more optionality. Hence the state of deals that Bristol-Myers Squibb has done and the repleteness of their pipeline. BMS has shown that being able to control those combinations gives them some extra strategic clout compared to these all being disparately held by diverse players.

34 Linda: Will companies like Juno and Kite and other companies involved in cell and gene editing be able to mount a sales force and become fully integrated pharmaceutical companies? Is that a plausible strategy within immuno-oncology given the need for combinations?

Jeff:

Well, you certainly see them doing deals. And other activity, like Aduro's acquisition of BioNovion, illustrates that the more you can control the various elements that are going to be a part of an optimized immuno-oncology therapeutic regimen the better off you are. To have control over the development and getting the approval and controlling the ultimate destiny of those products, including the ability to control the pricing of those regimens is a strategic strength.

35 Linda: Ferran, you spoke earlier about how oncologists need to be comfortable with therapeutics and the concern that many of them have with the complexity and safety of the ongoing clinical trials. Do you see this being resolved by knowing better how to use existing molecules or do you see this as necessitating the next generation of molecules?

Ferran:

I think it will be resolved, but only through the efforts of the medical affairs organizations. Pharma is stepping up to the plate by making a fantastic effort in terms of education, but a lot more is needed. In any case, the industry is doing the right thing and we'll eventually get there. There's now a better understanding of the value of education.

36 Linda: In terms of antigens, do you think that the solid tumor approaches in CAR T will be to known antigens currently explored with antibodies or will they need new antigens for solid tumors and CAR Ts?

Ferran:

I think it's clear by now that we need neoantigens. All the low hanging fruit have one problem or another. Theoretically it should not be difficult to find those antigens in the sense that you don't need the high levels of expression that you need in other drug modalities.

Jeff:

Cancer vaccines, antibodies, and even adoptive cell therapies are somewhat limited to a world of tumor specific, tumor associated antigens and fetal antigens, etc. To be able to broaden beyond that is appealing and maybe necessary. There are a number of companies out there who have ways to mine the immune system of responders or nonresponders, whether that's in immuno-oncology where people have been treated with checkpoints or other approaches or companies like Atreca, for example that has an interesting platform that discovers both antigens and the antibodies at the same time in elite controllers who have been treated with various checkpoint inhibitors. And there are other companies out there who have similar types of platforms; these seem to be surfacing. These tumor antigens are at least novel, whether they're different from what one might discover from other types of platforms remains to be truly vetted. But there is a hunger for more targets. At the extreme end of this is the focus on the new antigen side whether those will be used for actual vaccines that are individualized and autologous to a patient or whether those are used for adoptive cell therapy targets or whether those are ultimately broadened out to other types of therapeutic modalities for intervention. Then the question arises: Where on that spectrum does one need to play? At the very narrow individualized level of the target or the cell approach, or at the other extreme or is there something in between?

37 First Audience Question: What are the advantages of an autologous versus an allogeneic?

Jeff:

Autologous is scientifically ahead. It's where the science originated and it's what is readily tractable at the moment independent of the logistics of it. We have to see how the science and the data evolves. We don't have a real opportunity yet. We will, in the relatively short term, have the ability to compare and contrast how, for example, a Cellectis U-CAR T, a universal off-the-shelf Anti-CD-19 compares in clinical efficacy with various autologous CAR Ts. But that will still need to be tracked long term to see to what degree those responses persist or don't. We'll need to see what the safety profile looks like, not just the near term issue of cytokine storm, but the longer effects.

38 Second Audience Question: Describe a Phase I shotgun study to obtain human in vivo efficacy data in multiple tumor types.

Nate:

I'm not sure what a shotgun approach means, but as we look at programs externally we traditionally would see Phase I entry into a single tumor type with potentially a proof of principle or a proof of concept approach. Many of the programs we look at are beginning to think about how you do Phase I dose escalation and safety either by itself or in combination with another immuno-oncology agent and expanding that into tumor types to find a signal that makes sense. I don't think we'd call it a shotgun approach, although we might do multiple tumor types with a rationale that makes sense for why that tumor type is the right one for that molecule in combination. Phase I studies can lead toward a registration path if you find the right patient population with the right medicine and/or combination. It's important to find that as quickly as possible, so it is a way that both biotechs and large pharma can use early phase studies to explore for signals in a rational way that will decrease the amount of time that it takes to get to the patient that can hopefully benefit from the medicine.

39 Third Audience Question: What are the risks of CAR Ts and how are they addressed and tracked?

Jeff:

There's no doubt that being able to control safety is important. Whether it's an EGFR-based or caspase type of suicide switch or something else, we need to have a mechanism to knock those cells out completely. The ideal would be the ability to bring them down without completely knocking them all out, at which time they could repopulate.

In solid tumors, those switches will be important, but also there are other ways that we can improve that therapeutic window. Multivalency of targeting can bring specificity or maybe operate in both a positive and negative way, whether it's an antibody in a CAR T or a TCR, to mask those immune system effects until the signals get released at an actual tumor site through activation, through some aspect of the specific tumor microenvironment whether it's oxygen levels or pH. So, there are lots of avenues that can be pursued and need to be pursued at this point in order to be sure that the best safety efficacy window is possible.

40 Linda: Where will immuno-oncology be in ten years?

Axel:

Right now we're seeing long-term benefit for moderate numbers of patients. I expect to see this increase. I'm very encouraged by the standard of care changes from just the PD-1s and PDL-1s in melanoma and lung cancer. It's just the beginning of the story as biomarkers emerge and enable us to point these drugs in the right places. We are going to see great benefit for new populations that have not yet benefited. We have to expect that in ten years this is going to have a massive impact on cancer.

Jeff:

Much of the success we've seen historically with many types of drugs, like cytotoxic agents, may well have been because of the role of the immune system; we just weren't keeping our eye on it. The presentation that Jérôme Galon just did on Immunoscore and the role of the T-cell infiltrate correlating with an absence of metastases and improved colorectal cancer and prognosis with existing therapies is really quite amazing. Right now we're seeing a lot of successes with what were historically considered immunologically low-hanging fruit, like melanoma or bladder or RCC. But the fact that we're seeing the responses at this early stage with lung cancer, which was never on the top of the list of immuno-responsive tumors, suggests that we might be on the threshold of cracking this wide open. And not just with one agent, but with multiple agents and multiple approaches across multiple different tumor types enabled by the various profiling of different types of patients. This progress is going to accelerate at a dramatic pace. In ten years, I don't know if we will have eliminated cancer, but we'll be getting very close in substantive portions of many different tumor types.

Axel:

We always have to be cautious when using the word "cure" in oncology, but I see people more and more comfortable with using it now. We are seeing cancer patients that live a long time. If we throw all the tools into the mix and make effective combinations we will see great results for many patients and the word "cure" will become something that we will be able to use more comfortably.

About the Moderator

Linda Pullan, PhD

Linda offers biotech and pharmaceutical companies consulting in all aspects of partnering through Pullan Consulting (www.pullanconsulting.com).

Linda has a PhD in Biochemistry and a BS in Chemistry. She has more than 20 years of drug industry experience, beginning in drug discovery at Monsanto/Searle/now Pfizer and ICI/Zeneca/now AstraZeneca.

After doing licensing at what is now AstraZeneca, Dr. Pullan continued as head of oncology and hematology licensing for Amgen. She then joined Kosan Biosciences as VP of Business Development and experienced all the tasks of out-licensing and business development in a small company.

For several years, she has been providing companies help in identification, evaluation, valuation, negotiation and strategy for partnering in or out. She has an extensive deal sheet ranging from company acquisitions to Phase III compounds and from preclinical candidates to technologies, with both in- and out-licensing.

She writes a free monthly newsletter *Pullan's Pieces*, with tidbits of science and business for thousands of readers. Interested readers may sign up by sending an email to linda@pullanconsulting.com.

About the Panelists

Jeffrey M. Bockman, PhD

Jeff leads the Oncology and Virology Practices at Defined Health. Jeff has extensive commercial and strategic perspective on the pharmaceutical and biotech industries. He has directed hundreds of in-depth licensing opportunity and valuation assessments during his tenure at DH. He often speaks at conferences on scientific and commercial issues in cancer, biologics and personalized medicine.

Before joining Defined Health, Jeff was a Senior Research Scientist and Research Project Leader in the commercial development of oligonucleotide therapeutics for viral diseases and cancer at Innovir Laboratories; and an Assistant Research Professor at The George Washington University School of Medicine. He has worked closely with two Nobel Prize recipients: Dr. Sidney Altman on ribozymes, and Dr. Stanley Prusiner on prions, and holds four patents in the use of ribozymes as diagnostics and therapeutics.

Jeff is a member of the Licensing Executives Society (LES), the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), the American Society of Gene and Cell Therapy

Jeffrey M. Bockman, PhD (continued)

(ASGCT) and the New York Academy of Sciences (NYAS).

He received a BA from University of California at San Diego, a PhD in Medical Microbiology from the University of California at Berkeley, and an MA in English/Creative Writing from New York University.

With his wife he founded and has been running for over twenty years a well-regarded literary journal, *Literal Latte*. Jeff continues to write fiction, essays and book reviews that he publishes in various literary magazines.

Axel Hoos, MD, PhD

Dr. Axel Hoos is Senior Vice President, Therapeutic Area (TA) Head for Oncology R&D and Head of Immuno-Oncology at GlaxoSmithKline Pharmaceuticals (GSK). In this role he leads the Oncology TA and builds the immuno-oncology portfolio of GSK across the modalities of antibodies, small molecules, bispecific molecules and cell & gene therapies, for which he directs discovery and development.

Dr. Hoos also serves as Chairman of the Board of Trustees of the Sabin Vaccine Institute (SVI), a Global Health organization, Director on the Board of Imugene, a biotech company, Co-Director of the Cancer Immunotherapy Consortium (CIC) and Scientific Advisory Board Member of the Cancer Research Institute (CRI).

His efforts in Medicines Development and Global Health focus on novel therapies for life-threatening diseases, scientific and procedural innovation, and broad collaboration across multiple constituents. Through his leadership a new paradigm for the development of cancer immunotherapies has been defined, which helped launch the field of Immuno-Oncology.

Previously, Dr. Hoos was the Global Medical Lead in Immunology/Oncology at Bristol-Myers Squibb (BMS) where he developed Yervoy (Ipilimumab), the first life-extending therapy in Immuno-Oncology. Before BMS, Dr. Hoos was Senior Director of Clinical Development at Agenus Bio (previously Antigenics), a biotech company.

Dr. Hoos holds an MD from Ruprecht-Karls-University and a PhD in molecular oncology from the German Cancer Research Center (DKFZ) both in Heidelberg, Germany. He trained in surgery at the Technical University in Munich, Germany and further in surgery, molecular pathology and tumor immunology at Memorial Sloan-Kettering Cancer Center in New York City. He is an alumnus of the Program for Leadership Development at Harvard Business School.

Ferran Prat, PhD

Ferran Prat is Vice President of Strategic Industry Ventures at MD Anderson Cancer Center. He has a PhD in organic chemistry from the University of California, Los Angeles and a JD from the University of San Diego School of Law.

Prior to MD Anderson Ferran worked at Alere Inc., an international firm dedicated to developing health management services and solutions, including diagnostic tools and tests. At Alere, Ferran led a business turnaround and integrated three businesses in São Paulo and Belo Horizonte, Brazil. He also served as the head of the Oncology and Women's Health Divisions in San Diego where he was responsible for all pre-commercialization activities and post-launch product management.

Prior to Alere, Ferran held a number of industry and academic positions, including Vice President for Licensing at Biosite Inc., Management Consultant at McKinsey & Co., Engineer at Chromogenia-Units and Researcher at the University of California, Los Angeles. In these roles, he in-licensed and out-licensed new technologies, led and executed strategic plans, coordinated intellectual property agreements among private and public sector entities, and conducted basic science research that led to multiple peer-reviewed articles.

Nate Sanburn, MA

At the time of the first web panel discussion in October 2015, Nathan Sanburn served as the Business Development Director for the Oncology Business Unit at Lilly. He is now Lilly's East Region Director in Oncology US Medical Affairs. A molecular biologist by training, Nate has over 19 years of experience across R&D, clinical trials, and business transactions.

At Lilly his responsibilities have spanned operations of early and late phase clinical development programs, Oncology Scientific Search and Evaluation, Business Development Transactions/Collaborations, and Medical Affairs. Mr Sanburn played strategic roles in the global approvals of 3 launched products, the acquisition of Imclone, the negotiation of various licenses to preclinical and clinical oncology programs across biotech and academics, and building a new method for external input into clinical trials. He was also instrumental in providing the foundation for 17 clinical collaboration agreements combining Lilly pipeline molecules with ImmunoOncology and other investigational agents.

Prior to Eli Lilly, he worked in the National Gene Vector Laboratory at Indiana University Medical Center conducting research and manufacturing of retroviral vectors for gene transfer in human clinical trials. In this role, he served as the leading scientist for building a GMP facility producing and safety testing drug product.

Mr Sanburn received his BS in Biology from Indiana University, MS in Biology from Purdue University, and currently resides in Indianapolis, IN.

About ShareVault.

ShareVault® is the industry leader in supplying intuitive, innovative virtual data rooms that provide a simple and secure way to share sensitive documents with third parties during the due diligence process.

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The on-demand platform is an innovative cloud-computing solution that enables its customers to manage critical time-sensitive and document-centric processes faster and more intuitively. ShareVault offers the highest degree of security and reliability combined with unparalleled speed, ease of use and functionality. Backed by the experience of billions of dollars in successful deal transactions, along with industry-leading customer support, ShareVault can be a critical tool in accelerating deal transaction times and increasing deal success rates.

For more information, visit www.sharevault.com.

About Defined Health.

Defined Health is a leading business development strategy consulting firm that has been assisting clients in the pharmaceutical, biotech and healthcare investment industries for more than 25 years.

DefinedHealth
unconventional insight

Defined Health has three core lines of business, each focused on helping companies build and strengthen development-stage assets; compounds, portfolios and platforms: Opportunity Assessments, Portfolio & Platform Strategy, and Asset Identification & Evaluation.

Defined Health differs from other consulting firms in their unique depth and breadth of experience, in their people, and in the quality of their client interactions. The key to what they have come to call our unconventional insight is our unparalleled therapeutic area experience.

For more information, visit www.definedhealth.com.

About LES.

For more than 50 years, Licensing Executive Society (U.S.A and Canada) (LES) has been the leading association for intellectual property, technology, and business development professionals to achieve professional and personal success. Whether you are new to licensing or an experienced licensing executive, LES is your professional home.

LES is a welcoming business community that empowers, connects, and celebrates IP professionals through education, best practices, networking, participation, and mentoring.

LES is dedicated to evolving with its members' needs by providing up-to-date, relevant, and easy-to-access information. As a member of LES, you'll grow your network, hone your skills and knowledge, and advance your career.

For more information, visit www.lesusacanada.org.

About BIO.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

BIO also produces the BIO International Convention, the world's largest gathering of the biotechnology industry, along with industry-leading investor and partnering meetings held around the world. *BIOtechNOW* is BIO's blog chronicling "innovations transforming our world" and the *BIO Newsletter* is the organization's bi-weekly email newsletter."

With almost two decades of experience in the biotechnology, pharmaceutical, medical technology and life science technology sectors, the Trout Group offers its clients the knowledge base needed to clarify investment themes and leverage key relationships for increased exposure to the proper audience. The firm's global reach extends through a network of offices in New York, Boston, San Francisco, London, and Shanghai with contacts in all major financial centers, helping clients to connect with the right investors.

For more information, visit www.bio.org.

About Pullan Consulting.

As the lead consultant at Pullan Consulting, Linda M. Pullan, PhD, has been advising biotechs on the most effective ways to partner for many years. Prior to consulting, Linda worked for many years in licensing, BD, and research at small (Kosan) and big (Amgen, AstraZeneca, Monsanto/Searle) companies.

Services that Linda provides include any or all of the following:

- creating business plans
- seeking new opportunities to in-license
- making contacts
- setting up meetings
- pitching out-licensing opportunities
- structuring presentations & communications
- evaluating opportunities & competition
- preliminary market assessments
- managing the diligence process
- financial modeling and valuations
- negotiations (leading and advising)
- strategy advice.

For more information, visit www.pullanconsulting.com.

About the Trout Group.

The Trout Group is the leading global investor relations and strategic advisory firm servicing the life sciences industry. Since 1996, the firm has been providing companies with expert counsel and access to the institutional investment community.

With almost two decades of experience in the biotechnology, pharmaceutical, medical technology and life science technology sectors, the Trout Group offers its clients the knowledge base needed to clarify investment themes and leverage key relationships for increased exposure to the proper audience. The firm's global reach extends through a network of offices in New York, Boston, San Francisco, London, and Shanghai with contacts in all major financial centers, helping clients to connect with the right investors.

For more information, visit www.troutgroup.com.

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