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Immuno-Oncology 2.0 Roundtable: Scientific And Pricing Challenges Can't Slow New Therapies

by Mandy Jackson

Scrip spoke with executives from five companies about challenges that remain for the burgeoning – but still young – immuno-oncology field in Part 2 of a wide-ranging roundtable discussion.

In Part 2 of *Scrip*'s IO Roundtable, executives from *Tocagen Inc.*, *CytomX Therapeutics Inc.*, *Trillium Therapeutics Inc.*, *Xencor Inc.* and *Poseida Therapeutics Inc.* talk about what's still unknown in cancer immunotherapy and the challenges that lie ahead, including pricing and reimbursement for novel therapies.

Mandy Jackson moderated the discussion with Tocagen Vice President of Business Development and Marketing Nicholas Boyle, CytomX Chief Medical Officer Rachel Humphrey, Trillium President and CEO Niclas Stiernholm, Xencor President and CEO Bassil Dahiyat, and Poseida CEO Eric Ostertag while in San Francisco for the J.P. Morgan Healthcare Conference in January. Part 1 of the roundtable centered on differentiation of emerging immuno-oncology (IO) platforms and the vigorous appetite for dealmaking in this arena. (Also see "*Immuno-Oncology 2.0 Roundtable: Emerging Players Eye Crowded Field*" - Scrip, 3 Mar, 2017.)

Scrip: What do you see as the biggest challenges in this field, because relative to other areas like maybe neuroscience or antibiotics, IO looks easy.

Bassil Dahiyat: There's a lot to try.

Niclas Stiernholm: There's 12,000 combinations and they're growing. So we

The Companies

Tocagen Inc.

Tocagen develops cancer-selective gene

have to do exactly what Bassil said – we have to invest in understanding biology. The problem is that you have investors that want to see [complete responses (CRs)] in your first human trial and not do those [exploratory] studies that you really should be doing, and that's the struggle that we have. People aren't going to sit around and wait for biology for two years, so we've got to at the same time do something to satisfy the people that want to see some human clinical benefit.

Nicholas Boyle: Another important challenge in IO and in cancer therapy in general is patient participation in clinical trials. It's a well-known problem that a small percentage – a single-digit percentage of patients – actually participate in trials, yet that really is where the best outcomes often can come from.

In brain cancer, which is our initial focus, it is no different; there's about 6% participation in clinical trials. [The challenge is] innovative ways to get patients and their caregivers motivated, because it's often a complex conversation deciding on participation in trials. Obviously, you need the sites motivated – not just the [principal investigator (PI),] but the study coordinators and all the support staff have to be engaged. Without this, all the things that collectively we want to do in IO is going to take a lot longer.

[There] are things that we'd struggle to fix, but it is a problem facing the industry of what's going to motivate that

therapies. Lead product candidates Toca 511 and Toca FC are being developed together to treat recurrent high grade glioma and the US FDA recently granted a breakthrough therapy designation for the combination in that indication. Toca 511 delivers a gene called cytosine deaminase to cancer cells to infect the tumor and Toca Fc – the inactive prodrug 5-fluorocytosine (5-FC) – is converted to the active chemotherapy drug 5-FU to kill the infected areas of the tumor, the surrounding cancer cells and immunosuppressive myeloid cells, activating the immune system in the process to increase the tumor-killing effect. Tocagen recently completed patient enrollment in its registrational Phase II/III clinical trial and expects to report top-line results in the hard-to-treat brain cancer during the first half of 2018. (Also see "*Tocagen Aims Double Barrels At Glioma*" - Scrip, 1 Feb, 2017.)

CytomX Therapeutics Inc.

CytomX is using its Probody technology platform to develop targeted cancer immunotherapies with reduced toxicity. The technology involves amino acid-masking of the targeting end of an antibody or any other therapeutic modality. That mask comes off only in the presence of tumor-specific proteases, so the therapy is delivered directly to cancer cells. A recently initiated Phase I/II trial is testing CX-072, a PD-L1-targeting Probody therapeutic, as monotherapy and in combination with *Bristol-Myers Squibb Co.*'s *Yervoy* (ipilimumab) or *Roche*'s *Zelboraf*

community physician to refer one of their patients to an academic center or a local center that is offering clinical trials. What's going to motivate them to even have the conversation about clinical trials with their patient, because the surveys show most patients only spend five minutes in their entire disease course talking about clinical trials with their physician?

Bassil Dahiyat: My wife's a physician at UCLA; she's a pathologist, so whenever something comes up with a person we know or if someone we're somewhat familiar with has cancer, her first question when they say, "What do you think?" is "Do they have insurance and how educated are they and how much of an advocate can they be? Because [insurance coverage and education] are the two best predictors of your outcome in cancer. If you don't have insurance you're, frankly, dead; it's very sad and it's a horrible element of the system we have here. But the other one – how do you advocate for yourself – those are the guys getting into clinical trials; those are the people that are looking at the billboard on the freeway saying, "City of Hope Cancer Center: We make cures here."

Scrip: Is it a problem right now of the industry eating it's young, in a sense, because you've got Merck and others running hundreds of IO clinical trials?

Dahiyat: That's making the problem manifest more clearly, but no, that's not the problem. The problem is that you've got a lot of cancer patients in a

(vemurafenib) in various cancers. (Also see "*Pipeline Watch: Evolocumab, Roxadustat And SB-204, Top-line Results*" - Scrip, 6 Feb, 2017.) The company, which went public in October 2015, has inked several discovery and development partnerships. (Also see "*Is the Biotech IPO Window Closing?*" - Scrip, 22 Oct, 2015.) Also of note, Chief Medical Officer Rachel Humphrey supervised the Yervoy development program at Bristol-Myers from early R&D through one year post-approval.

Trillium Therapeutics Inc.

Trillium is developing immunotherapies that target CD47, but unlike its competitors the company's product candidates are not monoclonal antibodies. Lead drug candidate TTI-621 is a Signal Regulatory Protein (SIRP) alpha fusion decoy receptor. The drug targets the SIRP alpha receptor on macrophages, which are found in the tumor microenvironment, to turn on the "eat me" signal within the macrophages – a signal that CD47 blocks. TTI-621 is being evaluated in two Phase I trials, including a study in hematologic malignancies testing the drug as a monotherapy and in combination with other therapies. The second study in solid tumors enrolled its first participant at the end of January; the company is testing an intratumoral injection of TTI-621 in that trial. (Also see "*Trillium Looks To Lead The Immuno-Oncology Pack In CD47 Inhibition*" - Scrip, 11 Oct, 2016.)

Xencor Inc.

community doctor's office, who is really busy and who needs information and he needs a place send them in, but he or she is not greatly financially incentivized to refer them out [to participate in a study].

Rachel Humphrey: I think there's a fair number of those physicians who are not treating with immunotherapy now.

Dahiyat: A ton of them, I'm sure.

Humphrey: To your point, I suspect the size of the market is grossly underestimated and as we all build safety efforts it may expand further.

And, in terms of the patients, if you look at all of the studies that are open, I don't know what the pace of your enrollment was [at Tocagen], but in my experience at Bristol-Myers Squibb Co. and *AstraZeneca PLC* and even now, it looks like the patients are plentiful. You'd expect them to compete with each other, but the incoming from all over is impressive.

Eric Ostertag: In our experience in CAR-T, even though we haven't started the trials yet, we've lined up five sites. And very consistently, across the board, every site has said the demand for CAR-T far exceeds the supply. There are more patients that want to get in than there are companies able to deliver it.

Humphrey: You'd think that as the number of opportunities grows there's a saturation. I think that everybody's feeling that the saturation hasn't happened and they're throwing their very

Xencor uses its XmAb Antibody Engineering Platform to engineer monoclonal antibodies with altered Fc domains as a means for improving function and performance. The technology is a "plug-and-play" platform that can be used to alter almost any antibody, which has resulted in several discovery and development collaborations with big pharma and large biotech partners. Xencor executed a deal last year with *Novartis AG* that could be worth as much as $2.5bn. (Also see "*Novartis Deal Gives Xencor $150m Up Front, Up To $2.41bn In Milestone Fees*" - Scrip, 28 Jun, 2016.) *Johnson & Johnson*'s Janssen subsidiary and *MorphoSys AG* each have Xencor-engineered IO antibodies in Phase II/III trials and *Boehringer Ingelheim GMBH* has two IO molecules based on Xencor's technology in Phase I. Xencor also has two wholly-owned bi-specific antibodies that bind to T cells and antigens in early clinical trials. The company's next clinical bi-specific antibody programs in the IO space will target cells in the tumor microenvironment. (Also see "*Xencor's Coming Share Issue To Help Fund Immuno-Oncology Pipeline*" - Scrip, 2 Dec, 2016.)

Poseida Therapeutics Inc.

San Diego-based Poseida was spun out of Transposagen Biopharmaceuticals to use genome-editing technology in the development of chimeric antigen receptor T cell (CAR-T) therapies for cancer – including programs in collaboration with Johnson & Johnson's Janssen subsidiary – as well as gene therapies for other diseases. The company

reasonable creative hats into the ring, because it's still doable. It may stop being doable, but as long as we're generating data – and soon fantastic data, no doubt – that excitement will continue. And I suspect the patient base and the physician base will also expand.

Boyle: And imagine if we were able as an industry to double participation in clinical trials.

plans to submit an investigation new drug (IND) application for its lead CAR-T therapy this year with the intention of dosing the first patient in its first clinical trial during the fourth quarter. Poseida completed its Series A round for up to $30m in early 2015. (Also see "*Startups Stand Out As 13 Biotechs Raise More Than $409m*" - Scrip, 18 Dec, 2015.)

Humphrey: I wonder if it's gone up, because the interest I'm seeing is [high]. I'm in the industry 20 years on the clinical side and the enrollment up front is just very different. It used to be hockey sticks – the first [*Yervoy* (ipilimumab)] Phase III study [conducted by Bristol] that ended up changing the world had almost no patients in the first year, and then it had a hockey stick where they all came on in the last hour.

Scrip: How much of that is because of patient access to information now versus what it was 20 years ago?

Humphrey: I think it probably helps, because we're getting input from patients and their caregivers and the web is such a replete source of, hopefully, accurate information.

Boyle: I'm fascinated by the system in the US – I'm from the UK, so I had a different experience growing up – [where] those decisions are made about treatment pathways and the insurance companies play a very significant role in that. Imagine if the insurance companies were the ones saying, "Well hang on, have you considered a clinical trial?" It has to be a win-win for everybody. Insurance companies would need to be convinced that if patients did participate in trials then their outcomes may well be better and ultimately cost less.

Dahiyat: At least it's free enrolling in a trial.

Humphrey: You know, the [National Comprehensive Cancer Network (NCCN)] guidelines used to say that you should enroll in a clinical trial in the first line across the board. With the immunotherapies out there, they're actually not saying clinical trials up front, they're saying give them the PD-1 or whatever. So part of the challenge – and it's a legitimate challenge – is that penetrating the first line can be more difficult. But the more successful you are in first line, the more available the patients are in the second line. At the beginning of my career, lung cancer had no standard of therapy; it was universally a fail. Nowadays, we're on the fourth line now, and the fourth line never existed, the third line never existed and even the second line didn't exist. So,

it's a very interesting trend as patients become more available on the post-treatment range.

Dahiyat: It does make the bar higher, because they're sicker and worse off; they're just terribly less healthy.

Scrip: So in your mind, what are some of the biggest needs? Is it just information, more data on mechanisms and pathways and targets, or is it having the dollars to do what you want to do?

Humphrey: I think it's [a need for even more] good ideas.

Dahiyat: I think it's actually some data. I think it's actually seeing out of this mass of, at the moment, equivalently exciting sounding ideas, which ones actually deliver some efficacy results? What is the safety cost of those results and where? And, hopefully, we can glean mechanistic understandings from that, because I think mechanistic understandings as to how these incredible therapies work is very dim, and why they don't work in most patients is very dim. We just need a lot more data, which is why it's great we're doing all these trials. I could actually see in the timeframe of my career, as it remains, an enormous change in how much we understand what's going on in the molecular level of the immune system against tumors. That's amazing.

Stiernholm: Patience [is a problem]. PD-1 was discovered by [Japanese immunologist Tasuku] Honjo when I was in grad school. It takes a long time [to then develop drugs].

Humphrey: That's right, CTLA-4 was discovered in 1994.

Dahiyat: The IND for ipilimumab was opened in 2001 … and approval was in 2011.

Humphrey: I supervised [clinical development at BMS through] that whole period. Back in the day, when immuno-oncology [was young,] they handed me $100m and sent me in the back room, never believing it was going to work. [In terms of clinical trial enrollment, there were] so many years where you just didn't get the patients, because something else was sexy. Once ipilimumab opened the door a crack, I think what followed is much faster.

And, in retrospect, I sat in on meetings where people would stand up – [Richard Pazdur, director of the US FDA's Oncology Center of Excellence] was speaking and somebody stood up and said, "How come we didn't approve ipilimumab earlier? We had data from Phase II; why do you need to wait all the way to Phase III?" The answer was a fair one, which is to say, "We don't understand it well enough; we really need to get a risk/benefit story in a controlled setting."

I think as our hurdles drop [development programs move faster]. I think for [*Opdivo* (nivolumab)], once BMS got it started, it was approved in a very short period of time, and the new IO drugs are going even faster.

Dahiyat: I think also that's the difference between the infrastructure and resources and skill sets at [smaller companies.] The early development of ipilimumab was at Medarex, a mouse antibody company that was doing clinical trials, and the later development was at BMS.

Humphrey: It wasn't that much later, we picked it up early.

Scrip: How many innings are we in the immuno-oncology ball game at this point? Do you think it's still the first?

Dahiyat: Bottom of the first.

Ostertag: I would agree.

Humphrey: Someone asked me if immunotherapy was going to cure cancer at a talk I gave some time ago ... and I said, "Absolutely not." [There are] just a host of things we haven't learned yet and I suspect we're going to overshoot very soon; it's already happened.

There's a bit of a pendulum coming back and forth as we turn in the most effective things and patients get into trouble, which is why [Poseida has] an off switch for your CAR-T and why [Xencor is] paying attention to what you're doing at the Fc domain – so that we can make it safe – and [Trillium has] a magical way to get the cancer activated. There are plenty of examples we're going to see where the drugs are just extra potent, so we're still calibrating.

Ostertag: My Lyft driver asked me the same question.

Humphrey: Really, and what did you say?

Ostertag: I said I think we will cure some cancers in some patients, but clearly not all cancers in the next 10 years. The first CAR-T patient's still cancer-free four years out, so I think there will be clear wins.

Humphrey: Well there are already patients you could say are probably cured. Although, among the patients we treated on ipilimumab who are now 10 years out, this one fellow I have in mind finally said at the end, "I don't want maintenance anymore," and he was dead in 12 months, so there's a whole host of things happening there science-wise that we just don't understand.

Dahiyat: And there's what – 10% or 12% of people left ... that are long-term survivors.

Humphrey: No, 20% ... with 3 mg/kg of ipilimumab it's 20%.

Dahiyat: In melanoma?

Humphrey: In melanoma. And the PD-1s, have I guess five years. Nivolumab had a five-year follow-up and the proportions are even higher. The Kaplan-Meier Curve flattens at two years and it just stays flat.

Dahiyat: Those are the winners.

Humphrey: Because of reasons we still don't know.

Dahiyat: And there's gold in those hills for the patients, but it's going to be very complex, because the immune system does things in its own way and at its own pace and in the compartments where it wants to do them, not necessarily the compartments where we're looking or in the timeframes we're looking at.

Scrip: In immuno-oncology, it probably is never too early to think about payment, since these programs have been moving so fast toward approval. And with all the money that's being invested, and the time that you're spending looking at these complex questions, how do you feel right now about the payer environment that we're in even before Trump's [recent] comments?

Dahiyat: Next week Trump will be on something different and the market will go up 10%.

Trump Throws Pharma A Curve Ball On The Third Day Of J.P. Morgan

By Jessica Merrill, Mandy Jackson and Emily Hayes

12 Jan 2017
Pharmaceutical manufacturers have been waiting for Trump's ax to fall – and it finally did, on the final full day of the industry's biggest business meeting of the year.

Read the full article here

Scrip: But even before he made his comments, pricing was under pressure, even in cancer. I'm sure there are plenty of patients who aren't getting treatment; I know there certainly are patients that are refusing treatment with certain drugs, because they cannot pay for them, and there are doctors who have that conversation with their patients about what they can afford, not what's best for them.

Dahiyat: In terms of the pricing stuff, changes are coming. I don't think it's going to be political change; I don't think our political system's set up for that, but economics will drive it at some point.

Scrip: Does any of that make you nervous in terms of your programs and how do you incorporate that issue into your business?

Dahiyat: In particular, immuno-oncology is susceptible to this issue, because of the need for [drug] combinations, and the power we're going to get from combination therapies, and the desire to price each element of a combination at a premium. That's why big pharma companies are saying, "If we can get the third-best element of the combo, we can bundle, price and win on that." But when guys who've spent their life coming up with new myeloma therapies, like [Dana-Farber Cancer Institute's] Ken Anderson, sit up and say, "We cannot take $25,000 a month in therapy," it is not going to work – something's going to crack.

Immuno-oncology faces that [pricing pressure] profoundly. I have no idea what's going to happen, so let’s do good science trying to cure some patients and then figure it out. That's the perspective I'm taking, and shareholders get that there's an uncertain environment going forward in pricing.

And, honestly, one of the things that kind of offends me as a scientist is that we've been told [at Xencor] that an advantage of our approach to developing bispecific [and trispecific antibodies] is that it's one molecule, one vial, one infusion, one drug, one reimbursement, so maybe we can price if at half … the price of the combos.

Humphrey: You can co-formulate combinations; you put [them both] in the same bag. It's one reason why everyone has a PD-1, because you put it [all] in the bag; it's cheaper.

Dahiyat: You can, so these are all the tricks that are going to be forced on the industry. We're trying to make bi-specific antibodies, because the new biology can be very powerful, not because you can price it at 60% [of the combination therapy] and make a 10% premium off the [reduced] price.

Stiernholm: I'm not sure how many CEOs that I know in small companies lose sleep over this. We are busy trying to get this damn thing to work and then we'll figure out how we are going to get paid for it. But even if you are a scientist by training, I mean, your passion is to get the technology to work and help patients who need care.

Dahiyat: My impression of the big companies is that changes are coming, so make the money while you can.

Humphrey: But oncology is a bit protected, in some ways, because when you do the health economics and you look at the proportion of patients who are cancer patients in the overall health care budget, it's actually quite small. And the question isn’t really price, it's access.

When ipilimumab was priced – a high sum of $150,000 wholesale for a course of therapy – BMS worked extremely hard to manage access. Patients could apply to the company and actually get free drug under very specific considerations that offered a lot of people access. So I think [pricing

pressure] is coming, but it could be a long way off. Ipilimumab/nivolumab is priced as two separate bags and the market's tolerating it.

Furthermore, if you're going to put patients into a cure, the health economic equation is actually quite favorable, so there's room for premium pricing. Now, ultimately, there'll be price wars. Or, the fifth PD-1 will come on [the market] and get on the formulary, because it's cheaper, but not yet.

Boyle: I think some of the cancer types that hit people early in their lifetime, or in the prime of their life – and brain cancer is one of those, unfortunately – the impact of responses and outcomes particularly in that patient set makes a huge difference in the pharmacoeconomic model. In our own personal experience, we've had multiple [partial responses (PRs)] and [complete responses (CRs)]. Yet, it's not just [about the] PR and CR on the MRI, but [before treatment] the patient's not doing well. [After treatment] these patients are returning to work.

What does that do to society, having patients go back to work and lead a relatively normal life? I think there's a flight to value that's going on and [the American Society of Clinical Oncology (ASCO)] is all over it. They're saying, "Why am I paying X for this drug and Y for this drug when the outcomes are very different and the toxicity profile is very different?" When it comes to oncology, there will be a greater emphasis on looking at value that these new agents provide.

Dahiyat: I think that plays to immuno-oncology's favor, because though most patients don't do well, the patients that do well do extraordinarily well and they're really healthy. For most oncology therapies, the patients that respond to the therapy are still getting intensive management and care that's very expensive. The most expensive patients are cancer patients, and if you're getting an agent that's giving you an extra, say, 4.3 to 6.1 months of median overall survival difference, that two-and-a-half months was probably extraordinarily expensive in the health care system. IO kind of maybe can change that equation [by extending survival, but reducing overall cancer care costs].

Humphrey: The other thing that's worth knowing is that some of the strategies that we're using in Europe, like a pricing strategy where they only reimburse for patients who look like they're benefiting, is already being adopted in the United States.

The challenge is for the manufacturer to define what success is, but there are clever ways to drive value and help the patients and manage the costs without necessarily applying strictly price pressure. There's a whole host of things we can do before someone says, "Uncle! Everything has to be 50 cents or less," which I think will never happen, especially in oncology.

[Editor's note: The discussion has been lightly edited for length and clarity.]