EXPERT ROUNDTABLE

Clinical success of checkpoint inhibitors: what's next for combination therapy in I-O?

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Immuno-Oncology Insights 2020; 1(1), 97–115

DOI: 10.18609/ioi.2020.011

Q Where do you see the cutting edge in I-O combination therapy development, currently?

JF: From a clinical development perspective, I think novel trial design is really a key component of this.

I'm thinking in particular about platform trials and adaptive designs that allow us to quickly test multiple different combinations, and then apply some translational biomarker work in a rapid fashion to try to iterate on these combinations.

Obviously, there are tens of thousands of possible combinations at this point, given the pipelines of the biotech and pharma companies out there. So finding ways to process through these more quickly by utilizing these smaller trial designs and moving away from the traditional, straight line Phase 1-to-Phase 2 model is key. Look for a response rate, and then go.

JL: I think that the field has been hampered to some degree by the understandable need of companies to work on their own and protect their intellectual property. To some extent, some of the shared learning from individual patients could greatly enhance the speed at which we could develop drugs – for instance, as patients were profiled in a trial, they could

theoretically move on to different agents that had been identified as potentially relevant to their disease progression. That could improve things but again, it's a difficult thing to think through, because companies have to retain their IP.

I have advocated for some of the larger companies to consider a sort of platform approach where they would make some form of commitment to the patient that they would make something available to them – kind of a continuous feed-through on trials. In other words, if they get a research biopsy on a trial, and the patient's disease then progresses and they get another research biopsy, they could be given access to another pipeline agent that might be relevant to their peer.

These are complicated ways to think about clinical trial design, but we're losing a lot of information from individual patients where they progress on one study and then go onto another one, and neither of these studies were particularly well optimized, even if we talk about biomarkers. We need to harness our learnings from individual patients in a more robust manner.

JF: I totally agree. And I would add that we should be doing a better job learning from the patients when combinations don't work, too.

There's a lot more effort put into to the biomarker work when something is proceeding forward. We don't see it as often when we're trying to learn why a given combination may fail in the clinic. I think there's a lot to be learned there as well.

Q What would you rank as the chief 2–3 obstacles or challenges facing developers of oncology therapeutic combinations today?

RT: As I look at immuno-oncology drug development, one of the long-standing challenges is trying to interpret Phase 1 combination data and compare it to historical standards. It makes it difficult to know with certainty whether or not we're seeing activity of that combination.

I think there are two scenarios. One is where there is pure single agent activity of a drug, in which case one expects to see the combination will show at least additive or synergistic efficacy. (One also has to be aware there may also be synergistic toxicity, of course, which is going to be more difficult to anticipate).

The second (and more challenging) scenario, which is one that we're seeing a fair bit with immuno-oncology, is where there is limited single agent activity, but there is an expectation based on preclinical data that the combination will be active. I think this is where the interpretation of Phase 1 study results has been particularly difficult and has required us to go into randomized Phase 2 studies. A recent example was with Genentech's anti-TIGIT (tiragolumab) where there was limited single agent activity – it was initially studied in a second-/third-line non-small cell lung cancer environment, where it was probably more difficult to interpret the activity. But in the Phase 2, there clearly appears to be significant activity, at least in the PD-L1 positive group.

I think that's part of the challenge: being able to interpret combinations also requires knowing that you're seeing a difference between the combination and the monotherapy activity.

JF: Building on Jason's earlier comment on the need to look beyond

internal company pipelines, it's often unlikely that an individual company has all of the components for a given combination within its own pipeline. And even for those companies that are willing to collaborate and share work/data, it requires a tremendous amount of time and effort just to put those agreements in place and establish the cooperation.

From our perspective, we're seeing a greater willingness from industry to enter into such collaboration agreements, which I think is great and necessary if we are to move these combinations forward. However, the amount of work that goes into is really burdensome at this point.

Q What are the key lessons from the first wave of immuno-oncology combinations that you would like to see adopted and taken forward in future combination selection and development approach?

JL: We've learned a lot but for reasons that are unclear to me, we seem to be unwilling to use the information that we have learned.

It is now quite clear that the population of patients likely to respond to PD-1 or CTLA-4-based checkpoint blockade (and one would presume then, other interferon-associated target molecules) is an interferon-activated tumor microenvironment. That can easily be measured by PD-L1 status, by gene expression profiling centered on interferon signaling – that's very clear now in the field. The problem is that the majority of patients don't have that tumor microenvironment, and yet the field is still holding to this idea that drugs are going to be active when we know based on their biology they're not going to be active outside of that niche.

"We need to harness our learnings from individual patients in a more robust manner."

We've characterized that pretty well for frontline PD-1-based therapies, but the extent to which that biology exists in the second line in the PD-1 failure setting is very unclear right now. And it's shocking to me that we haven't dug into that question: that question underpins how to develop drugs in the second line or PD-1 refractory space, and yet very little data is available.

It is also quite shocking to me that a lot of colleagues I know from the bigger pharma companies can't read this question out from their own large trial datasets. In other words, they did their gene expression assays differently across a number of different large trials. So they can't even aggregate their own internal data, let alone some kind of unified data set we can take forward - for instance, with a PD-1 resistance TCGA (The Cancer Genome Atlas) kind of approach.

I would advocate the idea that what we do know about response to checkpoint blockade is that it associates with high levels of interferon gamma, high levels of tumor mutational burden. But that already sets a framework for patients who are very likely to respond to checkpoint inhibitor-based combinations, and those who are not. Tiragolumab, which was mentioned previously, proves the point, which is that the molecule is active in an

DOI: 10.18609/ioi.2020.011

interferon-activated tumor microenvironment and you only see the benefit when you study the drug there. And that is exactly what you would expect from such a molecule. For me, that is how we should attack this question: at least we know that. But we don't even use that knowledge in our clinical trials as they stand right now.

I think we should use that sort of framework as a basis for which to develop new biomarkers. There are some other biomarkers coming forward – for example, LAG3 looks like a potentially active target. It's borderline, but one would expect that's only going to be present in an interferon active microenvironment. So the question becomes, what population of patients are interferon high and LAG3 high? That's what it looks like from the data from BMS's relatlimab on who is likely to respond. Conversely, around A2AR blockade, some have advanced these myeloid signatures or adenosine signatures – so where's the overlap of that biomarker on this other framework? With this sort of approach, you can start to parse out subpopulations of patients that we might specifically be able to target in a clinical trial.

I compare this to the field of targeted therapy. We see tremendous, unbelievable responses to NTRK fusion, for example. But you would never treat an NTRK fusions with a BRAF inhibitor – it doesn't make sense to do so. And yet in immuno-oncology, we're trying to do that sort of thing all the time.

RT: One of the challenges in combination clinical trials is the question of whether you're going to see a real difference to, say, a checkpoint inhibitor alone – for example, if you're trying to target a population with low PD-L1 expression, where you're not necessarily expecting a checkpoint inhibitor to be active but you think a combination could be. In that scenario, you've got to compare historical data, as opposed to potentially doing a randomized study. (It may not be ethical to do a randomized study, because the checkpoint has already been demonstrated not to have activity in that population). I think it does make combination studies more challenging when you can't make that direct comparison, but you still expect that there may be potential for the combination to expand the patient population for a new therapeutic.

RB: This might be a little coy, but one of the lessons I've learned the hard way is that you don't know what you don't know.

With the first wave of I-O agents, we kind of sat there and relied on the biology to explain a lot of different combinations, a lot of different potential targets. But until they were actually tested, we really had no idea if they would work or not. One of the take-homes I took from this at the time is that you've got to see monotherapy activity. However, as has just been pointed out, TIGIT is a perfect example of something that has recently turned this idea on its head. So I think we've taken some lessons, but some are lessons that we probably wouldn't want going forward!

I think you really do need to test a combination, no matter how much rationalization you can present from a biology perspective, or how things have looked in the past.

JF: We've learned a lot in terms of the differences between immunotherapy and the targeted agents and chemotherapy – differences in how we measure benefit and how we think about safety. I think that's important to carry forward: setting different target endpoints; employing different thinking around the possibility that it's not just the response rate that is important, but the durability of the response; harnessing different statistical models relating to sample size to account for delayed separation of OS or PFS curves.

All of this is key towards ensuring we're not missing that long-term benefit data. There are definitely different ways of thinking about what success looks like with these I-O agents in combinations. We need to be ready to

adjust our approach to make sure we're not missing benefit by looking too early, or looking at the wrong end points.

Building on the safety management piece – which again, is obviously very different from chemotherapy – we obviously now have well-established approaches to managing immune-mediated adverse events that have come out of the first wave of checkpoint inhibitors and their treatment algorithms. And you see this coming out now in cellular therapy, with cytokine release syndrome and other things. We can hopefully take those learnings forward, too, and apply them to novel combinations.

JL: I like the comment about monotherapy activity – I actually continue to believe that drugs should have monotherapy activity, but the comment I want to make is that it is maybe not enough just in isolation. For instance, monotherapy activity might simply be a sample size game: if you treat enough people, maybe you'll finally get a responder.

I have proposed that perhaps we ought to consider either monotherapy activity or activity in a biomarker selected population. In the example we've been using of TIGIT, we do see some activity in the biomarker selected patient and/or randomized studies. As we think about advancing I-O molecules in future, seeing activity in one of those three clinical trial groups – either monotherapy unselected, biomarker selected, or randomized - really ought to be a prerequisite for advancement. Even if you're saying an agent is going to be an add-on that makes a PD-1 checkpoint inhibitor work, for example, it's still got to fit one of those groupings in the monotherapy setting before we can feel confident it's worth taking into a Phase 2 or Phase 3 in the combination setting.

Q Ren, as an analyst, what gives you confidence in a pharma or biotech company's strategic approach to combination therapy development? And equally, what sets off warning bells?

RB: In terms of what gives me confidence, first off is a solid biological rationale, of course. Admittedly, that's an easy box to check – every company that's developing a combination has some sort of biological rationale behind them. I love to see non-overlapping biology and toxicities. And as Jason pointed out, randomized Phase 2 data is something that we definitely want to see. Gone are the days of analysts being quite content to see a monotherapy study that goes off historical controls, although a lot of companies do still do this, because of finances and the like. Today, that's definitely a warning bell to which we pay particular attention.

Biomarker-based selection is another box I like to see ticked. I know everyone likes to use PD-L1 expression as a default, but ideally, we want to see something that could help to really home in on those patients who might respond to a combination – something that actually relates to the combination target that's been focused on, whether it's a TIGIT or any other LAG3 expression, for example.

Regarding warning bells, monotherapy activity is clearly one. I like Jason's comment in particular: even if you don't see monotherapy activity, if you do have data from a small but randomized Phase 2 study, that at least helps us to get over that particular hurdle.

The other thing that we try to stay away from is the line some companies employ that they are not particularly worried about showing clinical activity – so they have no overall responses or PFS – because they are really

DOI: 10.18609/ioi.2020.011

"every company that's developing a combination has some sort of biological rationale behind them. I love to see non-overlapping biology and toxicities. And … randomized Phase 2 data is something that we definitely want to see. Gone are the days of analysts being quite content to see a monotherapy study that goes off historical controls"

focused on immunological response. That's great – I understand we're going after the immune synapse, and you want to see more CD8 T-cells and CD4 T-cells. But we've often found that counting those cells and ascertaining whether or not that number actually translates into a clinical benefit is particularly challenging. I think back to the early days of cancer vaccines when we would always harp on about T-cell numbers, and how much those cells have expanded, but it just didn't translate into clinical benefit.

Q What for you will be the key tools and technologies in both non-clinical and clinical settings that will further enable an era of rational combination selection and development?

JL: Firstly, I think there are some very useful preclinical development methodologies that the larger companies do routinely employ, but which smaller companies may not have the bandwidth to do.

For example, one of the things I would highlight is showing activity in multiple models. Preclinical symptoms are quite finicky by definition – your MC38 is not my MC38, and your CT26 is not mine – and so being able to show that a drug has relative benefit in multiple models is certainly useful.

The other thing that I think is really helpful, but which companies frequently don't seem to mention, is benchmarking most or all of their preclinical experiments against a PD-1 or PD-L1 antibody. We'll often hear that a drug shows activity in a preclinical model, but then find there was no PD-1 in the system – therefore, is it any different to what we already have? And it's really not that hard to run that arm in parallel in your mouse experiments in order to gain what I think is a very useful piece of information. Some of this does come down to basic resources and logistics: when you're a biotech company and you've got a relative handful of staff, I do understand that it's difficult to have 8 different models running simultaneously. But to whatever degree you can possibly expand those kinds of activities before you nominate a therapeutic target as being worthy to go to clinic, I think can be really helpful.

Beyond that, in terms of preclinical technologies or tools, I think we are starting to

be some humanized systems emerging that may or may not start to gain more traction. Xenographs don't work so well for I-O, per se, but some of the genetically engineered mouse models that can help isolate the target might come into vogue moving forward. And I think some of the organoid systems will prove to be more and more useful in answering some of the translational questions. But brass tacks, we're still treating mice and not people; eventually, you've got to treat a human in the clinical setting to find out.

RB: I don't know this space particularly well, but it seems to me that a key enabling technology area to focus on would be biomarker identification strategy, whether that's through next gen sequencing or something else that is an improvement on current immunohistochemistry techniques.

RT: One of the challenges with, say, RNA expression profiling as a biomarker is there is heterogeneity in tumors. Looking at an immune phenotype to better understand what's happening in the tumor microenvironment may be something we really need as a tool for the future.

Looking at the different types of immune system simulation one sees in tumors, some are immune deserts where there's very little immune activation, others show this kind of fibrosis that prevents T-cells from entering the tumor, while others still are very active and hot. I think that understanding the mechanisms that create those different types of tumor will be a really important tool for the future. It's also going to be really important for the development of the next generation of therapeutics if we can understand how to target those different immune phenotypes.

JF: What I see as a challenge from the clinical standpoint is some of the technologies are now in place – single cell analysis and flow cytometry, for example – but we can't get those results quickly enough to correlate with the clinical data in a reasonable amount of time. It is sometimes the case that we reach our clinical endpoints long before we have our correlative outputs. I think it will be enormously beneficial to be able to pair those two things together, so that we can actually making decisions based on the entire dataset, and not just the early clinical data once all patients have been treated for six months.

As this technology advances, as we get higher throughput and are able to turn around analysis of these huge datasets faster, it will really make a significant difference to our clinical development approach.

JL: I think the observation that the technology is emerging rapidly is a smart one, but it's still just beyond our reach in the clinic at the moment.

We can do single cell sequencing of every cell in the patient's body, but the problem is it takes us 6 weeks to do that – we simply can't turn it around and make it useful in clinic right now. But that said, I don't think it is unreasonable to think we are too far away in this regard.

I think that technology will help as it comes through. And the other part, which I am somewhat surprised to admit, is that there may be the ability to develop some peripheral blood biomarkers that could be useful in the not-too-distant future. Even just a year or two ago, we thought there was no way that this might happen. But there have recently been several high-profile papers suggesting that early treatment changes in the peripheral immune compartment really might be good surrogates for treatment response. The issue there is going to be that we didn't collect the data and the samples properly in the past to allow us to study that question retrospectively. We would need large-scale analysis of patients getting immunotherapy moving forward to look at that.

DOI: 10.18609/ioi.2020.011

This goes back to my point about some kind of shared effort – I mentioned a shared PD-1 resistance TCGA type approach. I think we will need something like this – some kind of mechanism from the NCI, for example - to profile patients who are just getting PD-1 now and have that knowledge broadly available. Hopefully, some combination of shared resources and bringing that technology closer to clinic can help address some of these questions and move the field forward for the next generation.

Q As you consider the various emerging immunotherapeutic modalities in the oncology space, which one(s) stand out for you currently in terms of their therapeutic potential, particularly in combination with other agents?

RT: I tend to look at immunotherapy in two groupings. One is therapeutics that are designed to stimulate the immune system and restore natural immunity – I put the checkpoint inhibitors in that category.

The other approach is around what I call engineered immunotherapy – for example, a bispecific antibody designed to engage T cells and recruit them to a tumor.

I think both approaches have merit, but as of right now, I think we've gone through the first wave of those natural immune engagers and moving forward, I think we're going to see some interesting data coming from some of the engineered approaches. That includes the gamut of cell therapy approaches, which I think are evolving rapidly, although still to breakthrough in the solid tumor space. I'm also optimistic about what we're going to see from the engineered bispecific antibody approaches, either with the toll-like receptor (TLR) 7/8 agonists or the CD3 T cell engagers.

I think one of the big remaining unmet needs is in natural immunity, though, which is being able to activate the immune system to target cold tumors. I think those approaches are going to be really important as well.

RB: In terms of emerging technologies, I'll pick up on cell therapies. Obviously, we've seen some really good success in the hematological malignancy space. But as we have start to explore solid tumors, outside of TILs, which have shown some pretty promising results in melanoma and cervical, we haven't really seen too many good results. A lot of companies are now focusing on gene editing these cell therapies, or employing various other reengineering approaches. Whether it is knocking out a PD-1, or bringing in an additional co-stimulatory molecule, it seems like that is and will remain a key area of focus for a lot of companies as the gene editing and cell therapy spaces converge.

JL: I agree with Robin – I think the near-term improvements we're going to see are in the immunoengineering realm. We will continue to work with concepts that we know can have activity – CD3 redirection, for example, and some of the

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conjugated molecules are also showing early signs in solid tumors.

I think that is where we can get to over the near-term, but again, that really only helps those patients whom we already know how to help to some extent. As a more aspirational goal, we do need to figure out how to activate tumor microenvironments in patients who don't have evidence of a T cell response at baseline – who have so-called 'desert tumors'. I still retain hope that we will find a way to harness TLRs, NLRP3 agonists, STING agonists … the first wave of these maybe didn't do it as much as we wanted, but there are hints there might be something there. Over time, I believe those are still areas we can explore to hopefully expand the benefit of immuno-oncology.

RT: One further area of technological innovation that we're still waiting for is masking technologies. We've seen a number of immune targets are too systemically active to be delivered as the naked agonist or antagonist, and so you need a masking technology that will activate within the tumor microenvironment.

To date, I don't think anyone has really demonstrated they can be successful with this in the clinic, but there is some interesting preclinical data, and one can imagine there are a number of targets that could be of high interest in conjunction with this technology. These include some that are already on the market, such as CTLA-4. I think improving the therapeutic index for these products will be pretty critical towards being able to advance them.

RB: Robin, would that include some of the directed cytokines, whether it's to the tumor or not? For instance, a systemic IL-2 becoming a directed IL-2?

RT: Yes, absolutely. Being able to deliver the cytokines direct to the tumor and having them activated in the tumor microenvironment is a significant innovation. IL-2 is a great example.

JL: It's a very good point. If we could do that, we would dramatically expand our realm of possibility. IL-12, IL-15 - these are molecules you can't give systemically, but if you could put them in the tumor… I think the data from OncoSec with their electroporated plasmid IL-12 really suggests these molecules can be very active if you can put them in the right place.

RT: One other approach to targeting the tumor is by direct (intratumoral) injection. These approaches face some hurdles in terms of their practicality in broad application, but I'd be interested in the panel's view on them.

RB: I can tell you from my viewpoint that it's been largely discarded – or disregarded, if you will. We've been following the intratumoral injection space for a while, whether it's TLRs or various other therapeutics directly injected, and every time, it seems like people just move away from it.

I don't know if that's just because we don't have the correct molecules going in. Even IL-12, which OncoSec, Ziopharm, and others are injecting right to the place where you would expect it to have the best impact, is presenting variable results. And I don't know

DOI: 10.18609/ioi.2020.011

if it's because we don't have the right injection technology, or we're not doing it consistently, or it's the abscopal effect – we see that all the time with intratumoral injections. The bottom line is that we've not been able to consistently get it to the level where most analysts and investors will really get behind it.

Perhaps the one exception to that is the oncolytic viruses. The potential to use oncolytic viruses in combination with a checkpoint inhibitor may be something that jump-starts the field.

JL: Hopefully, we will have readouts in the next year – MASTERKEY-265 for T-VEC/pembrolizumab, and there's another study about to launch for TLR9/CMP-001. I think if either of those trials is positive and can show a benefit beyond the local site of injection, it would really change the paradigm there.

In melanoma we do see a subfraction, but still a real number, of patients who have progressed on an anti-PD1, who can get that local injection and get systemic response. I don't think it's robust enough yet to pin our hat on and say we're there, but as has been mentioned, I think the potency of these first-generation molecules perhaps isn't yet optimized. I do think there is still a possibility there, even though I am also a little skeptical about treating this tumor in this way and have the rest of it all go away, too.

The final thing I wanted to mention is something that was in vogue a few years ago but has fallen off the map: the idea of being able to bring neoantigen specificity into a clinical therapeutic. At the time, we also thought that neoadjuvant peptide vaccines were going to cure everyone with cancer but then, all of a sudden, nobody's doing that anymore. However, the preclinical science is still very good. We just haven't figured out how to make that work in the clinic. This bring me back to editing or reengineering cellular products. I don't believe it is pie in the sky to think that in the next few years we could do the real-time bioinformatics and engineering required to educate *ex vivo* immune cell populations against potential neoantigens. We would still face the same barriers we do now around getting those T cells into the tumor, because clearly there are active resistance mechanisms at the site of the tumor that won't let the cells in. But I think it would really change our perspective if we could engineer tumor-specific immune responses and then put them back into the patient, whether that be with chemotherapy or other resistance modifying molecules.

Q What will be the key readouts from current/ongoing combination clinical studies that you'll be particularly looking out for over the short-to-mid-term?

RB: The other panelists may have a much better view of this, especially from the large pharma side. I'm not as interested in the PD-1/CTLA-4 combinations, although I understand from a clinical perspective how important they are – that this combination can work and ideally, we can bring those toxicities down. Similarly, evaluating various types of PD-1s and PD-L1s in combination with each other doesn't particularly excite me, in general.

However, there are certain combinations, like nivolumab/cabozantinib combination in renal cell carcinoma (RCC) – I believe we're seeing that data at ESMO. (Editor's Note: this data was released at ESMO subsequent to the recording of this roundtable – see [1]).

Following the promising TIGIT Phase 2 data that came out, there are now multiple Phase 3 trials, all looking at combinations of TIGIT. Although those are probably not short- or even mid-term in terms of reading out, that is something that a lot of us are focused on. There was a lot of, for lack of a better word, hype around TIM3 and LAG3, which has all largely gone by the wayside now. But TIGIT seems to be a real hope for the field.

Jason mentioned the T-VEC/Keytruda combination study – that is definitely front and center for us, because it brings another modality in. It not just another chemotherapy/I-O or targeted agent/I-O combo – it's an oncolytic virus/I-O combo. I think that can completely open up the space, if it hits, because there are plenty of other oncolytic viruses being explored right now.

We are also focused upon the many Phase 2 bispecific antibody studies that are ongoing right now, even though that is two targets combined in a single molecule rather than a combination, per se.

JF: I generally agree with Ren about the PD-1/CTLA-4 combination picture, but I would just note that there are some next-generation CTLA-4 compounds coming through – different formulations with potentially a better safety profile.

In the context of PD-1/CTLA-4 combinations, and as we think about building upon them, it's fairly daunting to think about adding immunotherapies at the moment, plus there is a question around whether we are giving enough CTLA-4 in the first place. But at least in some of the conversations we've been having, there seems to be a sense that next-generation CTLA-4s with improved safety profiles may provide an opportunity to either increase dose, or to layer CTLA-4 into combinations where previously it might not have been feasible to do so on toxicity grounds.

> "...it is going to take time to really figure out if there is a way to bring these bispecific molecules into the clinic effectively enough to get over that tox profile."

JL: Just further to Ren's comment on bispecifics, I believe there is actually one pivotal study ongoing, looking at bintrafusp alfa, which is the bispecific fusion protein targeting TGF-β and PD-L1 from EMD Serono. That is going head-to-head with pembrolizumab for PD-L1 high tumors. We'll see how that goes. I do like the idea of at least running that randomized study, although I think it's maybe the wrong molecule to do that with – I'm not sure I believe that's the molecule that is going to beat pembro head-to-head, because I'm unconvinced about the TGF-β. But I think it does illustrate this point that you raised, which is that maybe bringing multiple targets to bear in a single molecule could be useful.

It's not a pivotal readout, but at ASCO we showed data for a bispecific PD-1/LAG3 with a HER2 antibody. And whereas the patients participating were HER2 refractory and all had low interferon-associated tumor microenvironment as mediated by PD-L1, we had a 40% response rate. So now we're starting to merge things. Immunologically, we can show that you would induce interferon response, and you could enhance that. I think that kind of approach – sort of taking a piece from here and a piece from there – might be part of where we need to go in the future.

In metastatic melanoma there are several randomized Phase 3 trials against PD-1 in the frontline ongoing. It will be very interesting to see what happens there: I think there are 4 randomized Phase 3s of x-plus-PD-1 versus PD-1 and if they're all negative it will

DOI: 10.18609/ioi.2020.011

certainly mean something, but if any of them hit, it could change the field.

I also wanted to note the comment around TIM3 and LAG3 not really working. This harkens back to our previous conversation: I really do wonder whether or not there was ever any chance they could have shown a signal purely down to the way the clinical trials were designed. We talked about how you need an interferon signal for interferon-associated gene expression to be present – in other words, LAG3 is only going to be there if the interferon signal is there. But in those early studies, all the patients were refractory to PD-1, a lot of them with tumor types that weren't likely to respond in the first place. So was there ever even a chance that any of those patients could respond? I'm not sure. My personal opinion is that the data that was seen with TIGIT (tiragolumab) plus PD-1 (atezolizumab/Tecentriq®) in the frontline with patients with high PD-L1 could maybe have been replicated if you did that study with a LAG3 or with a TIM3.

I think this also relates to the question about biomarkers and how you design these big trials. I do think Roche/Genentech did a smart thing in doing that randomized study and targeting that population moving forwards.

RT: I'm intrigued to see what happens with a lot of the different bispecific antibodies. The EMD Serono antibody mentioned earlier is really interesting – if that sort of approach can tackle fibrotic tumors it would be a breakthrough. But I also think that if the T cell engagers manage to hit the right therapeutic index it would herald a new era, because there are a lot of different targets that can be implemented with that approach.

RB: Around a year ago, we were planning a table on the entire bispecific field, but we got a lot of pushback because the toxicity data coming out at the time was just so significant that trying to identify the appropriate dosing schedule became the chief focus of every one of the companies involved. I'm curious, has this issue been overcome, or has focus shifted away from it – perhaps because we've seen some pretty interesting preliminary data at ASCO that's taken the response rate to a different level?

RT: Ren, you're right that toxicity was one of the big constraints. And I think it is going to take time to really figure out if there is a way to bring these bispecific molecules into the clinic effectively enough to get over that tox profile. That to my mind remains a big question.

JL: I'd just note that we probably have to be careful when we use the term 'bispecific' to make sure we clarify exactly what we mean, because when we talk about it for a hematological malignancy conjugating to CD3, that's going to be very different than in a solid tumor conjugating to CD3, and that in turn is going to be very different to a bispecific checkpoint molecule.

I've actually been concerned that the bispecific checkpoints that have been disclosed so far are not toxic enough. It makes one wonder about the way they have been designed, and whether or not they're doing what we need them to do.

One of things about CD3 redirection in solid tumors is we had to realize we had to dose escalate to go up. You couldn't just expose the patient right away, you had to precondition them. But a lot of those molecules in solid tumors have been limited by half-life considerations, and I think that again goes back to just basic fundamental principles of drug development. We have to figure out the PK and PD for some of these molecules and how we can really apply that in an ambulatory solid tumor setting, which is going to be very different to an inpatient kind of setting for a hematological malignancy like leukemia.

Q We've already discussed biomarkers quite a bit. Moving forward, how will the I-O field further enable biomarker discovery and development?

RT: For next-generation therapeutics, one of the key questions is always 'is there a novel biomarker that will help you identify a subpopulation where the drug will be active?' But I think that when you layer that on top of combining that therapeutic with checkpoint inhibitors, where PD-L1 expression itself provides a somewhat variable impact depending on tumor type, it makes things a little more complex. It is not trivial for any given tumor type to be able to look at a new biomarker as it relates to PD-L1 expression and how that will impact a combination therapy.

One of the challenges sometimes in looking at retrospective analysis, or being able to go back to archived biomarkers, is the consent that was implemented in the study to allow an analysis that was not initially foreseen. So I think to the extent that we can, it is important to run current and future studies with the idea of both learning as much as possible now, and potentially being able to answer questions in the future that we don't anticipate at the moment. It is key to consent patients appropriately so that they know the samples they're agreeing to will be used in the best way possible in future.

JF: That's a really good point. I would add that it relates to an ongoing shifting of priority for much of the industry away from pure speed of enrolment and towards getting quality patients put on trials.

For example, you might say a patient doesn't have enough tissue available right now, so we're not going to put them on the trial immediately – we'll wait another week or two so that we will be able to obtain enough. We're starting to see greater acceptance, at least from our investigators, of the fact that being able to get tissue at baseline is critical. We are seeing more advocating for on-study biopsies, where they are possible, and certainly for the blood work.

I think ten years ago some of that was an afterthought – it was a case of whatever we get is a 'nice to have'. Now it's really becoming critical to our ability to analyze these trials.

Q Jason, where do you see the greatest innovation in terms of combination therapy clinical study design currently – particularly in the early phases – and where is further improvement needed by the field in this regard?

JL: I think this goes along with what we said before about either sequential or adaptive clinical trial designs where patients might act as their own internal control.

For example, patients participating in a study having access to a number of different agents, and as they go through the study, they can get access to each one in series if they progress on the current agent. You could obviously learn from each patient on an ongoing basis.

I designed one such study, which is ongoing. We have learned a lot. We haven't cured cancer yet, obviously, but for the big pharmas especially, this is something I would

DOI: 10.18609/ioi.2020.011

suggest they think about. It could be very powerful for the field, and really could harness trial design as a way to move us forward quickly. There are lots of complications and complexity, but that is what I would advocate for.

Q And more specifically, Justin, how and where are we making real progress in terms of accelerating cancer immunotherapy clinical development and patient access to potentially game-changing therapeutics – again, particularly in terms of innovation in clinical trial designs?

JF: I would echo a lot of what Jason just said: the platform approach we're taking in having multiple small cohorts of novel combinations is really something we want to be our standard moving forward. It is the clinical collaboration piece that is so challenging – getting multiple companies, multiple organizations to buy into that model, to share to some degree, is the difficulty.

I do think that's shifting a little bit, though. And I do see this as the way we can get through the thousands of potential combinations that are out there – to try to start from a rational point, but to then iterate on it. So you might start with a two-drug or three-drug combination, learn something through the biomarkers and the clinical data that you see, even for a limited subset, but then quickly add another cohort of patients to try something a little different. It's a slight variation on the adaptive design, with patients being their own internal controls, but still always providing an outlet for our investigators to make novel combinations available to their patients.

I think what goes hand in hand with this is we've seen a degree of change in the regulatory approach, and more flexibility from the regulatory authorities regarding some of these novel-novel designs. Today, with the appropriate safeguards in place, with appropriate rationale and background data such as established Phase 2 doses, we can put some of these drugs together without the standard 3+3 dose escalation sort of approach. It's been a real partnership for us with the FDA in terms of letting these move forward in an efficient way, but with all the appropriate safeguards in place.

JL: I think this is a tough thing to ask our industry colleagues to comment on, but I guess I would flip it round anyway and suggest that maybe there should be more of an onus on us as the investigators. We think about trials like NCI-MATCH and ASCO TAPUR, where it is possible to leverage networks and large numbers of people, but we should remember that academics have a reason not to do that: they need to conduct their own investigator-initiated trials, and to be able to publish their own paper. But I think we need to try to leverage that kind of broad collaboration more as a

"...getting multiple companies, multiple organizations ... to share to some degree, is the difficulty. I do think that's shifting a little bit, though."

field, and I would challenge any such as myself who are reading to think about this as a possibility. We can't just keep saying the problem is pharma controlling their own assets. And I agree that there is more willingness for pharma to participate in collaborations these days. It's hard for them to volunteer but I think that if we build it, they will come.

Q Robin, how do you expect the oncology healthcare environment to develop over the foreseeable future, and how should those developing novel I-O agents prepare accordingly?

RT: That's a tremendously difficult question to answer, to be honest, but I'll give it a shot!

One of the clear trends we've seen in oncology over the last 20 years, has been the tremendous increase in development. Today, more or less any given target in oncology has multiple players developing drugs for it. What that means is oncology has become much more competitive. The average period of time for which a company will enjoy market exclusivity is probably going to be significantly reduced moving forward. There are two impetuses there. One is to be first to market; the other is to have the best-in-class therapeutic. Being able to achieve both of those will become increasingly difficult.

The other key area of evolution is clearly the payer environment. We live in a very different payer environment in the US versus the rest of the world, but the evidence requirements that we see for payers outside the States is obviously having an impact on drug development, particularly Phase 3, because of the growing need to demonstrate value as well safety/efficacy to payers.

So I would say that ultimately, any company developing new I-O therapeutics today should be prioritizing the demonstration of significant clinical value to patients and healthcare providers, because that's the best way to ensure there is a future for the product in the marketplace.

RB: On a related note, another thing we are seeing, especially with the ever-increasing number of blood-based diagnostic companies out there, is the potential to select for earlier-stage patients pretty much across the board in terms of cancer indications. This presumably allows I-O agents to have a much more profound effect. So getting earlier stage patients on your trial with the potential to demonstrate a much clearer survival benefit will become increasingly key.

Biomarker-driven patient selection will be another important area of focus. Whenever we have been able to identify and really specifically target molecules or drivers of tumors, we've typically seen very high response rates. And we know the US FDA is currently very willing to accelerate the approval of these therapeutics – we've seen several approvals just this year alone based on studies with comparatively very few patients.

The final thing for me is that we are getting much better at handling side effects. When

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we were looking at CTLA-4 initially, we were seeing the gastrointestinal side effects and everyone was very worried about those. Then with the cellular therapies, cytokine release syndrome and neurotoxicity were a source of huge concern. But the longer we handle these various therapeutics in the real world, the better we're getting at dealing with the side effects – perhaps approaching the point where we can start considering pushing doses even higher. So it seems to me as though the other side of the coin is improving our ability to manage patients through these therapies. I'd love to hear the views of the clinicians on the panel on that.

JL: I definitely think that is true. I think if we were to go back and look at the PD-1/CTLA-4 development programs that we've seen so far, if we did them today, the doses of CTLA-4 would be higher. If you take away those early toxicity concerns, there's no real, sensible immunological reason why the dose of ipilimumab has to be 3 or 1 in different tumor types, as though the human beings who have the cancer are different. It just doesn't make sense.

> "we need to become more judicious about identifying the patient populations who are likely to benefit from whatever novel therapeutic that we can use."

I was fortunate: I came into my attending career right when ipilimumab got approved, and nobody in the community would treat any of those patients. I treated lots of them. And now we give nivo/ipi everywhere. Platinum used to be impossible to give outside of an academic center, and now platinum is everywhere. I think the same thing will happen with TILs and with CAR T cells. So I absolutely take that point, I think it's a good one.

Q Finally, can you sum up your expectations for the future in terms of how the cancer combination therapy picture will continue to evolve?

JL: I think that near-term success in the development of immuno-oncology agents is probably going to be predicated on building on things we already know. We've talked about T cell redirection and we've talked about bispecifics. That's probably where the earliest near-term success will come, as well as some advances in cellular therapy.

But more broadly than that, I think I have to emphasize that the discovery of the PD-1/PD-L1 axis was probably a seminal event in human history, and that it's unlikely we're going to find another novel therapeutic that's active across almost all diseases. Therefore, I think we need to become more judicious about identifying the patient populations who are likely to benefit from whatever novel therapeutic that we can use.

And we can leverage learnings that we have, but as we discussed earlier, I think we need to be more diligent about drugs that are either active alone, that have a biomarker, or randomized data. Because I think without that we'll have another 5 years yet of expansion cohorts of 20 patients where one patient had 30% disease reduction and we're not sure if the drug is active.

JF: I think along very similar lines to Jason. The likelihood of finding the next PD-1

is very low, so the need for collaboration is so important – establishing better mechanisms for collaboration, bringing companies to the table, and increasing that willingness from industry to get involved. And I think you made a good point earlier, Jason, about having investigator push to bring companies to the table.

As these combinations are put forward based on preclinical data and other evidence, I think the investigators' voices will carry a huge amount of weight in saying that this is something we think has potential for success. That sort of approach may well help to continue bringing the drug manufacturers to the table, whether they are small biotechs or big pharmas.

RT: I think we're going to see different approaches that are going to be initially most effective in the tumors with high PD-L1 expression, where we're already seeing the activity of checkpoint inhibitors. That's the place where we know that these approaches tend to be most active.

I think the big breakthrough will come if we are able to see an ability to convert cold tumors to hot tumors. And so even though the probability there is likely to be lower in the near-term, I think if we see a breakthrough there it will have huge impact in terms of expanding the eligible population for immunotherapies, and the impact those therapies could have.

RB: I think the world is our oyster in terms of cancer therapeutics.

The tools that we have in our toolbox to evaluate and really interrogate the tumor microenvironment, as well as the patient, just continue to grow. And I think the more knowledge and understanding we have, the better we will get at honing the ideal therapies for each patient.

I think that's one thing that I really see developing. Not a one-size-fits-all but a more tailored kind of approach.

We're already seeing that with Foundation Medicine assays, for instance – everything that's available in that realm is starting to provide a much better sense of how one patient's tumor is different from another's, and how that one patient might respond to a particular therapy versus somebody else. I think that will continue to gain momentum.

We've been talking for a while about how cancer will be treated more and more as a chronic disease – I believe we've made great strides, and I continue to believe in this goal. I think we'll wind up with multiple therapies for all the different stages of disease, and while everyone will want to come upfront for market purposes, we all know that these drugs will wind up being cycled at various stages of disease.

Finally, I would say that biotechs have got become much smarter. There was a time not so long ago when biotech companies would ignore niche indications, because the market simply wasn't there. They felt they needed more patients. They would run large studies with completely heterogeneous patient populations, then wonder why their drugs failed. The upshot of this was they got the drug our for neither the niche nor the broader patient populations. I think what we're seeing in recent times is a change in focus. Companies are really diving in and figuring out that if they can get their drug approved for a niche indication, with high activity, the investor dollars will be there to allow the drug to be explored further in different and larger indications. I think that's a trend that's going to continue to build as well.

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DOI: 10.18609/ioi.2020.011

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *Dr Luke is on the scientific advisory boards for 7 Hills (no stock), Spring bank (stock) Actym, Alphamab Oncology, Arch Oncology, Kanaph, Mavu, Onc.AI, Pyxis and Tempest. He has carried out consultancy with compensation for AbbVie, Array, Bayer, Bristol-Myers Squibb, Checkmate, Cstone, Eisai, EMD Serono, KSQ, Jansenn, Merck, Mersana, Nektar, Novartis, Pfizer, Regeneron, Ribon, Rubius, Silicon, Tesaro, Werewolf, Xilio and Xencor. He has received research support (all to institution for clinical trials unless noted) from AbbVie, Agios (IIT), Array (IIT), Astellas, Bristol-Myers Squib (IIT & industry), Corvus, EMD Serono, Immatics, Incyte, Kadmon, Macrogenics, Merck, Moderna, Nektar, Spring bank, Tizona, Xencor. He has received travel support from Pyxis. Dr Luke also has the following provisional patents: Serial #15/612,657 (cancer immunotherapy), PCT/US18/36052 (microbiome biomarkers for antiPD-1/PD-L1 responsiveness: diagnostic, prognostic and therapeutic uses thereof). Mr Fairchild reports grants from Cancer Research Institute and Bristol Myers Squibb.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Transcript of a roundtable held on September 17 2020, which can be found here.*

Publication date: *November 5 2020.*

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