| **Topic** | **Minutes** |
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| **Welcome***Fabian Ricard* | * The PINTAD group will send placeholders out for meetings. Please be sure to use the link included in the actual meeting invite when joining PINTAD sessions.
* Please kindly stay on mute during the sessions unless you are speaking
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| **Survey Results***Brenda Kurland* | * Survey Results – We received 48 responders from a range of roles in the industry
* PINTAD topics votes were as follows (multiple selections allowed):
	+ 34 Theranostics
	+ 33 Response criteria
	+ 32 Imaging Biomarkers
	+ 26 Artificial Intelligence
	+ 17 Patient- centered
	+ 10 regulatory
	+ 7 non-oncology
	+ Comments included topics including COVID imaging, acceptable use of archival trial data, iRECIST clean-up, adoption of new criteria, networking/career development, virtual round table lunches, reader studies (blinding, site/central)
* Logo
	+ Received some choice comments and criticisms
	+ Decided to regroup and rethink the logo
* Upcoming meetings in October and December, likely one to be a presentation, and one to be a discussion about future working groups
* If you want to suggest topics or offer to speak, contact Fabian Ricard or Brenda Kurland
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| **Introduction***Colin Miller* | * Welcome to the event
* We are going to try to use the chat function at the end for questions and answers
* Delighted to introduce Gregory Goldmacher, MD, key and lead author on the itRECIST criteria
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| **itRECIST***Greg Goldmacher* | Background* Response Criteria for Intratumoral Immunotherapy in Solid Tumors
* Just published this year in JCO
* Tailored for solid tumors and intratumoral (IT) injection in trials
* Concept behind IT therapy: Injection in a tumor, teaches the immune system to recognize whatever is there locally, and it activates the immune response
* Distinct effects you can expect locally and systemically
* Avoided the term abscopal effect, because that implies a claim that system effect is caused specifically by local injection. Studies using itRECIST will likely also be administering a systemic therapy.
* There is only one approved intra tumoral therapy now - TVEC
* There are limitations in RECIST and iRECIST
	+ In RECIST 1.1/iRECIST, any local treatment renders the lesion NE
	+ RECIST 1.1/iRECIST do not adapt to change in injected/non-injected lesions
	+ iRECIST is used to distinguish true PD from pseudo PD and doesn’t account for change lesions injected at time of progression

Questions to answer and data to collect* What is the overall response? As similar to RECIST 1.1 as possible.
* What is the maximal effect of treatment on non-injected lesions – is there a systemic effect?
	+ Keep non-injected lesions non-injected for as long as possible to determine maximal change in these, compared to the baseline
* What happens to lesions that are injected?
	+ Because injected lesions may change, there is no stable single time point baseline against which to compare injected lesions.
	+ During trial, compare injected lesions to the previous time point (“iterative”); after trial, aggregate maximal effect across lesions and across time points.

Initial Lesion Classification Algorithm* Target lesions followed quantitatively can be injected or non-injected - up to 5 injected, and 5 non-injected target lesions are allowed
	+ Keep non-injected, non-injected for as long as you can
* Four lesion categories; target injected, target non-injected, non-target injected, and non-target non-injected
* Lesions can be re-categorized in a limited way
* If you run out of non-target injected lesions, non-injected non-target may become injected non-target
* If non-injected target lesions grow (progress), or there are no other lesions to inject and the non-injected targets aren’t shrinking, you’ve attained the maximal non-injected effect, so may start to inject these injected target
* There is an “impassable wall” between target lesions and non-target lesions – once target, always target once non-target, always non-target

Overall Response* The overall response takes into account the target lesion response (injected and not), the non-target lesion response (injected and not), and new lesions
* When a non-injected target lesion is injected, the non-injected target lesion response is not evaluable NE, but the overall response is *not* NE.

Non-Injected Response* The non-injected target lesion response is based on just changes in the non-injected target lesions
* The current sum of diameters is compared to:
	+ Baseline for PR
	+ Nadir for PD
* Once non-injected lesions enlarge, or there are no other lesions to inject, non-injected lesions may be injected, but the non-injected response becomes NE from that point on.

Injected Target Lesion Response* The injected target lesion response is based on just the changes in the injected target lesions
* During trial
* Calculate SOD of lesions injected at prior timepoint, now and that that prior timepoint, and look at change

What happens at progression* If patient is clinically unstable, treatment stops
* If patient is clinically stable:
* New lesions are typically selected for injection
* Lesions that are growing are favored for injection
* Patients are re-scanned 4-12 weeks later (iRECIST is 4-8) – the longer time between re-scans accounts for the fact that new lesions are being injected

Assessment After Progression* Non-injected response, and injected response (both based on target lesions) are assessed in the same way as before progression
* Measurable new lesions that are injected become part of the target injected lesions SOD
* The overall responses are very similar to those in iRECIST, with the exception of iTPD, which is added in itRECIST
* What would be iCPD in iRECIST, it iTPD in itRECIST when injected lesions show a benefit from the treatment - treatment can continue until the patient is not seeing a benefit
* Treatments can continue until there is evidence of clinical progression, intolerance to treatment, or progression of the injected lesions

Outcomes reported* Overall responses per visit can contribute to best overall response (BOR) and progression free survival (PFS), just like RECIST 1.1 and iRECIST
* Non-injected lesion BOR is the maximal SOD reduction in the non-injected target lesions (until any such lesion is injected)
* For injected lesion BOR: the baseline size for each lesion is the first time point that the lesion was injected and the final size is the smallest size after injection. The best response is the change from the “baseline” SOD to the “final” SOD (both baseline and final may come from multiple time points).
* Can also have a time-to-event endpoint for injected lesions: time until injected response (iterative) is PD.

Wrap Up* Supplement to the paper has more details on case report form design, and sample cases
* Investigators are too busy to do all of these assessments, but they should be able to give an overall response and provide time point of lesion injection, then data management can back out the calculations
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| **Q&A** | Question: *Colin Miller** If you are using a central read, the PI has to clearly identify when lesions are injected and transferring the information
* For central review, the central reviewers are doing a RECIST 1.1 read without knowledge of the injected lesions

Discussion: *Greg Goldmacher** The PI documents which lesions are injected and dates, locations can be ambiguous if you only have a location name from a form, ideally you need a visual documentation of needle placement (guided CT, US. etc) and with a marker
* If it is done by visual inspection or palpation, then a photo is needed with a marker (doesn’t need a ruler) to show where it was
* In one approach being used by Merck now, central reader will do an initial read and a then a second pass where the lesion assessment from the initial assessment is locked, but they can add which lesions were injected between each visit
* Readers should be generating RECIST 1.1 assessments, and enough data for the data managers to calculate injected/non-injected responses

Question: *David Raunig** Have you determined the operating characteristics of these rules as compared to RECIST?

Answer: *Dr. Goldmacher** No. Will first go to some existing data sets to try to do that retrospectively, and then build this into trials prospectively
* All itRECIST assessments will be exploratory until its proven that there are meaningful correlations with clinical outcomes

Question: *Fabian Ricard** How could we optimize the journey of these criteria from being exploratory/surrogate to being primary/validated? Is there a need for a PINTAD working group to work on this?

Answer/Discussion: *Greg Goldmacher** The criteria were presented to FDA. Great discussion and feedback from FDA which is incorporated into the paper. itRECIST endpoints will have to be exploratory until there is a good base of evidence, but the path to validation is not clear. The overall response assessment is very like RECIST 1.1 except that injection does not render a lesion NE. This overall response could become a registrational output. Expect that we need to show that there is a good correlation between the injected lesion overall response and survival, and also the non-injected overall response and survival.

Discussion:* *Dave Raunig:* There has to be some correspondence to clinical outcome and there are different ways to be able to do that statistically.
* *Colin Miller*: Going to be an ongoing discussion

Question: *Ninad Mantri** How do you handle comparing site versus central when central sees progressing lesion but then it isn’t injected by the site

Answer/Discussion: *Greg Goldmacher** Sites select some lesions and central selects others. This is why there is such a strong need for visuals of injected lesions

Risk of discordance. Have not found the optimal way to balance the requirements for truly independent review. Need to get the concordance as close as possible. Generally, sponsors are in the best position to do this type of analysis. Since site will tell the central vendor which lesions were injected (even if target lesions don’t align), sponsors should be able to reconcile.Discussion: * *Jayanth Narang:* Some scenarios may come up that are not explicitly covered in the paper. Example, non-target injected, becomes large enough to be injected, now it’s a non-target injected.
* *Greg Goldmacher*: If that lesion grew enough to cause PD, its overall PD. The lesion WILL NOT be measured or become a “target.” They will not contribute to the injected target response.
* *Jayanth Narang:* Could be many more scenarios that could come up and may not be covered. Is there a way for people to raise these questions to Greg Goldmacher, or a working group, so there is more harmony, and everyone is handling these scenarios in the same way?
* *Greg Goldmacher*: Question and answer session would be terrific; the criteria needs to be pressure tested to dig into such scenarios. Keep the criteria as close to RECIST as possible.
* *Jayanth Narang*: I you have an overall progression, like iRECIST where you are saying itRECIST: you inject a new lesion (iUPD), then that lesion shows response, but there is significant progression of other disease
* *Greg Goldmacher*: The clinician perspective is that if the injected lesions shrink, or at least don’t grow, they want to continue injecting. If injected lesions are growing it is iCPD.
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| **Wrap-Up and Close Out** | * *Colin Miller:* Thank you for your questions, there were a lot of them, and we did not get to all of them. This is a discussion we may well continue.
* *Brenda Kurland:* Echoed and yielded
* *Fabian Ricard:*
* We will collect all the questions in the coming days and maybe have another session. We will send an e-mail to collect all of the questions
* Post-meeting note: question can be sent directly to Greg Goldmacher for discussion. PINTAD may not organize another iRECIST session.
* We are working to collaborate with other groups so you may receive an e-mail from us with a QIBA survey that we would ask you to complete
* In the future we may try to collect questions prior to talks like this
* *Greg Goldmacher:* We are going to create a training course for itRECIST. The courses we created for RECIST 1.1 and iRECIST are being adopted by TransCelerate, and will soon be hosted by the Society for Clinical Research Sites (free and with certificate for sites). The website is <http://myscrc.org>, though the courses aren’t up yet (just a placeholder for them).
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| **Post-Meeting Notes** | * Phantom/phantom software survey is at <https://rsna.az1.qualtrics.com/jfe/form/SV_3KU8Euvy5wY3qnj> and open until October 31.
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