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FDA PUBLIC WORKSHOP:
ANTIBODY MEDIATED REJECTION IN KIDNEY TRANSPLANTATION

Tommy Douglas Conference Center
10000 New Hampshire Avenue
Silver Spring, Maryland 20903

Reported by: Michael Farkas
Capital Reporting Company

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| <p style="text-align: right;">Page 6</p> <p>1 DR. NICKERSON: Thanks very much, Renata. 2 It's a pleasure to talk about post-transplant 3 monitoring, diagnosis, treatment of AMR. And just 4 before we start we are going to try and keep all the 5 speakers on time today. We're going to try and finish 6 by 1:00 given the fact that this is going into a long 7 weekend and we're wanting -- mindful of traffic is 8 probably going to flow early today. So we're going to 9 try and finish by 1 so if everybody can please stay on 10 time. 11 Our first speaker is going to be Dr. Chris 12 Weibe, my college from the University of Manitoba. 13 Chris? 14 DR. WIEBE: Okay. Thank you very much for 15 the invitation to be here. I have no disclosures. 16 And I want to start by actually talking about the 17 prevalence of de-novo DSA and incidence rate as it was 18 mentioned by Arjang yesterday in her introduction. 19 If you look at the literature it's actually 20 quite heterogeneous. As you can see on this slide 21 we've reported a 2 percent incidence in the first year 22 at the same time other centers are reporting up to 20</p> | <p style="text-align: right;">Page 8</p> <p>1 positive. 2 And I think if you look in the red column 3 where you see the incidence of de-novo DSA being 4 called in the first month that really highlights that 5 this is in many cases a recall response. Whereas if 6 you're very conservative at ruling out DSA pre- 7 transplant, you would expect to see very low rates in 8 the first six months to a year period. 9 Now I won't dwell on this slide as it's been 10 shown multiple times, but clearly this has to be taken 11 in the context of the patient adherence as well. And 12 why do we care about do-novo DSA? 13 Well, as we have shown back as early as 14 2012, there's about a 40 percent lower graft survival 15 at 10 year in patients with de-novo DSA. And this is 16 largely driven by the clinical cohort, which has the 17 worst graft survival seen in the red line here. 18 But also clearly the subclinical de-novo DSA 19 patents do decline if you wait for it and follow them 20 in the long term, as shown in the blue line here, and 21 have similar rates of graft loss as the other AlloMune 22 and non-AlloMune causes of graft loss in kidney</p> |
| <p style="text-align: right;">Page 7</p> <p>1 percent incidence in the first year. 2 So how can this both be true? Well, if you 3 look at these five selected studies here and you look 4 in the column in blue, you'll see that actually 5 incidence rates have been reported everywhere from 27 6 percent at one year down to 2 percent at one year. 7 But what's actually remarkable is after that first 8 year all centers kind of agree that the incidence rate 9 is around zero to 5 percent per year thereafter. 10 So what's the difference in the first year? 11 I think although they're -- we could argue that there 12 are many possibilities, the real driver is how did 13 that center choose to rule out DSA at the time of 14 transplant? 15 It should be no surprise that if we use an 16 insensitive test or a less sensitive test to rule out 17 DSA at the time of transplant, we are going to either 18 intentionally or unintentionally miss some low-level 19 antibodies that we're calling negative. And when that 20 recipient, then, is re-exposed to the donor antigens 21 post-transplant that antibody can increase in titer 22 and go from being called negative to being called</p> | <p style="text-align: right;">Page 9</p> <p>1 transplant patients. 2 And it's important to note that 76 percent 3 of this cohort of 508 patients has actually had stable 4 function and was doing well. And I'm going to talk 5 more about what that means specifically. 6 To get into some of the detail of this we 7 looked at this cohort of 500 patients and we actually 8 had nearly 13,000 eGFR reports that we could really 9 dig down to see how their function was changing over 10 time. 11 And the first interesting observation is 12 what you see here in the stable group. You can see 13 that their rate of eGFR decline was about 0.43 mils 14 per minute per year which is interesting for the 15 reason that it's actually very similar to what's been 16 reported in the age-matched healthy non-transplant 17 population going back to the studies in the 70s where 18 these types of things were being studied. 19 And so it does suggest that if you can avoid 20 DSA, you can avoid rejection and obstruction and these 21 other causes of graft dysfunction the kidney 22 transplant recipients can do very well and are</p> |

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| <p style="text-align: right;">Page 10</p> <p>1 declining at the same rate as the rest of us. 2 The de-novo DSA patient population, on the 3 other hand, even before DSA ever developed you can see 4 that they have a four-fold higher rate of eGFR 5 decline. And after the onset of the antibody this 6 rate is again significantly accelerated and, in fact, 7 doubled. And this makes sense when you think about it 8 pathologically because now we have new arms of the 9 immune system like the antibody dependent cellular 10 cytotoxicity and the compliment pathway that can start 11 to lead to graft damage. 12 And this was actually very consistent across 13 the subclinical and clinical groups. Both had higher 14 rates of decline early on and accelerated rates of 15 decline later after the antibody was developed. And 16 really the big difference between these two groups is 17 that there's also a step-wise decline in the clinical 18 group. 19 So what this looks like in pictures is shown 20 here on the top where you can see that the clinic 21 group if you look just in the red line in those first 22 one to two years, many of the patients with clinical</p> | <p style="text-align: right;">Page 12</p> <p>1 Now, like many other centers, we have been 2 interested to see if there are serologic predictors 3 that would help us to discern which patients are going 4 to progress more quickly to graft loss after DSA 5 development. And we've looked at titrating these 6 antibodies down to figure out their relative strengths 7 and we've also looked at the C1Q status. 8 And as you can see here both in all comers 9 on the left or just the subclinical cohort on the 10 right titration and C1Q status were both kind of weak 11 to moderate univariate predictors of post-DSA 12 survival. 13 However, after when we actually adjusted for 14 some of the more robust predictors like non-adherence 15 or the clinical/subclinical phenotype these serologic 16 predictors fell out of the model. And I should frame 17 my comments to say that many of the C1Q studies done 18 to date have either been in a mixture of pre- 19 transplant and post-transplant DSA or in some cases 20 when they have looked exclusively at de-novo DSA it 21 hasn't been in the setting of monitoring. It's been 22 in the setting of at the time of graft dysfunction so</p> |
| <p style="text-align: right;">Page 11</p> <p>1 de-novo DSA lost their grafts early whereby the 2 subclinical group almost by definition did well in 3 those first two years. 4 After the first two to three years -- and 5 this is from the time of antibody onset forward, not 6 from the time of graft -- not from the time of 7 transplant. But after those first two to three years 8 you can see that the lines are actually relatively 9 parallel. But because of the early difference the 10 median graft survival is nearly five years different 11 in these two phenotypes. 12 And in terms of eGFR what this looks like in 13 pictures is we have the green line at the top there 14 where we have the stable graft slowly declining over 15 time and we have the de-novo DSA patients represented 16 by the black line where even before the antibody 17 develops they do have a faster rate of decline. And 18 then at the inflection point when the antibody 19 develops we have a step-wise decline in the clinical 20 group, but after antibody development both the 21 subclinical and clinical group are declining at a 22 faster rate.</p> | <p style="text-align: right;">Page 13</p> <p>1 many -- there has been a discrepancy in the literature 2 in this regard. 3 So one of the things we're interested in 4 doing with this data is really looking at how we could 5 design a clinical trial. And I'll start by talking 6 about graft survival. 7 If we were to design a trial that was a 8 five-year study looking at graft survival assuming a 9 sample size power of 80 percent, an alpha of .05 and a 10 drop load of 10 percent and we took all DSA patients 11 who I've already showed you have a median five-year 12 graft survival of 60 percent and assuming we had a 13 treatment that could reduce that risk of graft loss by 14 either 25, 35, or 50 percent, you can see across the 15 top of this table that we would need 600, 300, or 150 16 de-novo DSA patients in that study. 17 And keep in mind that only 5 to 10 percent 18 of the average tacrolimus-treated patient population 19 will develop DSA at five years so this is a 20 substantial cohort that would be needed. 21 On the other hand, if we wanted to enrich 22 that population we could look at the de-novo DSA</p> |

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| <p style="text-align: right;">Page 14</p> <p>1 patients that have clinical dysfunction. And I'm 2 showing here that their median five-year graft 3 survival rate is 28 percent and so you can decrease 4 the number as needed to study by about a third in each 5 of those scenarios.</p> <p>6 But the caveat that was mentioned yesterday 7 and is certainly true that in this patient population 8 90 percent of the patients have either subtle or overt 9 nonadherence making them less than ideal patients that 10 you may want to enroll in a multicenter, multi-million 11 dollar clinical trial.</p> <p>12 And I'll, again, frame those comments that 13 if you actually had a good intervention to address 14 nonadherence that may be a very good idea.</p> <p>15 So what about other potential surrogates? 16 eGFR, as you know, has been already considered by the 17 FDA to be a valid surrogate endpoint in the CKD 18 literature for predicating and staging of disease. 19 And here doubling of serum creatinine which is a 57 20 percent decline in eGFR as a valid surrogate endpoint. 21 And also in a consensus paper by Thompson, et al, they 22 discussed the 40 percent decline in eGFR over two</p> | <p style="text-align: right;">Page 16</p> <p>1 What about the pathology scores? One of the 2 things that we did to create this table we used over 3 1,000 biopsies of which 371 of those biopsies were 4 from the de-novo DSA patients. And we were interest 5 in what were the multivariate (mic drops) and so what 6 you're seeing here (mic drops) the CG -- each row here 7 is its own independent multivariate model.</p> <p>8 So you can see for the CG scores in the 9 first three rows that after adjusting for time post- 10 transplant and nonadherence and cellular rejection de- 11 novo DSA is a very strong predictor of the CG scores 12 as been reported previously. However, de-novo DSA 13 does not predict the IFTA scores. These are, in fact, 14 driven by cellular rejection time and nonadherence.</p> <p>15 Furthermore, if you actually look at CG and 16 how it can predict graft survival, this is looking at 17 just biopsies done in de-novo DSA patients. And the X 18 axis here is time post-biopsy. And there are 70 19 patients included in this analysis and I actually just 20 created this figure last week so it's unpublished 21 data.</p> <p>22 But you can see that using CG score at the</p> |
| <p style="text-align: right;">Page 15</p> <p>1 years assuming a baseline eGFR of 50 mils per minute, 2 which is actually quite consistent with the average 3 transplant patient.</p> <p>4 And we did look at this in our cohort and we 5 saw that for each 1 mil per minute decrease in the 6 eGFR at three years post-DSA onset that there was a 7 hazard ratio that was highly significant for graft 8 loss.</p> <p>9 And so crunching the numbers what that looks 10 like is if you were to do a two-year study you would 11 expect an eGFR decline of around 7.8 mils per minute 12 in that two-year period. And if you had a therapy 13 that could reduce that eGFR decline by either 50 or 70 14 percent, you can see you need 550 or 282 patients. 15 And the numbers in brackets there are the expected 16 risk reduction in graft loss.</p> <p>17 And if you extended that study to three 18 years you can see the numbers do go down slightly. So 19 these represent slight decreases from using the gold 20 standard of graft survival, but probably the major 21 advantage here is just that the duration of the trial 22 could be shortened somewhat.</p> | <p style="text-align: right;">Page 17</p> <p>1 time of the biopsy the red line is the CG score of 2 zero, green is a combination of CG score 1 or 2, and 3 blue is CG score of 3 that clearly these do separate 4 out and that's highly statistically significant.</p> <p>5 So the rationale to use a Banff CG score, 6 then, as a potential surrogate endpoint is, first of 7 all, it does correlate strongly with de-novo DSA. 8 Secondly, it's actually quite infrequent at the time 9 of de-novo DSA.</p> <p>10 We've reported in our cohort where we are 11 routinely monitoring at least annually for de-novo DSA 12 that 87 percent of those patients will have a CG score 13 of zero at the time of the DSA onset. And this is 14 important because it suggests that we do have time to 15 intervene in these patients before they go on to 16 develop scarring.</p> <p>17 And that when we follow these patients over 18 time we're seeing an increase in the CG grade of 19 approximately one point for every three years 20 thereafter. And as I showed you already in the last 21 slide CG score does have prognostic significance. 22 The caveat, of course, is that we would</p> |

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| <p style="text-align: right;">Page 18</p> <p>1 first need to validate that preventing the progression 2 to CG would also correlate with improved graft 3 survival. 4 And I think also mentioned yesterday is that 5 perhaps this isn't even the best way to look at this 6 question since we now have electron microscopy. 7 Looking at peritubular basement membrane multi- 8 layering may be both, number one, a more sensitive 9 method to define this evolution and, number two, it 10 actually provides you potentially a wider range of 11 values to study since you're not stuck in the CG score 12 of zero, 1, 2, or 3. You could actually maybe have a 13 score of zero to 10 or even higher if you're looking 14 at peritubular basement membrane multi-layering. 15 So to summarize some of the important points 16 -- and I know that this figure from our review paper 17 last year was shown yesterday, but it's important to 18 highlight that the AlloMune causes of graft loss 19 really are driven by IFTA and CG. And IFTA is largely 20 driven by TCMR. 21 As we talked about yesterday, this can be 22 clinical or subclinical. And the reality is that this</p> | <p style="text-align: right;">Page 20</p> <p>1 tubulitis was an independent multivariate predictor at 2 that time point for progression to graft loss. 3 So, in other words, at all time points that 4 we actually look for TCMR in these patients we're 5 finding either subclinical or clinical TCMR in many of 6 them. And this should probably be no surprise because 7 both the ABMR and the TCMR are really driven by the 8 same two major risk factors. 9 We have the AlloMune risk which as Peter 10 mentioned yesterday is likely most precisely defined 11 by the degree of epitope mismatch. And we have the 12 degree of immunosuppression which, as mentioned 13 multiple times, can in many cases be under 14 immunosuppression which is either nonadherence at the 15 patient population or in cases physician guided. 16 So to summarize what I said, the enrichment 17 strategies that we may be able to use to increase the 18 endpoint frequency to study this patient population 19 are DSA titer, medication nonadherence, tubulitis, and 20 CG scores. 21 And really the best endpoints are still 22 graft loss, but I think Delta eGFR or Banff CG scores</p> |
| <p style="text-align: right;">Page 19</p> <p>1 is smoldering in many patients. And just to give you 2 an example of that from the de-novo DSA patients we 3 have published that in the early time points in the 4 zero to six-month time points patients who will 5 eventually go on to develop de-novo DSA actually have 6 higher rates of both clinical and subclinical TCMR in 7 that first six months. 8 And when we went on and biopsied those 9 patients for protocol or surveillance at six months we 10 observed higher levels of tubulitis, interstitial 11 inflammation, and, as mentioned yesterday, peritubular 12 capillaritis in the patients who don't yet have 13 antibodies but are destined to go on and get them at a 14 later time point. 15 And as I mentioned, TCMR even after these 16 time points is an independent multivariate predictor 17 of de-novo DSA. And lastly, when we find de-novo DSA 18 sometimes at four or five years post-transplant or 19 longer and we biopsy those patients right at the onset 20 we again are seeing a high level of mixed rejections 21 and both -- this is driven by both the interstitial 22 inflammation and the tubulitis. But specifically</p> | <p style="text-align: right;">Page 21</p> <p>1 can be considered. I'll stop by saying thank you very 2 much for invit- -- the invitation. And thank you to 3 my mentors, especially Peter Nickerson and David Rush. 4 Thanks. 5 DR. NICKERSON: Thanks very much. Our next 6 speaker is Dr. Lakhmir Chawla who will be talking 7 about the best ways to assess renal functional status. 8 DR. CHAWLA: Good morning and thank you for 9 the invitation. I'm going to take you through 10 something that's a little bit different regarding the 11 assessment of kidney function. It's a little old and 12 some things are a little new 13 These are some important disclosures. I'm 14 currently on sabbatical at a company in San Diego, 15 California, which has absolutely nothing to do with 16 the kidney at least for now. And I do have some other 17 relevant disclosures due to companies that work in the 18 biomarker space. 19 So when we think about stress testing 20 clinically we're all very deeply aware of what this 21 is. If a patient comes in with angina we know what to 22 do, if they have intermediate assessment or</p> |

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| <p style="text-align: right;">Page 22</p> <p>1 intermediate biomarker we ask the question do you have 2 a critical lesion, we put them on a treadmill with 3 dobutamine thallium in them, we stress them. We have 4 like 19 flavors of cardiac stress testing. 5 We have precisely zero for the kidney and so 6 we set out to make the assessment as to whether this 7 might be valuable. 8 Now as everyone here is aware whether you're 9 talking about acute kidney injury or chronic kidney 10 disease or patients with disease in transplantation 11 the tubule is very important and the interstitium is 12 very important. And I hope to convince you that this 13 might be a relevant way of approaching them. 14 Now thanks to Andy Levey and the MDRD group 15 and CKD-EPI we now have data of the transplant 16 population. I ask a fellow what is someone's GFR 17 through the day and this is the line they will 18 typically draw, right. That's your eGFR, it's 75. 19 Everything is great in the world. 20 But that's actually not your GFR through the 21 day. This is what your GFR looks like through the 22 day. So your GFR is not a straight line. It's not a</p> | <p style="text-align: right;">Page 24</p> <p>1 range there are individuals who will go above 200. 2 So if you have a nice ribeye at Ruth's Chris 3 plus or minus the butter on top and you have healthy 4 kidneys you will have an amazing GFR. You should call 5 Guinness and go, "Check this out, I hit 200." 6 But you won't notice it and no one will 7 really care, but it does tell you about your renal 8 reserve. Now you can do this intravenously, you can 9 do this through an oral load, but all this is very 10 effective and it does tell you about your reserve. 11 What reserve do you have? 12 Now the reason why this is relevant is 13 because you can test this in individuals. You can 14 look at this baseline GFR. As you work your way up on 15 the protein load you hit a plateau. I refer to this 16 as the Bosch limit because Juan Bosch is the one who 17 actually discovered or revealed renal reserve. 18 And if you have a patient who has an 19 allograft or a kidney donor is a better example and 20 you stress them, what you will see is they do not, in 21 fact, have this ability to increase their eGFR. Their 22 GFR does not go up after a big protein load. It stays</p> |
| <p style="text-align: right;">Page 23</p> <p>1 pulse rate of 55 all day long. Your kidney responds 2 primarily, as it turns out, to protein. And what 3 you're looking at are three healthy meals a day with a 4 reasonable protein balance. 5 And as it turns out vegetarians because they 6 eat less protein have lower GFRs and they have no 7 kidney disease. So I don't want to attack eGFR. I 8 think it's incredibly useful. It is a good surrogate 9 marker. It does work in large populations. But for 10 individuals creatinine is a 60-year old test and we 11 should probably do better. 12 Now in cardiology we have robust assessments 13 of pathological stress, physiologic stress, and we 14 have testing to look at those things. We do not do as 15 well with the kidney. And this is just to show you 16 what your baseline eGFR is and this is what happens 17 when you get a large slug of protein. 18 This is 1 gram to 2 grams and what you can 19 see is after about 1 gram of oral protein loading your 20 GFR goes up from a mean of around like 110 to about 21 150. And you can see in some individuals this number 22 goes well above 180. And if you look at the actual</p> | <p style="text-align: right;">Page 25</p> <p>1 flat because they do not have reserve because they've 2 lost 50 percent of their renal mass. 3 And this is how we can measure this. And we 4 also know that patients with subclinical kidney 5 disease lose their functional reserve before they 6 begin to dig in. So once a regular patient bumps 7 their creatinine they have lost 50 percent of their 8 reserve. 9 This is lost on most of my colleagues who 10 take care of patients in the floor because the 11 creatinine goes up .3 and it's much to do about 12 nothing, but I make the point that if you'd lost your 13 kidney you'd probably notice. 14 So the issue about glomerular reserve has 15 been known since 1985. And to be honest with you the 16 reason why this hasn't really taken off is because as 17 a society taking care of patients with kidney disease 18 we really are not interested in pre-CKD in the way we 19 are prediabetes. We probably should be, but we're 20 not. 21 So if you are someone who think you might 22 have prediabetes they'll bring you in for an oral</p> |

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| Page 26 | Page 28 |
| <p>1 glucose tolerance test, we'll look at your hemoglobin 2 A1C. If it's off, we begin to intervene. It's almost 3 certainly the case that would work with patients at 4 risk for CKD and hypertension, but it's just too much 5 work and too much trouble to do this assessment. And 6 no one has really done the science yet, but it makes 7 sense that this would likely be the case.</p> <p>8 But in addition to glomerular reserve 9 there's also a construct of tubular reserve and these 10 two things are not the same. Now this is a study done 11 by Herrera and Rodriguez-Iturbe in Venezuela. And 12 what they did is they took cohorts of patients to 13 healthy patients and patients with CKD and they gave 14 them a test meal which basically is a large protein 15 slug.</p> <p>16 And what you see here these are your 17 patients with -- who are healthy this is the increase 18 in GFR. So you see an increase. It's not massive. 19 But this is the increase in the CKD patient. CKD 20 patients also have a mild reserve and this is probably 21 because they took a baseline in the morning and this 22 is their reserves for the day.</p> | <p>1 creatinine clearance goes up dramatically and that's 2 because your tubule secretes creatinine and it does it 3 very effectively and it can be induced.</p> <p>4 And these are healthy patients. These are 5 patients with a single allograft. These are donors 6 who have given a kidney and these are your CKD 7 patients who have no tubular reserve whatsoever. They 8 have no change.</p> <p>9 And so we asked the question, well, if 10 tubular reserve dissociates from glomerular reserve 11 this might be informative for both acute and chronic 12 diseases of the kidney. And so if you set out to look 13 at this we know that we can assess glomerular reserve. 14 We probably should, but we don't. But we know how to 15 do this. This is well established. There's hundreds 16 of protocols if not thousands that have been done in 17 the last 25 years.</p> <p>18 But the question is is can we assess tubular 19 reserve? And the answer is almost certainly yes and 20 I'll show you some of those data in a moment. But 21 also and importantly the question is is does reserve 22 matter? And I would argue strongly that it does and</p> |
| Page 27 | Page 29 |
| <p>1 But this is what happens with their tubular 2 reserve here. It -- and this is your eGF- -- I'm 3 having a little bit of -- here we go. This is what 4 happens when -- that's inulin. This is what happens 5 to your creatinine clearance. This is much bigger 6 jump up and you see a flattening here.</p> <p>7 And I'll show you the next slide which will 8 put this into context. So then what they decided to 9 do is the same group then gave a cohort of patients 10 who were healthy kidney donors and CKD patients 11 intravenous creatinine. This has never been done 12 before that I can find in the literature.</p> <p>13 So they got a bunch of people. Where they 14 got their creatinine, how they made it safe and GMP 15 for intravenous I don't want to know and I prefer not 16 to ask, but they did it. And this is what you see. 17 What you're looking at on the left is inulin when you 18 give someone a lot of intravenous creatinine and 19 nothing happens to their GFR.</p> <p>20 So the fixation on creatinine is interesting 21 since it doesn't do a thing to your GFR, but that's 22 neither here nor there. But what does happen is your</p> | <p>1 that we do it for every other disease and we have made 2 enormous gains when we do this. We should consider 3 doing this for the kidney, but that is a different 4 talk and we don't have time to delve into that right 5 now.</p> <p>6 We decided to assess and develop a tubular 7 reserve test for patients with acute kidney injury. 8 And if you think about acute kidney injury the vast, 9 vast majority of pathology is considered to be 10 tubular. And the area of the kidney that we're most 11 interested in is the S1, S2, S3 segment and the loop.</p> <p>12 And so if you think about the interest level 13 this is really what you want to test. This is what 14 you want to be able to functionally assess in real 15 time. Now there's some very fancy things and if you 16 have a mouse you can do everything, but humans at the 17 bedside who are critically ill on vasopressors with 18 nine tubes in them are not amenable to this kind of 19 intervention.</p> <p>20 So we decided to use furosemide as a way to 21 test the kidney. Now furosemide is uniquely suited 22 for this role. The reason why is furosemide is not</p> |

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| <p style="text-align: right;">Page 30</p> <p>1 filtered at all. Furosemide is very tightly bound to 2 albumin. And the way it gets excreted is by active 3 secretion through the proximal tubule. 4 Furosemide is not filtered at all so in 5 order for you to get furosemide out of your body and 6 in order for it to be a diuretic it has to go from the 7 blood side of the kidney, it has to be actively picked 8 up by the human organic anion transporter and actively 9 secreted into the proximal tubule. 10 And we basically made the assessment, well, 11 if this is glomerularly independent we can test the 12 tubule and the readout's very straightforward if the 13 furosemide can get from the blood into the lumen and 14 get to the loop there's a nice readout. It's urine 15 output. 16 So what we did is we basically developed an 17 assessment where we gave a standardized dose of 18 furosemide in a highly controlled fashion and we 19 looked at the urine output. And very simply we gave 1 20 mg per kg and we replaced the urine that you put out 21 so we didn't hurt anybody and make the volume 22 depleted.</p> | <p style="text-align: right;">Page 32</p> <p>1 50 milligrams. The older you are the more you're 2 willing to give for reasons that we can't get into now 3 either. 4 So you give this giant slug of furosemide, 5 nothing happens. And they go, oh, boy, put a catheter 6 in. And it works. It's actually quite effective. 7 It's incredibly crude, but we basically took that 8 insight that has been sort of floating around critical 9 care medicine and nephrology for 50 years and we 10 standardized it. 11 What's cool is how well it performs. It 12 gives you an AUC curve of .87. And for those of you 13 who don't live in diagnostic land .87 is really good. 14 Troponin lives at .91. So, you know, we were alarmed 15 that physiology worked. It was quite stunning, in 16 fact, but, you know, there you have it. 17 So, you know, you can use a simple test 18 that's 10 cents for the furosemide, it's \$1 for the 19 saline. The medical student depending on your 20 institution is free or costs you millions so it's your 21 call on that one. But nonetheless it's a simple test. 22 It gives you a nice readout and it performs well.</p> |
| <p style="text-align: right;">Page 31</p> <p>1 And this is the study which is in your 2 packet. I'll let you read this at your own time and 3 leisure. But we basically looked at the standard 4 KDIGO criteria at the time they were called akin. And 5 what you see here -- and I hope this is projecting 6 well -- is the people who progressed have the stripe 7 bars. They basically lose and do not have the ability 8 to increase their urine output. The patients who did 9 well are the ones who could actually increase their 10 urine output. 11 And there's no special genius to this. This 12 was being done for 50 years in nephrology and critical 13 care medicine, right. Usually the story goes 14 something like this: Hey, I got a patient, they're 15 really sick. I want you to dialyze them and it's like 16 Friday at like two in the afternoon. And nobody wants 17 to put a catheter and dialyze somebody Friday at 2:00 18 in the afternoon. 19 So the attending tells the fellow to tell 20 the intensivist to give a giant slug of furosemide and 21 they do. And they pick some random dose depending on 22 your decile of training it goes from 500 milligrams to</p> | <p style="text-align: right;">Page 33</p> <p>1 This has been validated now on multiple sets. 2 And we then actually looked at this head to 3 head against biomarkers. I won't take you through 4 this, but it's .87. Every other biomarker was under 5 .7. This was not good news for the people I 6 collaborate with in industry by the way. They did not 7 like this. 8 Anyway, it performs well. And the key take 9 home point is that you can do this, it does work, and 10 it has a high performance level. And I apologize for 11 blowing through this so quickly but it's in your 12 packet. 13 But I want to show you why else I think it's 14 important. We've actually done this now in DGF so as 15 many of you are aware surgeons love to see urine come 16 out of the patient. It makes them feel very happy and 17 warm on the inside. 18 So what most transplant surgeons do is as 19 they're closing they give 100 milligrams of 20 furosemide. They do this for two reasons. One it 21 kind of tests to see if things are working. The 22 second thing is that it makes them look really good</p> |

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| <p style="text-align: right;">Page 34</p> <p>1 when a patient arrives to the ICU after an allograft 2 like, look, I put the thing back together again, 3 there's blood flowing, there's urine coming out, 4 everything is better. 5 So some colleagues of mine, Blohm Macleman, 6 took advantage of this and basically said, well, let's 7 use this as a furosemide stress test and see what the 8 urine output after an allograft does and looked at the 9 two hour and six hour, you know, random FST for lack 10 of a better word, it wasn't perfectly standardized by 11 weight, and these are your results. 12 There you see a curve value in 300 patients. 13 This is a convenient sample. This isn't even 14 standardized it's .84 and .86. This is holding up in 15 DGF, as well. 16 So for the acute management of patients a 17 simple physiologic test if highly valuable. I don't 18 have time in this talk to go through it, but this 19 pairs well with biomarkers and they work in 20 conjunction with one another. 21 It also pretty good length of stay. And 22 that's not entirely surprising because if you don't</p> | <p style="text-align: right;">Page 36</p> <p>1 there are risks with biopsies and if you could do it a 2 better way it'd be worth investigating. 3 Now there's an important question which is 4 when you have fibrosis do you, in fact, have loss of 5 tubules or do you have secreted matrix? 6 This is an animal study which basically show 7 you -- shows you what happens after acute kidney 8 injury. If you look out a couple of months, and this 9 is what happens in people, the kidney shrinks. Well, 10 if the kidney is shrinking the likelihood is this 11 matrix being secreted is unlikely because when that 12 happens and like amyloidosis the kidneys get bigger. 13 So most pathologists -- and we don't know 14 this -- suspect that most of the fibrosis you see is, 15 in fact, loss of tubules. Now no matter how good your 16 glomerular look if you're not connected to a tubule 17 you're not filtering anything. 18 And this (indiscernible) looking at what's 19 called a tubular glomeruli so there are beautiful, 20 lovely glomeruli that are fully intact that are 21 decapitated. They do not connect to their 22 corresponding nephron tubule and they are non-</p> |
| <p style="text-align: right;">Page 35</p> <p>1 get better and if you're on dialysis you're not going 2 to leave the hospital sooner, you're going to leave it 3 later. 4 I want to spend the last two minutes of my 5 talk trying to impress upon you where I think the 6 value is in chronic kidney disease and allograft. So 7 there's an important issue which everyone here is 8 aware of who takes care of patients and that is if you 9 have fibrosis in your interstitium the kidney is 10 toast. That's always bad. 11 No matter how good or bad it may look if the 12 interstitium is bad everyone knows bad things are 13 going to happen. And the big problem is we largely 14 don't know what to do about it. 15 So following someone's interstitium is 16 something we would like to do and we would like not to 17 have to do it with a biopsy all the time. Now for 18 certain centers that take care of transplant patients 19 they have protophized (phonetic) biopsies, they're 20 very good at it. They promise me they never hit an 21 acrid artery in their entire life. I'm sure that's 22 true, but I'm not 100 percent sure that's true. And</p> | <p style="text-align: right;">Page 37</p> <p>1 filtering glomeruli. And they do not contribute to 2 GFR and they don't do anything to help the kidney. 3 And those tubules are not online and they 4 don't work. And this is likely why fibrosis is such a 5 disaster for these patients because there's no way to 6 reconnect them. 7 So in patients with CKD we are also now 8 looking at not just the urine output, which is 9 surrogate, but also measuring the furosemide in the 10 urine because it allows you to assess proximal 11 function from distal function. And we think that this 12 may represent a way of having a noninvasive functional 13 assessment. 14 We do not think this should replace biopsies 15 but we do think that if you get a biopsy and you index 16 it to a thoughtful assessment of tubular function you 17 could probably track that over time. 18 And basically I'm finishing. Thank you. 19 These are the next steps which is we need to do these 20 studies and many of these are underway so stay tuned. 21 And with that I'm happy to take questions during our 22 session. Thank you.</p> |

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| <p style="text-align: right;">Page 38</p> <p>1 DR. NICKERSON: Okay. Our next speaker is 2 going to be a double header here with Dr. Mark Haas 3 talking about diagnosis of acute and chronic using the 4 Banff and pathologic correlates of graft survival and 5 the utility of molecular diagnostics. 6 Mark? 7 DR. HAAS: Thank you, Peter. Thank you to 8 the organizers and for putting together such an 9 excellent and informative workshop. 10 I'm a pathologist. I'm going to spend the 11 first part of my talk reviewing the pathology of 12 transplant rejection correlates with graft survival. 13 So I'm going to talk about the pathology of acute of 14 active antibody mediated rejection, chronic active 15 antibody mediated rejection, and a little bit -- just 16 a little bit about pathologic factors influencing 17 graft survival following treatment of antibody 18 mediated rejection. These are my disclosures. 19 So as we've learned a lot in the last day 20 and a quarter, antibodies are very important in terms 21 of the prognosis and outcome in patients who receive 22 renal allografts. But it wasn't always known that</p> | <p style="text-align: right;">Page 40</p> <p>1 But this started to change in the 1990s and this was 2 one of those early studies that came out of the 3 Edmonton Group of Phil Halloran in which they studied 4 and compared rejection patterns in patients who did 5 and did not have antibody HLA. And these were class 1 6 antibodies. 7 And this was not at the time of 8 transplantation, but this was subsequent to 9 transplantation. So this was acute rejection, not 10 hyperacute rejection. And what they found in that 11 patients who did not have antibodies was the typical 12 finding of T-cell mediated rejection characterized by 13 inflammation and tubulitis. 14 But that in patients who did have anti-HLA 15 antibodies this was seen in only about half the cases. 16 And the findings that were predominant in these 17 patients were those of microvascular inflammation -- 18 glomerularitis, inflammation of the glomerular 19 capillaries, fibrin thrombi, the result of 20 inflammation in vessels, peritubular capillaritis, 21 margination of neutrophils and of monocytes in the 22 peritubular capillaries.</p> |
| <p style="text-align: right;">Page 39</p> <p>1 this was the case or appreciated that this was the 2 case. 3 Very early on antibody -- preexisting 4 antibodies were a big problem in transplantation. 5 You'd put the kidney in and it would essentially stop 6 functioning right on the operating table and turn blue 7 or pale and you would have hyperacute -- a process 8 called hyperacute rejection due to preexisting 9 antibodies in the recipient against either blood group 10 antigens or HLA on the donor kidney and this would 11 inevitably lead to rapid graft loss sometimes just 12 right there on the table. 13 But shortly after that cross matching 14 techniques were developed that prevented hyperacute 15 rejection. And essentially for the next 20, 25 years 16 after that with a few exceptions -- and Paul Terasaki 17 was clearly one of those exceptions -- antibodies were 18 really forgotten about and the focus really became 19 diverted to cell mediated rejection. 20 And the first few Banff classifications for 21 acute rejection in the kidney barely mentioned 22 antibodies. It was all about cell mediated rejection.</p> | <p style="text-align: right;">Page 41</p> <p>1 And all of this microvascular inflammation 2 was reminiscent of the early findings of hyperacute 3 rejection and this really seemed to be sort of a 4 hyperacute rejection like kind of a picture. 5 And so what the kinds of findings that they 6 were seeing were here thrombosis in the glomerular 7 capillaries, margination here of neutrophils in the 8 peritubular capillaries, margination of leuko- -- of 9 mononuclear leukocytes in the glomeruli, so called 10 glomerularitis, and peritubular capillaries, 11 peritubular capillaritis. 12 And these mononuclear cells were 13 predominantly CD68 positive monocyte macrophages, not 14 lymphocytes which are CD3 positive. And, in fact, 15 CD68 immunostaining is actually used in diagnosis of 16 antibody mediated rejection in heart allografts as a 17 very -- excuse me -- important tool in these 18 allografts. 19 However, none of these findings is specific 20 for antibody mediated rejection. These are markers of 21 microvascular injury, endothelial injury, and can be 22 seen with just about anything that injures the</p> |

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| <p style="text-align: right;">Page 42</p> <p>1 endothelium.</p> <p>2 So pathologists were quite pleased when C4d</p> <p>3 came along. C4d is a split product of complement</p> <p>4 factor C4 which is part of the classical pathway of</p> <p>5 complement activated by antigen antibody interactions.</p> <p>6 And when C4 is cleaved C4d is formed. And</p> <p>7 what makes C4d special is it binds covalently at the</p> <p>8 sight of its formation and thus it's a relatively long</p> <p>9 lived -- and when I say "long lived" I'm talking about</p> <p>10 two weeks here -- marker for humeral immunity.</p> <p>11 And what we see in allografts is we see C4</p> <p>12 that are undergoing antibody mediated rejection and</p> <p>13 are exposed to donor-specific antibodies in many cases</p> <p>14 is linear staining by immunofluorescents of C4d in the</p> <p>15 peritubular capillaries.</p> <p>16 The glomerular staining is actually quite</p> <p>17 non-specific. And it's the peritubular capillary</p> <p>18 staining which is really indicative of an antibody</p> <p>19 reaction.</p> <p>20 The first evidence that C4d might be</p> <p>21 prognostically important in the kidney and might be</p> <p>22 related to humeral activity came from Helmut Feucht in</p> | <p style="text-align: right;">Page 44</p> <p>1 there had to be serologic evidence in terms of donor-</p> <p>2 specific antibodies, but there also have to be</p> <p>3 immunohistologic evidence, generally C4d staining,</p> <p>4 within the peritubular capillaries.</p> <p>5 And we were very happy with this and this</p> <p>6 lasted a number of years until we started to find that</p> <p>7 we seemed to be missing cases of what appeared to be</p> <p>8 antibody mediated rejection. That these biopsies</p> <p>9 occurred in patients who had donor-specific</p> <p>10 antibodies, who had microvascular inflammation, but</p> <p>11 were being called no antibody mediated rejection</p> <p>12 because the C4d was negative.</p> <p>13 And there were two key studies, one I'll</p> <p>14 point out here and one in my next talk, that really</p> <p>15 established the presence of C4 -- the viability that</p> <p>16 antibody mediated rejection could occur in the absence</p> <p>17 of C4d.</p> <p>18 And this is a protocol biopsy study done by</p> <p>19 Alex Loopy and colleagues in Paris where they do three</p> <p>20 month and one year protocol biopsies in all of their</p> <p>21 DSA-positive patients. And they looked at the</p> <p>22 findings at one year based on the findings at three</p> |
| <p style="text-align: right;">Page 43</p> <p>1 Germany who was really way before his time in 1993 who</p> <p>2 studied 93 for cause renal allografts and looked at</p> <p>3 peritubular capillary C4d deposition and noticed that</p> <p>4 those biopsies that had peritubular capillary C4d were</p> <p>5 associated with a very poor graft survival at one year</p> <p>6 compared to those biopsies that were C4d negative.</p> <p>7 Furthermore, C4d was associated with re-</p> <p>8 transplants and an elevated PRA suggesting its</p> <p>9 association with antibody. And this was subsequently</p> <p>10 confirmed in quite a number of studies that were done</p> <p>11 around the year 2000 showing that C4d was highly</p> <p>12 specific for the presence of donor-specific antibodies</p> <p>13 with ranges of specificity in the 90 to 100 percent</p> <p>14 range.</p> <p>15 Pathologists became so enamored with C4d</p> <p>16 that when the first Banff classification for antibody</p> <p>17 mediated rejection was published in 2003 that C4d</p> <p>18 staining in the peritubular capillaries was one of</p> <p>19 three findings that was required for the diagnosis of</p> <p>20 antibody mediated rejection.</p> <p>21 There had to be histologic evidence in terms</p> <p>22 of microvascular inflammation as I showed you before,</p> | <p style="text-align: right;">Page 45</p> <p>1 months. And the findings at three months could be</p> <p>2 classified into three categories. These were all</p> <p>3 protocol biopsies of stably functioning grafts.</p> <p>4 So there were those with subclinical</p> <p>5 antibody mediated rejection that were C4d positive,</p> <p>6 they were DSA positive, and had microvascular</p> <p>7 inflammation. There were those with clearly no</p> <p>8 antibody mediated rejection, C4d negative, and no</p> <p>9 microvascular inflammation. And there were those that</p> <p>10 were suspicious C4d negative but with microvascular</p> <p>11 inflammation.</p> <p>12 And at one year predictably the patients who</p> <p>13 had subclinical AMR had a low GFR, had frequent</p> <p>14 tubular atrophy and interstitial fibrosis of IFTA, and</p> <p>15 43 percent had transplant glomerulopathy. Patients</p> <p>16 with no antibody mediated rejection had a good GFR.</p> <p>17 Some had mild IFTA, but usually not. There was no TG.</p> <p>18 Patients who were suspicious looked more</p> <p>19 like the subclinical antibody mediated rejection --</p> <p>20 low GFR, frequent IFTA, and even some transplant</p> <p>21 glomerulopathy. So apparently antibody mediated</p> <p>22 damage to the kidney resulting in fibrosis and</p> |

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| <p style="text-align: right;">Page 46</p> <p>1 transplant glomerulopathy could occur even in the 2 absence of C4d. 3 So for the sake of time I will skip this -- 4 the next slide and just go right to the revised Banff 5 classification which now includes C4d, but does not 6 require C4d for an absolute diagnosis. You still need 7 to have microvascular inflammation, you still need to 8 have donor-specific antibodies, but now the C4d 9 requirement has been replaced by evidence of recent 10 antibody interaction with the allograft which can be 11 in the form of C4d but can also be in the form of more 12 severe microvascular inflammation. And I'll talk 13 about this a little bit more in the next talk, but 14 again there are C4d positive and C4d negative forms of 15 antibody mediated rejection. 16 So moving to chronic antibody mediated 17 rejection the classic lesion of chronic antibody 18 mediated rejection is transplant glomerulopathy 19 characterized by double contours of the glomerular 20 basement membrane evidenced on a silver or PAS stain 21 which highlight this basement membrane. 22 But like microvascular inflammation, TG is</p> | <p style="text-align: right;">Page 48</p> <p>1 antibodies. 2 But note this, that TG at least by light 3 microscopy is rarely seen in the first year post- 4 transplant. And the unfortunate thing about that is 5 that once we seen transplant glomerulopathy it's 6 generally accepted that this graft is going to fail. 7 Whether it's going to fail fast or whether it's going 8 to fail more slowly is of some debate, but transplant 9 glomerulopathy means that the graft is eventually 10 going to fail and fail faster than a graft without 11 transplant glomerulopathy. 12 So is there a way to diagnose or at least 13 predict TG faster than just diagnosing it be routine- 14 like microscopy? And clues to this came from a study 15 that came out of Sidney, Australia, by Wavamunno and 16 Nankivell in 2007. 17 And this is also -- and I'll again defend 18 the use of surveillance biopsies here even though I 19 know that they're -- they are very suboptimal in terms 20 of the patient experience in transplantation. 21 But in Australia they do quite a few 22 surveillance biopsies. And what Brian and his</p> |
| <p style="text-align: right;">Page 47</p> <p>1 not absolutely specific for antibody mediated 2 rejection. And in this study here by Bonu Sys 3 (phonetic) they found evidence of either C4d 4 positivity, donor-specific antibodies, or both in 5 about three-quarters of patients who developed C- -- 6 who developed transplant glomerulopathy. 7 Meaning that approximately 25 percent of the 8 cases seem to be associated with something else other 9 than donor-specific antibodies. And what were these? 10 Well, this is a study from Bob Colvin's group that was 11 published awhile back in Kidney International showing 12 that Hepatitis C can be associated with transplant 13 glomerulopathy, forms of thrombotic microangiopathy 14 such as acute or persistent calcineurin inhibitor 15 toxicity, and there's evidence that TG can be a 16 manifestation of cell-mediated rejection as well, but 17 most of the time antibody-mediated rejection. 18 We've seen a number of curves like this 19 showing that TG is associated with poor graft 20 outcomes. This is a study from the Mayo. And that TG 21 is associated with the presence of donor-specific 22 antibodies particularly anti-class 2 donor-specific</p> | <p style="text-align: right;">Page 49</p> <p>1 colleagues did in this study is they looked at 2 patients who ultimately were diagnosed with transplant 3 glomerulopathy back two to five years post- 4 transplantation. And they went and they looked by 5 electron microscopy at their -- excuse me -- early 6 biopsies one to three months post-transplantation and 7 was there anything on there early biopsies that 8 predicted transplant glomerulopathy. 9 And what they found were three findings by 10 electron microscopy that seemed to be associated with 11 subsequent development of TG -- endothelial cell 12 swelling. And, again this is the glomerular 13 capillary, the basement membrane, and the endothelial 14 cell which is swollen. There's a sub endothelial 15 electronic loosened widening. And if you can 16 appreciate here very early wisps of new basement 17 membrane formation not apparently by light microscopy, 18 but apparently very early on by electron microscopy. 19 And when you take patients with these early 20 findings plus donor-specific antibodies who have had 21 subsequent biopsies but have these early findings and 22 DSA within their first three months post-</p> |

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| <p style="text-align: right;">Page 50</p> <p>1 transplantation if these patients are not treated for 2 antibody mediated rejection they are virtually certain 3 to develop transplant glomerulopathy within the first 4 two years post-transplant. 5 DR. NICKERSON: Mark, I've just got to 6 caution you. You're already near the -- you're over 7 the -- 8 DR. HAAS: Okay. 9 DR. NICKERSON: -- you're over your first 10 talk. So I just want make sure -- 11 DR. HAAS: Okay. 12 DR. NICKERSON: -- you're not going to run 13 over overall. 14 DR. HAAS: All right. And so -- and this 15 can be prevented by treatment for antibody mediated 16 rejection. So just to -- so just to summarize the 17 value of Banff 2013 this is a study that came out of 18 Quebec City basically showing that by the additions 19 that we made to Banff 2013, particularly C4d negative 20 antibody mediated rejection, that this not only 21 increased the sensitivity for diagnosis of antibody 22 mediated rejection, but also increased the association</p> | <p style="text-align: right;">Page 52</p> <p>1 specifically found was that if one had these molecular 2 markers, these ENDATs, endothelial associated gene 3 transcripts, plus C4d, plus donor-specific antibodies 4 there was a high rate of graft loss. 5 However, if one did not have C4d but still 6 had the ENDATS and the donor-specific antibodies there 7 was still a high rate, albeit somewhat reduced, rate 8 of graft loss again indicating that one could have 9 antibody-mediated damage to the graft without C4d 10 deposition. And, again, this was again one of the 11 earlier markers of C4d negative antibody mediated 12 rejection. 13 The Banff classification specifies that if 14 C4d is not present that a higher level, a higher 15 threshold of microvascular inflammation is required to 16 diagnose antibody mediated rejection than if C4d is 17 present with a threshold -- a microvascular 18 inflammation threshold or glomerulitis plus 19 peritubular capillaritis score of at least 2 rather 20 than 1 simply -- and this was put in rather 21 empirically simply to prevent us from over diagnosing 22 antibody mediated rejection.</p> |
| <p style="text-align: right;">Page 51</p> <p>1 of the diagnosis with subsequent graft loss. So 2 basically the sensitivity and the specificity was 3 increased in Banff 2013. 4 So now I will go on and talk about some 5 molecular markers in -- and molecular diagnosis in 6 diagnosis of antibody mediated rejection. 7 Again, my disclosures. This is, again, the 8 initial allograft antibody mediated rejection 9 classification which required C4d in the -- in 10 diagnosis of antibody mediated rejection. And 11 molecular studies were important in addition to the 12 protocol biopsy study of Alex Loopy, et al., in terms 13 of identifying C4d negative antibody mediated 14 rejection. 15 Because here we have this study of Bonu Sys 16 who used molecular markers in the biopsy tissue 17 identified by genechip analysis. And these were 18 endothelial-associated markers and found that these 19 were predictive of graft loss. 20 And here are some of these endothelial 21 markers. Von Willebrand's factor was the most 22 associated with graft loss. But what they</p> | <p style="text-align: right;">Page 53</p> <p>1 But we weren't really sure if the 2 2 threshold was really the right threshold. But this 3 study again using molecular techniques from the Albert 4 Einstein Group studying biopsies with different levels 5 of microvascular inflammation validated this threshold 6 of 2. 7 So here we see this is -- these are these 8 gene transcripts associated with antibody mediated 9 rejection. And the numbers in red, the P values in 10 red indicate an increased level of these gene 11 expressions of these inflammation-associated 12 transcripts. 13 And when comparing a microvascular 14 inflammation score of 1 versus zero there was no 15 difference. But this difference became significant 16 with a threshold of 2 versus zero or 2 versus 1 17 suggesting that this threshold of 2 was, in fact, 18 appropriate for diagnosing C4d negative antibody 19 mediated rejection. And we see here that C4d, itself, 20 did not influence these molecular markers. So 21 microvascular inflammation score of 2 appeared to be 22 validated in the Banff classification.</p> |

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| <p style="text-align: right;">Page 54</p> <p>1 A very important topic that came up at the 2 last Banff meeting was what to do when we have 3 microvascular inflammation but no donor-specific -- no 4 detectable donor-specific antibodies. How do we know 5 if this is antibody mediated rejection or some kind of 6 non-specific effect because we know that microvascular 7 inflammation is not, itself, specific for DSA? 8 Well, the obvious thing would be to check 9 for non-HLA antibodies, but this is not done in all 10 laboratories and can take time. And you don't want to 11 delay treating somebody with antibody mediated 12 rejection. 13 And one possibility would be a molecular 14 test that might determine the likelihood of antibody 15 mediated rejection. And for the sake of time I'm only 16 going to refer to one of these tests here which is the 17 molecular antibody mediated rejection classifier 18 score. 19 And this is based on gene analysis within 20 the biopsy tissue was also developed by Phil Howard in 21 the Edmonton Group based on 30 non-redundant gene 22 probes selected from comparisons between biopsies</p> | <p style="text-align: right;">Page 56</p> <p>1 failure in those patients who did not ultimately 2 develop graft failure and increased the predictive 3 value of the biopsy in the majority of those patients 4 who did develop graft failure. 5 And to put this another way here looking at 6 biopsy correlates with graft loss at three years. 7 When the molecular test for ABMR was negative and the 8 biopsy showed no evidence of antibody mediated 9 rejection the graft survival was good at three years. 10 When both of these were positive the graft survival 11 was poor. 12 But, again, adding the molecular test here 13 improved on the prediction of graft loss compared to 14 just the conventional biopsy data alone. And, in fact 15 if one had to use just one of these two, the molecular 16 classifier actually seemed to be superior to histology 17 in predicting graft outcomes. 18 And I guess that's my last slide. I thought 19 I had a final slide, but -- oh, yes. So, anyway. So 20 this is just sort of a table summarizing how molecular 21 studies can be employed in addition to histology in 22 terms of aiding the diagnosis of antibody mediated</p> |
| <p style="text-align: right;">Page 55</p> <p>1 showing histologic antibody mediated rejection in the 2 presence of donor-specific antibodies. 3 And predictably most of these probes are 4 associated with cell types that have been associated 5 with AMR -- endothelial cells and NK cells -- as well 6 as macrophages. And what Phil found when they looked 7 at the antibody mediated rejection score versus 8 histology is they found that approximately 90 percent 9 or close to 90 percent specificity for this molecular 10 classifier for determining if a biopsy showed antibody 11 mediated rejection. 12 More importantly, adding this classifier to 13 the histology increased the predictive value of the 14 biopsy in determining which patients did and did not 15 get graft failure after the biopsy. 16 So we see here that this is based on the 17 biopsy features alone and this is the probability of 18 developing graft failure in patients who did not and 19 did develop graft failure. 20 And in those patients here in the blue 21 adding the molecular score to the histology identified 22 and lowered the probability of predicting graft</p> | <p style="text-align: right;">Page 57</p> <p>1 rejection. 2 So if we have no histological evidence of 3 antibody mediated rejection at all, we probably don't 4 need molecular studies. And if we -- but if we have 5 an inadequate biopsy then the ABMR classifier which 6 actually works on medulla which cannot be used for 7 histologic diagnosis of antibody mediated rejection, 8 but does seem to work in giving a molecular score can 9 be used in terms of increasing the probability that 10 we're dealing in a biopsy with antibody mediated 11 rejection. 12 And here if we have microvascular 13 inflammation but no donor-specific antibodies if the 14 molecular score is greater than this cutoff value we 15 might want to treat the -- consider treating the 16 patient with antibody -- for antibody mediated 17 rejection. Whereas if the molecular score is less 18 than 2, probably -- probably refrain from treating the 19 patient for ABMR. 20 And these molecular tests are being refined 21 all the time. Their specificity is constantly being 22 increased since the days of ENDATs. And hopefully</p> |

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| <p style="text-align: right;">Page 58</p> <p>1 these might be incorporated into the classification in 2 2019.</p> <p>3 And with that I apologize for going over and 4 I will stop. Thank you.</p> <p>5 DR. NICKERSON: Thank you very much, Mark. 6 Our next speaker is Dr. Steve Woodle from the 7 University of Cincinnati talking about the treatment 8 of AMR updates since 2010 standard of care and 9 emerging therapies.</p> <p>10 Steve?</p> <p>11 DR. WOODLE: So I'm not sure how I can do 12 all of this in ten minutes or so, but we'll give it a 13 shot.</p> <p>14 DR. NICKERSON: You have 10 minutes on the 15 schedule because it's 9:30 to 9:45.</p> <p>16 DR. WOODLE: I'm sorry?</p> <p>17 DR. NICKERSON: You have 15.</p> <p>18 DR. WOODLE: Oh, okay. The schedule said 19 only 10, but that's okay. Okay. So I just wanted to 20 mention this. Over 50 years ago Tom Starzl was one of 21 the groups that was doing kidney transplants. And 22 back then they didn't know about ABO compatibility,</p> | <p style="text-align: right;">Page 60</p> <p>1 There are two primary ways that antibodies 2 can damage the graft. We know of the third way which 3 Elaine Reed has described, but I'm not going to -- I'm 4 going to leave that aside for now because that's 5 difficult to measure.</p> <p>6 But the important point here is that the 7 focus has been almost entirely on complement 8 inhibition for years. But it's important now that we 9 understand that there are complement independent 10 mechanism and rejections that actually present in 11 patients to consider the FCR mediated effects. And 12 for that we need tests that can diagnose and tell us 13 when an antibody's capable of binding an FC receptor 14 and also tests of being able to identify when FC med- 15 -- FCR mediated injury is occurring.</p> <p>16 And I think that's part of the future of 17 where the field needs to go to move beyond the almost 18 unifocus on complement.</p> <p>19 So we heard yesterday about the issues of 20 distal complement inhibition with eculizumab. We'll 21 talk a little bit about that story. But the field is 22 actually moving in the direction of proximal</p> |
| <p style="text-align: right;">Page 59</p> <p>1 but they found out real fast when they had some 2 antibody mediated rejections.</p> <p>3 These are described in this book which copy 4 right is 1964. And he and Ken Porter, and outstanding 5 renal pathologist, described antibody mediated 6 rejection in ABO incompatible transplants. And that 7 description is what I went to the first time when I 8 started dealing with these clinically in the late 9 1980s. And they described the presence of substantial 10 edema, mixed infiltrates with polys, transmural 11 arteritis, and endofelial targeting.</p> <p>12 And so for any of those interested in the 13 history or particularly interested in understanding 14 histopathology, Ken Porter and Tom Starzl's 15 descriptions 50 years ago are very instructive.</p> <p>16 The talk -- I've divided the talk into 17 complement inhibitors followed by immunoglobulin as a 18 target which we've already discussed a little bit. 19 Some of these areas I'm going to go over it quickly 20 because we've had a lot of discussion about them 21 yesterday. And then wind up with plasma cell targeted 22 therapies primarily based on protease inhibition.</p> | <p style="text-align: right;">Page 61</p> <p>1 complement inhibition and we'll talk about three 2 agents that are being used that are targeting the C1q, 3 C1r, C1s complex.</p> <p>4 This targeting is asking a fundamental 5 question. And that fundamental question is is can one 6 prevent the TG that does not get prevented by 7 eculizumab?</p> <p>8 And critical to that is whether or not the 9 alternative pathway is also involved. Because if it 10 is there's a possibility that these classical pathway 11 inhibitors at the level of C1q, C1r, and C1s may not 12 work.</p> <p>13 So eculizumab binds the C5, prevents 14 conversion C5A, it prevents membrane attack complex 15 generation. It's approved for PNH at 2007 and 16 atypical HUS in 2011. It is a very expensive drug 17 with cost estimated \$400,000 a year or more. And this 18 is made -- made -- played a major role in diminishing 19 the use of that drug in this meeting. If this drug 20 didn't cost that or cost a fraction of it we'd be 21 talking about it a lot more today.</p> <p>22 The first study that came out came out of</p> |

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| <p style="text-align: right;">Page 62</p> <p>1 Mayo. It was a single-arm study with historical 2 control that showed substantial reduction of AMR from 3 a historical rate around 40 percent to around 10 4 percent. 5 Follow-up studies showed that the AMR still 6 occurred despite terminal complement inhibition. And 7 beyond one year outcome showed that transplant 8 glomerulopathy will still occur even if you do this. 9 And that was a major negative effect on this 10 particular strategic approach. 11 So there have been two major trials 12 sponsored by Lexion. This is one we talked about a 13 lot yesterday. It was a strategy to prevent antibody 14 mediated rejection in living donor kidney transplant 15 recipients that required desensitization. 16 I won't move on for it -- I'll move on from 17 this trial just to say that the drug worked. It just 18 didn't work as much it was predicted beforehand. And 19 I don't view this as a failure of the drug. It's a 20 failure of the trial design and, more importantly, 21 trial execution. But really the ultimate 22 responsibility lies in the leadership of the company.</p> | <p style="text-align: right;">Page 64</p> <p>1 And for those of you who are interested in 2 doing studies in chronic AMR it would really be 3 instructive to read this study and understand all the 4 trials that they went through to get this. Enrollment 5 was a major problem. It is difficult to enroll 6 patients when you have really strict inclusion and 7 exclusion criteria. 8 So let's move on to proximal complement 9 inhibition. It's important to understand one of the 10 reasons why the C1q test is negative when antibodies 11 are low. When antibodies are not in saturating 12 conditions you cannot get a hexagonal array of C1q. 13 So C1q's this inverted umbrella. It has six globular 14 heads that need to attach to the complement binding 15 regions in the FC portions of antibodies. 16 Once that's stabilized adequately the 17 molecule can then engage C1r and C1s. So you need 18 saturating conditions with antibody to activity 19 complement at least in vitro. In vivo I don't know 20 that this is absolutely true. We do see C4d staining 21 in some patients whose antibody levels are considered 22 to be less than saturation in a single antigen BSA.</p> |
| <p style="text-align: right;">Page 63</p> <p>1 There's another trial that's going on. This 2 is primarily in Australia and also in Europe. It's in 3 deceased donor recipients. And it's sensitized 4 deceased donor recipients. A total of 80 patients, 15 5 sites. It was last updated in Clinicaltrials.gov in 6 October. Estimated study completion is June of 2017 7 so we're looking very much forward to hearing about 8 the results from this trial. 9 This is an interesting study that's been 10 published. It was done by Sanjay Kulkarni and Jordan 11 Pover at Yale. And it looked at eculizumab for 12 chronic antibody mediated injury. And it was a pilot 13 trial. 14 And as such, although it didn't show an 15 effect, this study highlights the real difficulties in 16 conducting a trial in this setting. A primary 17 endpoint was actually estimated GFR. 18 This slide doesn't project well, but it's 19 actually a spaghetti plot of the GFRs in both control 20 and treated patients. And what it shows is the -- 21 what the study wanted to show is a change in the rate 22 of decline of GFR.</p> | <p style="text-align: right;">Page 65</p> <p>1 So what happens with C1 inhibitors is that 2 they bind to and disrupt the interactions between C1r, 3 C1s, and C1q and that prevents activation of the 4 classical pathway. 5 There are three of these agents in 6 development that we can tell so far. Two of them are 7 actually plasma derived products and one of them is 8 recombinant. 9 There have been some publications. This is 10 -- there have been two pilot studies published with 11 the CSL bearing product. This is from Stan Jordan's 12 group, 20 patients. And then there's another smaller 13 study that was from Denny Gladson, Carmen Lafalshay 14 (phonetic). 15 There's also the Shire product. There's a 16 phase 2B randomized, double blind, placebo-controlled 17 study, yes, in a complement inhibition trial. A 18 randomized, double blind, placebo-controlled study and 19 18 patients. 20 And so I won't talk much about these pilot 21 trials because you can't tell. They're small numbers 22 of patients. But these are important drugs to follow</p> |

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| <p style="text-align: right;">Page 66</p> <p>1 up because they're asking fundamental questions about 2 the role of complement and how we -- how we employ 3 drugs to inhibit complement mediated injury. 4 So -- and I've already mentioned these. 5 So we talked a little bit yesterday about 6 immunoglobulin. Now immunoglobulin, itself, is a 7 target for drugs. And this is the IdeS molecule. 8 It's been talked about. It's a product derived from 9 strep pyogenes. 10 It's assisting proteinase so it really 11 attacks the disulfide bonds that are present that are 12 necessary to stabilize and link the heavy chains and 13 light chains and add further stability to the antibody 14 molecule. 15 The degree of cleavage we're not really 16 exactly sure about. It appears that certainly the 17 heavy chain undergoes further cleavage other than just 18 the disulfide bonds. 19 Humans during infection normally produce 20 neutralizing antibodies against this and they decline 21 over time. These anti-IdeS neutralizing antibodies 22 are commonly found in humans because most of us had</p> | <p style="text-align: right;">Page 68</p> <p>1 So a fundamental question in all of this 2 work is do we have to eliminate the antibody? And if 3 we don't have to eliminate it, how much do we need to 4 reduce it? And it's a fundamental question that is at 5 the development of therapeutics in this area. 6 So, anyway, so this is the phase 1, 2 trial 7 that Stan Jordan has. Obviously also Bob Montgomery 8 is using this drug. So and I think the other -- so 9 I've mentioned one of these questions. 10 The other question, of course, we talked a 11 little bit about yesterday. What was going to happen 12 with renal function when it's suddenly faced with a 13 requirement to excrete large volumes or grams of 14 intervascular protein. 15 So for plasma cell targeting we're going to 16 talk. Mainly the focus to date has been on distal 17 inhibition of the protease. That is inhabitation at 18 the level of enzymatic proteolytic activity. 19 The constitutive proteasome inhibitors are 20 what we're going to focus on. And we'll a little bit 21 of data in irreversible inhibitors with -- as 22 primarily evidenced with carfilzomib. We'll also talk</p> |
| <p style="text-align: right;">Page 67</p> <p>1 strep infections when we were younger. And so this 2 anamnestic xeno response against this drug is going to 3 be something very important to pay attention to as 4 this drug is developed. 5 The structure of this molecule has been 6 worked out in a collaboration between the proponents 7 of the drug who are from London University and also 8 from Max Planck. This is data that I referred to 9 yesterday about Jill showing the degree of degradation 10 of the antibody molecule. 11 This is actually an in vivo study in 12 rabbits. You can see the level of IG does down 13 quickly over the first few days, but importantly that 14 antibody rebounds. So starting within about four to 15 five days completely back to the exact levels that 16 were present prior to treatment within a week or less. 17 So a fundamental issue in this strategy 18 which is a fundamental issue in a lot of clinical 19 trials that we have is can you leave the antibody at 20 the levels it was when the patient had rejection or 21 before they were transplanted and expect to have good 22 long-term function or not have further injury.</p> | <p style="text-align: right;">Page 69</p> <p>1 about studies ongoing that are targeting deliberately 2 the plasma cell niche and also survival factors. And 3 then at the end talk a little bit about other 4 combinatorial approaches. 5 So the innovator drug here was bortezomib. 6 Everybody knows that. It works by inhibiting the 7 enzymatic activity in the 20S core. The primary 8 mechanism by which proteasome inhibitors are thought 9 to work in multiple myeloma which we think also exists 10 for their use in targeting normal plasma cells is by 11 the induction of ER stress. 12 When a protein is synthesized the first 13 thing that happens when it enters the interior or the 14 endoplasmic reticulum is met by chaperones and 15 foldases which correctly fold that protein. 16 If it is misfolded it exposes hydrophobic 17 residues that are toxic. If this is not dealt with 18 and they've built up to a certain level, the cell will 19 commit suicide. 20 The natural response is to induce hundreds 21 of proteins in a process called the unfolded protein 22 response. And this is a response that's meant to</p> |

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| <p style="text-align: right;">Page 70</p> <p>1 refold the protein, fix it, or if it can't be fixed 2 ubiquitin label it, shunt it out, and degrade it the 3 proteasome. 4 If one blocks the proteasome all of this 5 builds up. And it's like having -- you know, you've 6 seen pictures of the garbage in New York City when 7 their garbage workers are on strike. That's kind of 8 what happens in the ER when you use a proteasome 9 inhibitor. 10 I ran a search back to 2010 on proteasome 11 inhibitors and kidney transplant and I turned up about 12 250 papers. And I'm just going to summarize some of 13 our papers and what they've shown. 14 Following our initial paper we went and 15 showed the proteasome inhibitors work as primary 16 therapy, not just as rescue therapy for antibody 17 mediated rejection. 18 To date the results from proteasome 19 inhibitors for antibody mediated rejection in my 20 opinion the results for early AMR and the results for 21 late AMR are equivalent to those for IBIG-based 22 regimens. Therefore, I think they should be</p> | <p style="text-align: right;">Page 72</p> <p>1 And so the way you recover from that is that 2 you have to make new proteasomes. With bortezomib 3 it's gone in 12 hours. Proteasomes back to business 4 as usual after about three or four half-lives. I 5 mean, I'm sorry, the half-life is 12 hours. 6 And so this is actually a data that -- a 7 paper that's come out recently on the use of 8 carfilzomib to treat antibody mediated rejection in a 9 pulmonary allograft. It is from Pittsburgh. Advise 10 you to read it and take a look at it. It presents 11 preliminary evidence. The problem is it's also 12 combined with IBIG in this regimen so it's hard to 13 sort out the differences. 14 One area in which we have not -- don't have 15 a problem sorting out differences is a desensitization 16 trial we're doing on carfilzomib. And we have data 17 from carfilzomib model therapy out to four weeks. 18 This is a proof-of-concept trial. It has an iterative 19 design. It also has an adaptive enrollment that's 20 based on precision estimates using abrasion statistic. 21 And we have biologic assessment of bone marrow niche 22 resident plasma cells in the study.</p> |
| <p style="text-align: right;">Page 71</p> <p>1 considered as a standard of care equivalent to that of 2 IBIG. And with 250 papers and literature I think 3 that's pretty substantial. 4 We've shown that the variability in results 5 is a result derives at least in part and we think 6 predominantly from the differences between early and 7 late antibody mediated rejection. 8 We've also shown that there are actually 9 improved results in pediatric recipients. There's 10 data from our group with hearts, but there's also data 11 from other organs suggesting that there's a 12 fundamental difference in plasma cell biology and B- 13 cell biology in infants as compared to adults. And 14 we've also outlined the toxicity profile. 15 There are two new proteasome inhibitors that 16 are considered second-generation proteasome 17 inhibitors. They also work on the same set of three 18 enzymatic activities in the 20S proteasome. The 19 difference is carfilzomib is fundamentally different 20 because it's an irreversible proteasome inhibitor. So 21 once you bind the proteasome that proteasome is 22 irreversibly damaged. It can't do any work anymore.</p> | <p style="text-align: right;">Page 73</p> <p>1 This is recovery of CD138-positive bone 2 marrow plasma cells. We have shown that if you take 3 CD138-positive plasma cells and culture them in vitro, 4 take the culture supernatant and do a single antigen 5 BSA, the profile from that culture soup is identical 6 to what's in the circulation. 7 That means the first -- if the first bar is 8 82 and the second one's B7 and the next one's DR51, 9 they're exactly aligned. So these are the cells that 10 are responsible for long-lived permanent antibody 11 production in the marrow. 12 We see a 70 percent reduction in these cells 13 with three -- just over three weeks of carfilzomib 14 therapy, mono therapy alone. So clearly this is 15 unequivocal evidence that we are depleting the long- 16 lived plasma cell population in the marrow. 17 We've taken this further and done single- 18 cell RNA seq analysis. This is 2,000 cells where the 19 messenger RNA in each individual cell was measured 20 2,000 cells across this way, about 1,000 genes in this 21 direction. 22 One of the things we found very interesting</p> |

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| <p>1 is there's a population of cells that's actively 2 proliferating in the marrow. And when you treat with 3 a proteasome inhibitor this population expands. So it 4 suggests that these plasma cell populations are 5 capable of repopulating once -- from their own 6 population once you delete them.</p> <p>7 This is interesting work that you're going 8 to hear in a few merits -- minutes from Stuart 9 Knechtle's group which is doing very interesting work 10 in primates suggesting that there may be another 11 source by which plasma cells may regenerate.</p> <p>12 We've also shown that there's an induction 13 of immunoproteasome which is a mechanism why which 14 resistance may be achieved in the remaining plasma 15 cells.</p> <p>16 A little bit about targeting the plasma 17 cell. When it sits in its niche in the bone marrow 18 which confers years of survival to these there are a 19 number of factors involved in keeping the cell there 20 and also keeping it alive.</p> <p>21 One of the cells that keeps -- one of the -- 22 the primary mechanism by which plasma cells are</p> | <p>1 synergistic to proteasome inhibitors. And what this 2 type of analysis has done is given us multiple 3 pathways by which we can start to achieve synergy in 4 the future.</p> <p>5 The future is going to exist in looking at 6 proximal proteasome inhibitors such as deubiquitinase 7 inhibitors and ubiquitin binding protein inhibitors, 8 ER stress inhibitors, autophagy inhibitors.</p> <p>9 One of the things that happens -- one of the 10 major reflexes that protects plasma cells from death 11 is that if you can't degrade protein in the proteasome 12 you can possibly degrade it in the -- by a process 13 called autophagy.</p> <p>14 And there's massive induction of autophagy 15 genes in humans treated with carfilzomib in their bone 16 marrow plasma cells.</p> <p>17 And this just shows here's prox- -- this is 18 distal complemented inhibitor where the bortezomib and 19 carfilzomib work. But there are inhibitors in the 20 proximal portion of the proteasome proximal that can 21 give you blocks and series to achieve synergy.</p> <p>22 DR. NICKERSON: Steve, if you could wind up?</p> |
| <p>Page 75</p> <p>1 thought to be homed to the marrow and tethered is by 2 an interaction between CR4 in the plasma cell and CL12 3 on the bone marrow stromal cell.</p> <p>4 Blockade of this with an FDA-approved drug 5 called mozobil or plerixafor made by Sanofi can 6 potentially mobilize these cells. This is the same 7 drug that's used to mobilize CD -- CD34-positive stem 8 cells for stem cell transplantation.</p> <p>9 We've shown now and will show at the 10 American Transplant Congress that there's a 11 progressive mobilization of these cells into the 12 peripheral blood plasma cells from the marrow out of 13 their niche. And when they get into the peripheral 14 blood they start to die. They go from 13 percent dead 15 rate to a 37.9 percent. Proof of concept that if you 16 mobilize these cells from the marrow you can kill 17 them.</p> <p>18 We've also shown -- I'm looking at the known 19 pathways for death that there's certain mitochondrial 20 factors such as noxa that are probably driving this 21 and it's counter balanced by an increase in BCL2. 22 So it's possible that BCL2 inhibitors may be</p> | <p>Page 77</p> <p>1 DR. WOODLE: Okay. All right. I'll move -- 2 skip through this. The only thing I would leave is 3 that there are BAFF inhibitors which are major growth 4 factors. We have a trial of bortezomib and belimumab 5 that is ongoing so this will actually be a BAFF 6 blocker.</p> <p>7 There are IL-6 blockers. I don't know how 8 much interest there is in Genentech to use tocilizumab 9 in this area. Stan Jordan has done some work. It's 10 very interesting to follow.</p> <p>11 There's also another interesting IL-6 12 blocker that's coming out by a company called Viteras 13 that is actually an FC-engineered product.</p> <p>14 So in conclusion, I would say there's a 15 number of innovative approaches that have emerged 16 since the last meeting that we had here seven years 17 ago. The classic complement cascade early inhibitors 18 are being developed. That story's going to be 19 written.</p> <p>20 There are drugs that can actually attack the 21 antibody and degrade it and completely eliminate 22 fully-formed antibody for a period of up to a week.</p> |

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| <p style="text-align: right;">Page 78</p> <p>1 There are newer proteasome inhibitors, irreversible 2 inhibitors. There are -- there are proximal 3 proteasome inhibitors and plasma cell niche components 4 that can be targeted. 5 We believe the future -- and this has been 6 said before. But we believe the future in development 7 of antibody humeral therapies is going to be 8 combinatory regimens. It's not going to be individual 9 drugs, but it's going to be drugs that are 10 specifically designed in targeting the biology in a 11 rationale way that will move this field forward. 12 Thank you very much. 13 DR. ALBRECHT: So before we go to discussion 14 we're going to have one public presentation. Dr. 15 Robert Woodward of Caredex will be speaking about 16 donor-derived cell-free DNA in AMR. 17 You have eight minutes, please. 18 DR. WOODWARD: Thank you to the organizers 19 for the opportunity to discuss donor-derived cell-free 20 DNA in the diagnosis of AMR in kidney transplant 21 recipients. 22 Cell-free DNA in the circulating blood is a</p> | <p style="text-align: right;">Page 80</p> <p>1 are also indications that this rise may be identified 2 earlier than clinical or histopathological signs of 3 rejection. 4 Third, donor-derived cell-free DNA decreases 5 following successful treatment of rejection returning 6 to the level of stable transplant recipients. 7 There are numerous publications that 8 demonstrate increased levels of this biomarker in 9 allograft rejection. Publications not listed here 10 showed a proof of principle from single centers in 11 small numbers of patients. 12 The publications selected here represent 13 studies with a large number of patients or samples 14 with significant group sizes for analysis. 15 The AlloSure method that we have developed 16 from measuring donor-derived cell-free DNA has been 17 described in three major publications that have 18 appeared in the last six months. This method 19 amplifies a panel of sequence variants and then uses 20 clinical-grade next-generation sequencing to count the 21 recipient and donor alleles without the need for 22 genotyping the donor or recipient.</p> |
| <p style="text-align: right;">Page 79</p> <p>1 product of physiological cell turnover and 2 pathological cell death such as necrosis. The 3 fraction of plasma cell-free DNA originating from an 4 allograft called donor-derived cell-free DNA is higher 5 in situations of active allograft injury than in 6 healthy, stable transplant recipients. 7 We and others have developed methods to 8 quantify the differences between the genomes of the 9 donor and the recipient that are both represented in 10 circulating cell-free DNA. 11 Recent publications have used these methods 12 to demonstrate several characteristics. First, the 13 level of donor-derived cell-free DNA is very low in 14 stable transplant recipients. 15 In heart transplant patients the median 16 fraction of donor-derived cell-free DNA is only 0.07 17 percent. In kidney transplant patients the median 18 fraction of donor-derived cell-free DNA is 0.21 19 percent. 20 Second, donor-derived cell-free DNA is 21 elevated at the time of rejection. Usually man fold 22 higher than in stable transplant recipients. There</p> | <p style="text-align: right;">Page 81</p> <p>1 Gerscovich published the clinical validation 2 for heart transplantation last November increased 3 donor-derived cell-free DNA with rejection and 4 decreased donor-derived cell-free DNA with treatment 5 for rejection. 6 The Bloom and Bromberg publications this 7 March demonstrate clinical validation of donor-derived 8 cell-free DNA in kidney transplantation which I'll 9 discuss more in the next few slides. 10 To be considered for clinical use a 11 molecular diagnostic assay should be rigorously 12 analytically validated. The AlloSure analytical 13 validation study was published last November in the 14 Journal of Molecular Diagnostics. 15 The established lower limit of 16 quantification of AlloSure is 0.2 percent donor- 17 derived cell-free DNA. Results below this level are 18 reported not as a quantitative value, but as a 19 valuable result indicating cell-free DNA could be 20 measured successfully, but the level of the donor 21 contribution was indistinguishable from zero. 22 The quantifiable range of the test is 0.2</p> |

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| <p style="text-align: right;">Page 82</p> <p>1 percent to 16 percent covering the range of critical 2 values observed in all publications in heart and 3 kidney transplantation and including the decision 4 point for kidney transplant of 1 percent donor-derived 5 cell-free DNA. 6 All of the studies were performed with 7 reference materials that have been validated on an 8 orthogonal technology. 9 The Bloom publication in the Journal of 10 American Society of Nephrology demonstrated that 11 AlloSure donor-derived cell-free DNA discriminates AMR 12 from no AMR. The reference standard for diagnosis of 13 antibody mediated rejection was histological findings 14 meeting the BANFF 2013 criteria for chronic active or 15 acute active antibody mediated rejection. And the 16 control group was all other diagnosis found on all 17 other biopsies. 18 The area under the curve of an ROC plot is 19 0.87 demonstrating a high level of accuracy to 20 discriminate between AMR and no AMR. At a threshold 21 of 1 percent the sensitivity of AlloSure for AMR is 81 22 percent and specificity is 83 percent.</p> | <p style="text-align: right;">Page 84</p> <p>1 biological variation match the above threshold range 2 in AMR. 3 A case study is shown on the right. This 4 patient had low levels of donor-derived cell-free DNA 5 in the first few months and biopsies at 30 days and 60 6 days were non-specific. 7 At five months post-transplant de-novo DSA 8 were detected and a third biopsy diagnosed AMR. The 9 donor-derived cell-free DNA was also significantly 10 elevated up to nearly 4 percent. 11 The serum creatinine is high, about 1.7 to 12 2.1, but little changed over time. This suggests that 13 AlloSure could have picked up the AMR earlier if it 14 had been measured in the month prior to the AMR. 15 So donor-derived cell-free DNA provides a 16 quantifiable direct measure of allograft damage. The 17 results of the studies in kidney transplantation 18 provide a clear indication of clinical utility to 19 reduce unnecessary biopsies in patient management and 20 provide clinical utility for several aspects of 21 clinical trials such as the CTOT 19 in which it is 22 currently being used.</p> |
| <p style="text-align: right;">Page 83</p> <p>1 The negative predicted value is very high, 2 96 percent, calculated using the overall prevalence of 3 AMR in this multi-center study population which is 4 representative of UNOS. 5 In this study, 75 percent of for cause 6 biopsies were negative for rejection. And a test with 7 a high NPV can reduce the number of unnecessary 8 biopsies. 9 An AlloSure test result above 1 percent in a 10 patient who also has DSA means a patient is likely to 11 have AMR. A low AlloSure result can be used to rule 12 out AMR or when measured serially in a patient be used 13 to indicate recovery or response to treatment of 14 rejection. 15 The Bromberg publication defines the 16 AlloSure performance metrics in the stable transplant 17 recipient population. In contrast to the median level 18 and AMR of 2.9 percent donor-derived cell-free DNA 19 reported in Bloom, the median value of 390 samples 20 from 93 stable, healthy patients is 0.21 percent. 21 The 96 percentile is again 1 percent 22 indicating that values outside the range of normal</p> | <p style="text-align: right;">Page 85</p> <p>1 As a marker for antibody mediated rejection 2 donor-derived cell-free DNA can provide a prognostic 3 tool to forecast the likely course of disease, a tool 4 that estimates the extent of injury, and a predictive 5 tool for forecast the likely response to treatment. 6 A potential clinical trial application would 7 be evaluating safety and efficacy of a treatment for 8 antibody mediated rejection. Existing endpoints might 9 be biopsy-based histological findings for evaluation 10 of transplant glomerulopathy six months after 11 treatment. 12 But measurement of donor-derived cell-free 13 DNA can provide non-invasive measures of the degree of 14 AMR active injury that can be followed at relatively 15 narrow intervals. 16 AlloSure testing would also ensure 17 consistent baseline status or allow stratification of 18 study subjects at the time of the initial biopsy-based 19 diagnosis of AMR. 20 AlloSure testing could also provide an 21 accurate and precise measure of recovery from AMR 22 injury that can be performed frequently to follow the</p> |

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| <p style="text-align: right;">Page 86</p> <p>1 trajectory of the response to treatment.</p> <p>2 So in summary, AlloSure is a clinical</p> <p>3 testing service to quantifying donor-derived cell-free</p> <p>4 DNA which is clinically validated by our marker in</p> <p>5 AMR. AlloSure is available for Caredex Clinical</p> <p>6 Laboratory both for patient management and for support</p> <p>7 of drug-developed clinical trials.</p> <p>8 Diagnostic donor-derived cell-free DNA</p> <p>9 complements the knowledge provided by biopsy, the</p> <p>10 prognostic qualities of DSA, and other tests useful in</p> <p>11 AMR studies.</p> <p>12 AlloSure offers a new dimension by providing</p> <p>13 a quantitative measure of ongoing injury which can be</p> <p>14 repeated at frequent intervals. Thank you for the</p> <p>15 opportunity to present these data.</p> <p>16 DR. ALBRECHT: Thank you for your comments.</p> <p>17 Could the questions for session 4 please be projected?</p> <p>18 DR. NICKERSON: And if there's any -- before</p> <p>19 we get to those is there any clarifying questions of</p> <p>20 any of the speakers? I'd invite those now from the</p> <p>21 audience or from the table.</p> <p>22 Yes?</p> | <p style="text-align: right;">Page 88</p> <p>1 question first. You have an isolated endoneuritis and</p> <p>2 so it's -- the question is, you know, what does an</p> <p>3 isolated endoneuritis mean?</p> <p>4 There is -- I think a lot of that depends on</p> <p>5 when the biopsy was done. The data that come from</p> <p>6 Edmonton suggests that a late isolated endoneuritis,</p> <p>7 that is more than one year post-transplant, is more</p> <p>8 likely to be antibody mediated than cell mediated.</p> <p>9 So I would suspect that if it's a later</p> <p>10 biopsy, that is more than one year post-transplant, I</p> <p>11 would definitely test for donor-specific antibodies.</p> <p>12 If the DSA are positive, I would treat that patient</p> <p>13 for antibody mediated rejection.</p> <p>14 If it is an early isolated V-lesion, the</p> <p>15 data from Edmonton suggests that it is more than</p> <p>16 likely either, one, cell-mediated rejection or, two,</p> <p>17 perhaps non-specific.</p> <p>18 The -- there's no real, you know, DSA type</p> <p>19 of test to determine that so if it -- if you're</p> <p>20 dealing with an indication biopsy associated with an</p> <p>21 elevation in serum creatinine and there's no other</p> <p>22 explanation on the biopsy for the elevation in serum</p> |
| <p style="text-align: right;">Page 87</p> <p>1 DR. OZDEMIC: My name is Handan Ozdemic.</p> <p>2 I'm a renal pathologist and a transplant pathologist</p> <p>3 from Baskent University, Ankara, Turkey.</p> <p>4 My question is for Dr. Mark Haas. In my</p> <p>5 daily routine I'm staining HLA-DR in parallel to C4d.</p> <p>6 I noticed that the patients who have C4d negative d</p> <p>7 there's loss of peritubular capillary HLA-DR</p> <p>8 expression in the areas of C4d negative areas.</p> <p>9 Could it be possible the peritubular</p> <p>10 capillary HLA-DR expression -- the loss of HLA-DR</p> <p>11 expression can be the sign of antibody mediated</p> <p>12 rejection especially in patients with C4d negative?</p> <p>13 And second question is I have a -- for</p> <p>14 example, we have a biopsy. And in this biopsy you</p> <p>15 have only minimal tubulitis in few tubules. And</p> <p>16 interstitial inflammation lower than five persons and</p> <p>17 vascular rejection.</p> <p>18 What will be your final diagnosis? Is this</p> <p>19 vascular rejection pointing out a (indiscernible)</p> <p>20 rejection or a (indiscernible) rejection? Thank you</p> <p>21 very much.</p> <p>22 DR. HAAS: Okay. I'll take your second</p> | <p style="text-align: right;">Page 89</p> <p>1 creatinine, perhaps treatment of this with a short</p> <p>2 pulse of steroids might be appropriate or you may</p> <p>3 simply just want to follow the patient and if there</p> <p>4 hasn't been a decline in graft function and see what</p> <p>5 happens from there.</p> <p>6 But if there has been a decline in graft</p> <p>7 function then maybe treatment as T-cell mediated</p> <p>8 rejection would be appropriate. And the studies from</p> <p>9 Bonu Sys suggested that these early isolated Vs do</p> <p>10 frequently respond to steroid therapy.</p> <p>11 The second question is a lot more</p> <p>12 complicated and because you're dealing with a number</p> <p>13 of different factors. One of the problems that we</p> <p>14 deal with in terms of evaluating peritubular</p> <p>15 capillaries is that in patients who have chronic</p> <p>16 antibody mediated rejection PTCs are lost over time.</p> <p>17 And this is one of the factors contributing to</p> <p>18 interstitial fibrosis.</p> <p>19 And tubular atrophy is the loss of PTCs. So</p> <p>20 is the decline in HLA-DR staining, you know,</p> <p>21 reflecting a loss of PTCs or endothelial injury,</p> <p>22 itself.</p> |

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| <p>1 One way to show that might be, you know, to</p> <p>2 also stain for an endothelial marker. If there's --</p> <p>3 clearly if there hasn't been a decline in the level of</p> <p>4 PTCs, it's possible that it could be a marker for</p> <p>5 early endothelial injury. In DSA -- if the DSAs are</p> <p>6 positive, possibly antibody mediated endothelial</p> <p>7 injury. But obviously that would need to be, you</p> <p>8 know, validated in some kind of a controlled study.</p> <p>9 If there's clearly decreased peritubular</p> <p>10 capillary density then -- you know, then you're</p> <p>11 dealing with a chronic process and probably not</p> <p>12 something you necessarily want to treat.</p> <p>13 Does that answer your question?</p> <p>14 DR. OZDEMIC: Yes.</p> <p>15 DR. HAAS: Okay. Thanks.</p> <p>16 DR. NICKERSON: Other questions? Yes,</p> <p>17 Stuart?</p> <p>18 DR. KNECHTLE: I wanted to ask Dr. Woodward</p> <p>19 what is the ability of the cell-free DNA assay to</p> <p>20 distinguish between antibody mediated rejection and</p> <p>21 cell mediated rejection or between acute tubular</p> <p>22 necrosis from either preservation injury or drug</p> | <p>1 microvascular injury association with mediated</p> <p>2 rejection may be why. There may be other injuries</p> <p>3 that also have some microvascular that aren't</p> <p>4 rejection, but why it wouldn't be associated with them</p> <p>5 I'm not sure.</p> <p>6 DR. WOODLE: I could have missed it, but</p> <p>7 what are the markers that you're looking at to</p> <p>8 designate the donor? Are they actual HLA gene</p> <p>9 sequences that you're -- that you're amplifying or are</p> <p>10 they other gene low SI expression markers?</p> <p>11 DR. WOODWARD: They are a set of single</p> <p>12 nucleotide polymorphism that differ between the donor</p> <p>13 and recipient, but are not associated with disease.</p> <p>14 They're just snips that are different between the</p> <p>15 donor and recipient.</p> <p>16 DR. WOODLE: And those snips you're looking</p> <p>17 at how many different genes do they -- are they</p> <p>18 analyzing?</p> <p>19 DR. WOODWARD: They're not located within</p> <p>20 genes. They're in non-genetic parts of the geno.</p> <p>21 DR. HAAS: Yeah. So you mentioned that the</p> <p>22 donor-derived cell-free DNA did not seem to be</p> |
| Page 91 | Page 93 |
| <p>1 toxicity?</p> <p>2 DR. WOODWARD: It seems pretty specific for</p> <p>3 rejection. Sorry. It seems pretty specific for</p> <p>4 rejection. When we looked at other types of injury</p> <p>5 that were no T-cell mediated or antibody mediated</p> <p>6 rejection there didn't seem -- there wasn't a</p> <p>7 reproducible or significant increase.</p> <p>8 In the studies so far the lowest level of T-</p> <p>9 cell mediated rejection, a grade I, did not have high</p> <p>10 levels of cell-free DNA. But other levels of T-cell</p> <p>11 mediated rejection as well as antibody mediated</p> <p>12 rejection had high levels of cell-free DNA.</p> <p>13 Whether it could distinguish between them</p> <p>14 we'll need much larger studies maybe, maybe not.</p> <p>15 DR. KNECHTLE: Why do you think that the</p> <p>16 assay is specific for antibody mediated rejection?</p> <p>17 Why should it be?</p> <p>18 DR. WOODWARD: Based on the concept that it</p> <p>19 is looking at DNA that's being produced by injury from</p> <p>20 the graft we think it's probably mostly it's</p> <p>21 reflecting microvascular injury.</p> <p>22 And all of the talks that we've seen about</p> | <p>1 increased in 1A rejections. Was it increased in 1B</p> <p>2 cell mediated rejections do you know?</p> <p>3 DR. WOODWARD: Yes.</p> <p>4 DR. HAAS: It was? Okay. So clearly these</p> <p>5 are cell mediated rejections so it -- I guess one of</p> <p>6 the problems is that in some cell mediated rejections,</p> <p>7 particularly the more severe cell mediated rejections</p> <p>8 like a 1B, there is quite a bit of peritubular</p> <p>9 capillary inflammation.</p> <p>10 So, again, microvascular inflammation is not</p> <p>11 specific for ABMR. So it would -- obviously something</p> <p>12 needed to be perhaps combined with another test, but,</p> <p>13 you know, all -- but if it can be used to eliminate</p> <p>14 some biopsies, that's a good thing.</p> <p>15 DR. WOODWARD: Yes.</p> <p>16 DR. NICKERSON: Chris?</p> <p>17 DR. HAAS: Not necessarily for me, but.</p> <p>18 DR. NICKERSON: Chris?</p> <p>19 DR. WIEBE: One more question while you're</p> <p>20 up there.</p> <p>21 DR. WOODWARD: Uh-huh.</p> <p>22 DR. WIEBE: As you've heard from a number of</p> |

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| Page 94 | Page 96 |
| <p>1 talks there's this concept of smoldering rejection</p> <p>2 especially in high-risk patients which can be defined</p> <p>3 as recurrent rejection or high AlloMune risk.</p> <p>4 Have you noticed that there's a different</p> <p>5 baseline in these high-risk subsets versus low-risk</p> <p>6 subsets?</p> <p>7 DR. WOODWARD: We haven't looked. And I'm</p> <p>8 going to take what we've learned today and see if we</p> <p>9 can go back and identify any of those high risk or</p> <p>10 smoldering categories in patients in the population of</p> <p>11 the dart study and see if we can identify a</p> <p>12 difference.</p> <p>13 It's something that we've been interested</p> <p>14 in, but haven't looked at yet.</p> <p>15 DR. NICKERSON: I believe I just have my own</p> <p>16 question to -- oh, sorry.</p> <p>17 DR. MANNON: I'm sorry. I have like a</p> <p>18 zillion questions, but, Anita, go first.</p> <p>19 DR. NICKERSON: Okay.</p> <p>20 DR. CHONG: In a related question -- thanks,</p> <p>21 Ros -- how about smoldering CMV infection of polyoma?</p> <p>22 Could you tell the difference or are you just looking</p> | <p>1 combination of the two.</p> <p>2 And I think that if you're going to inhibit</p> <p>3 function, then the question is are you going to</p> <p>4 inhibit short term and expect that to have an effect</p> <p>5 on the long-term outcome or are you going to have a</p> <p>6 long-term maintenance therapy that will go along with</p> <p>7 it?</p> <p>8 I think it's a fundamental question if</p> <p>9 you're therapy leaves the donor-specific antibody in</p> <p>10 the circulation for prolonged periods of time, what is</p> <p>11 that going to do to graft function?</p> <p>12 Most of what I'm hearing today is that --</p> <p>13 and what I've heard all along is that the presence of</p> <p>14 a DSA is deleterious to the graft. And so that's one</p> <p>15 of the reasons just -- it's just my personal</p> <p>16 intellectual bias that elimination or reduction of</p> <p>17 antibody is -- is a preferred approach to take if</p> <p>18 you're developing drugs for this particular</p> <p>19 indication. Otherwise I think that you may be looking</p> <p>20 at long-term maintenance therapy.</p> <p>21 Now even with plasma cell deletion</p> <p>22 approaches you're going to prob- -- it looks like now</p> |
| Page 95 | Page 97 |
| <p>1 at injury?</p> <p>2 DR. WOODWARD: So in -- so far we've had two</p> <p>3 BK virus infections and they both had elevated donor-</p> <p>4 derived cell-free DNA. We have not yet observed any</p> <p>5 CMV.</p> <p>6 DR. NICKERSON: Ros?</p> <p>7 DR. MANNON: This is on a completely</p> <p>8 different scale. Okay. So different question. So</p> <p>9 question number 1 for bachelor number 1, Dr. Woodle,</p> <p>10 you indicated -- and I sense a lot of optimism about</p> <p>11 complement inhibitors.</p> <p>12 But you also mentioned in one of the other</p> <p>13 comments about IDS was removal of antibody. So how do</p> <p>14 you sort of put those two together because obviously</p> <p>15 the complement inhibitors mitigate injury, but they</p> <p>16 don't, you know, intrinsically remove antibody.</p> <p>17 So do you think they're going to be</p> <p>18 monotherapy or dual therapy?</p> <p>19 DR. WOODLE: I don't know. I think it's --</p> <p>20 the -- if you look at the approaches in general that</p> <p>21 are being taken for AMR, it's either elimination of</p> <p>22 the antibody or inhibition of its function or a</p> | <p>1 the field is headed towards the need for long-term</p> <p>2 maintenance therapy to inhibit the reflexive responses</p> <p>3 that occur. And you're going to hear more about that</p> <p>4 later on today in merian model and a primate model.</p> <p>5 I'm not sure if that answers your question.</p> <p>6 And if it didn't --</p> <p>7 DR. MANNON: No. I mean I --</p> <p>8 DR. WOODLE: -- can you restate it?</p> <p>9 DR. MANNON: -- kind of wanted to get an</p> <p>10 opinion because my sense from you is this -- and my</p> <p>11 own personal optimism of complement, but it doesn't</p> <p>12 really effect DSA. And I know several years ago we</p> <p>13 really debated that.</p> <p>14 And I think it's either going to come down</p> <p>15 to multiple approaches, we salvage grafts with AMR and</p> <p>16 hyperacute in the cases of incompatible. And I just</p> <p>17 kind of wanted to get your opinion. I'm just --</p> <p>18 DR. WOODLE: Yeah. So I think complement --</p> <p>19 you know, for almost the entire history of AMR</p> <p>20 complements almost been a singular focus. And I think</p> <p>21 now with the C4d negative forms of rejection and</p> <p>22 understanding that you really need saturating levels</p> |

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| <p>1 of antibody to activate complement that we have to be 2 considering the non -- the complement independent 3 mechanism for rejection because I think once you wipe 4 out complement those are still going to be there if 5 the antibody remains present in the serum. 6 The issues with the IdeS I think is IdeS, as 7 I see it, is almost like a plasmapheresis. 8 DR. MANNON: Okay. 9 DR. WOODLE: That you eliminate the antibody 10 for a period of a week to ten days or so, but then 11 after that the antibody is back in full force at the 12 same levels. 13 It's not clear to me whether or not you're 14 going to have reflexive responses from that sudden 15 elimination of antibody. We know that when you reduce 16 antibody there are homeostatic mechanisms that come 17 into play. And you'll hear more about that I think 18 from Stuart and Anita. 19 And so it's really going to be an 20 interesting experiment. I mean, IdeS is really a very 21 intriguing molecule. And, you know, we got two guys, 22 Stan Jordan and Bob Montgomery, who have as much</p> | <p>1 But as Steve noted and others, there's a 2 rebound of antibody following the IdeS treatment. So 3 you get the antibodies down and you get the transplant 4 in, but then you're going to have to allow your other 5 therapies to keep the -- to limit the amount of 6 rebound. And whether that's proteasome inhibitors, 7 whether that's anti-CD20, that's -- you know, that's 8 the question. 9 But I think IdeS is more of a, one, 10 desensitization-type therapy and possibly, two, a 11 rescue-type therapy in patients who develop high 12 levels of DSA and very severe AMRs. But I think 13 that's going to be its primary usefulness. 14 DR. NICKERSON: Dr. Colvin? 15 DR. COLVIN: Yeah. I'd like to get to 16 another topic which has run through many talks 17 yesterday and today. And that is transplant 18 glomerulopathy. We heard from Dr. Wiebe and Dr. Haas 19 how important this is in terms of a measure of 20 antibody mediated rejection and as a prognostic 21 aspect, a prognostic surrogate. 22 What I want to emphasize is how poorly the</p> |
| Page 99 | Page 101 |
| <p>1 experience as anybody in this field, really a couple 2 pioneers of the field, looking at it. So it's going 3 to be -- it's a really fun time I think. 4 DR. NICKERSON: Do you have more? 5 DR. MANNON: Yeah. They're unrelated, 6 though, to this so I don't know if you want to go to 7 those questions. I was actually going to now -- 8 DR. HAAS: Can I say something about the 9 IdeS? 10 DR. MANNON: Yeah. 11 DR. HAAS: Oh, with -- just a brief comment 12 with regard to IdeS. At least, you know, for what a 13 lot of the purposes what people are looking at IdeS 14 for right now, including Stan Jordan, is that IdeS not 15 necessarily as a long-term treatment for antibody 16 mediated rejection or prevention in any way of 17 antibody mediated rejection, but as a means for 18 desensitizing patients who cannot be desensitized 19 through more sort of standard of care means like 20 rituximab plus plasmapheresis plus IVIG that these 21 patients can be desensitized using IdeS and be allowed 22 to have a transplant.</p> | <p>1 Banff system scores transplant glomerulopathy. It's 2 an ordinal system. It has four categories. And it's 3 based on the findings of one glomerulorist, one most 4 affected glomerulorist. 5 And I would urge those of you who are 6 proposing or doing clinical trials to develop a more 7 accurate, more objective way of scoring transplant 8 glomerulopathy. 9 And one way to do this which I've been 10 involved in is to use digital whole slide images which 11 Bonu Sys has shown that increases the reproducibility 12 of pathologists even scoring with the Banff system. 13 Use whole slide images which can be 14 archived, individual capillaries can be scored not 15 just the whole glomerulorist globally, and the system 16 is auditable. There's an audit trail of the scores of 17 individual pathologists for each individual capillary. 18 So I do think this is an important endpoint 19 or at least an indicator, a secondary endpoint of 20 these clinical trials for chronic antibody mediated 21 rejection. 22 And there are methods that have been</p> |

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| <p style="text-align: right;">Page 102</p> <p>1 developed to do this in a way that's beyond what Banff 2 is using. 3 DR. NICKERSON: Maybe just a follow-up 4 question, then. Bob, what about electron microscopy 5 in that regard? 6 DR. COLVIN: I love electron microscopy and 7 I love electron microscopists, but their sample size 8 is even more dismal than what we see in a light 9 microscopic biopsy. 10 I agree that they can see early signs. They 11 can see early signs of things that don't end up to e 12 antibody mediated rejection. And the studies that 13 Mark has shown you I think those are mostly pre- 14 sensitized patients where you'd expect the early signs 15 to be there in a few months. 16 We always do electron microscopy to evaluate 17 antibody mediated rejection so I am supportive of 18 that, but I don't think it's the way to score it. 19 It's the way to detect early changes, but probably not 20 the best way to quantitate just because of the 21 sampling problem. 22 DR. WOODLE: Just as a non --</p> | <p style="text-align: right;">Page 104</p> <p>1 glomerularis that has some notable feature otherwise 2 we just choose a representative glomeruli. 3 But if you take three, four, or five little 4 pieces you'll be lucky to get three of four glomeruli. 5 Mark, do you want to comment on that? 6 DR. NICKERSON: I think Renata wants to move 7 on to the questions -- 8 DR. COLVIN: Oh, okay. 9 DR. NICKERSON: -- at this point. I think 10 the pathology discussion you could have at the coffee 11 break so let's keep moving. 12 DR. MANNON: Can I just ask a very quick 13 clarification from Dr. Chawla's presentation? Because 14 I have a feeling we won't get a chance to talk about 15 it in these questions. 16 But has anybody done this furosemide stress 17 test in either brain-dead donors or candidates for 18 donation that may be DCDD before they donate, yes or 19 no? 20 DR. CHAWLA: Here we go. Sorry. Not that 21 I'm aware of. And we obviously want to look at that 22 because that could be a nice way to decide, you know,</p> |
| <p style="text-align: right;">Page 103</p> <p>1 DR. COLVIN: But I would welcome Mark's 2 comments on that. 3 DR. WOOLDE: Just as a non-pathologist how 4 many glomeruli do you normally examine under an EM? 5 DR. COLVIN: Well, one to two typically, 6 sometimes three or four. Depends on the sample and 7 depends on what you're looking for. 8 DR. WOODLE: Okay. And do you usually look 9 under -- do you look under light and choose one to 10 actually -- or do you look at the specimen to choose 11 which one to look at? 12 DR. COLVIN: Yes. 13 DR. WOODLE: And do you usually choose the 14 most pathologic one -- so is it a worst-case scenario 15 that you're doing under EM? 16 DR. COLVIN: Well, not necessarily. The way 17 it's done is a small portion, as you know, is put in 18 the EM fixative. And then thick sections -- what we 19 call thick sections are made of those. 20 And we use those to select the glomeruli. 21 We obviously don't want to study a sclerotic 22 glomerularis and we obviously do want to study any</p> | <p style="text-align: right;">Page 105</p> <p>1 on a marginal donor does it work or what kind of 2 opportunities do you have. 3 DR. ALBRECHT: So I actually think that's 4 question 3. And if there are other comments about -- 5 DR. MANNON: I'm sorry. 6 DR. ALBRECHT: No, no. This is -- 7 DR. MANNON: Renata, I didn't even pay 8 attention. 9 DR. ALBRECHT: No, no. But it's actually 10 one that we would like to have some discussion on so 11 please go ahead and share your views and comments. 12 DR. NICKERSON: So I have a couple comment 13 -- maybe one comment about the deceased donor. It's 14 going to be very hard to separate that out to some 15 degree for someone who has brain death because you're 16 going to have diabetes insipidus basically with the 17 lack of ADH. 18 DR. CHAWLA: Yeah. That's exactly right. 19 So I think from a urine output standpoint it's not 20 useful. But the other thing we did and I didn't have 21 time to go into it is we actually measured furosemide 22 concentration in the urine.</p> |

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| <p style="text-align: right;">Page 106</p> <p>1 And so that allows you to actually look at 2 direct tubular transport. And for those of you who 3 are interested in horse racing, furosemide testing is 4 routinely used in horses and I won't get into why, but 5 it's cheating if you don't do this in horsing race -- 6 racing.</p> <p>7 So the assays are very good because there's 8 a lot of money in horse racing and they're 9 quantifiable. And what we've been able to demonstrate 10 is that the furosemide concentration is not always 11 linear with the urine output. And what that suggests 12 in at least some patients is that their proximal 13 tubular functions intact, they can lose furosemide 14 across but they don't respond.</p> <p>15 And there's others who move relatively less 16 furosemide across but have a really brisk response. 17 And that might be informative because you may or may 18 not have the opportunity to look at tissue. You get 19 on the back table but by then you're kind of committed 20 to some degree.</p> <p>21 And if there are -- if the test was done as 22 a convenience sample and then you did a back table,</p> | <p style="text-align: right;">Page 108</p> <p>1 DR. HAAS: With regard to furosemide and 2 acute kidney injury, I mean, furosemide as we know 3 acts by inhibiting the transporter in the thick 4 ascending limb in the apical membrane. And in pa- -- 5 and the thick ascending limb is very sensitive to 6 ischemia.</p> <p>7 And when patients develop ischemia -- and 8 this maybe relate to Ros's question -- when there's 9 either ischemia reperfusion injury or whether there's 10 cold ischemia these transporters in the apical 11 membrane actually are -- become incorporated into the 12 cytoplasm and there's a loss of -- there's a loss of 13 transporters in the apical membrane.</p> <p>14 So how does acute -- so one might expect 15 furosemide to have a lesser increment on urine output 16 in patients who have ischemic acute kidney injury. 17 Does acute kidney injury affect the -- you know, the 18 usefulness of the furosemide assessment of reserve?</p> <p>19 DR. CHAWLA: Yeah. So this is a very 20 important question, but I think that one of the things 21 that we've come to realize is that the acute kidney 22 injury which was formerly viewed to be ATN is not ATN.</p> |
| <p style="text-align: right;">Page 107</p> <p>1 you could probably then marry that data later on and 2 see if it's informative.</p> <p>3 But in general I want to be very clear that, 4 you know, functional testing should never be done in 5 isolation, you know. Everything we do clinically at 6 the bedside when you take a functional test and you 7 add it to something else you typically get better 8 fidelity of information.</p> <p>9 And I think that it's important that we not 10 get really sort of, you know, siloed in our thinking. 11 You know, look at what the cardiologists have 12 effectively done. They use functional testing and 13 they use other biomarkers, they put the two together. 14 And additionally if you can have imaging that's your 15 trifecta.</p> <p>16 In nephrology we are weak in our imaging at 17 least at the bedside. We do better with allografts 18 because they're more accessible, but in a native 19 person it's very challenging. And we don't have good 20 functional tests and so we need to do a lot better in 21 all those domains in my view.</p> <p>22 DR. NICKERSON: Mark?</p> | <p style="text-align: right;">Page 109</p> <p>1 And we know -- we know that this notion that decreased 2 blood flow drives acute kidney injury is wrong.</p> <p>3 Most patients with sepsis inflammation who 4 are resuscitated in ICU have increased blood flow, not 5 decreased. They have a primary microcirculatory 6 defect. Blood flow is maldistributed in the kidney 7 and it's maldistributed in a medullary and a cortical 8 fashion and so you have a very heterogeneous injury.</p> <p>9 And most of that is localization of ischemia 10 and a lot of dysfunction primary mediated through what 11 appears to be a stunning phenomenon which is probably 12 highly adaptive.</p> <p>13 And so what you don't know in any of these 14 individual patients is time of injury, depth, and 15 severity. And that functional test gives you a rather 16 blunt readout. And I think there are a manifest -- 17 manifold reasons why you have poor response.</p> <p>18 And I think we need to step back and 19 recognize we just don't know on a person-to person, 20 individual-to-individual basis what's happening at the 21 cellular level. And we need to prognosticate and make 22 thoughtful decisions to give therapies.</p> |

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| <p style="text-align: right;">Page 110</p> <p>1 I think many of the reasons you've outlined 2 could be why there's some resistance to furosemide, 3 but we just don't know. And there's probably at least 4 ten reasons why this occurs. 5 There was also a question over there. 6 DR. VELIDEDEOGLU: I just want to comment on 7 the same subject. Before moving onto the furosemide 8 or other types of stress testing I think the 9 fundamental issue is that -- is the preservation of 10 renal function, the ultimate goal. I mean, that's 11 what we are striving for to preserve renal function, 12 to prevent any nephron loss as a consequence of 13 rejection mediated or other types of damaging kidney 14 transplant patients. 15 As Dr. Chowla explained, there's quite a bit 16 of renal reserve in healthy people. So one of the 17 questions probably that needs to be answered is that 18 how much renal reserve if there's any do transplant 19 patients have? 20 And I know that there are some studies 21 performed on this, but in my opinion probably needs 22 some further work. And is that also dependent on the</p> | <p style="text-align: right;">Page 112</p> <p>1 means through glomerular reserve, is mitigated. And 2 those -- that -- those studies have not been done at 3 least from a glomerular standpoint. 4 I also think that your second question is 5 very important that if you do have injury, what we 6 have clearly demonstrated is that you have sustained a 7 hit even if you're creatinine comes back to normal. 8 So it is very uncommon to rare that an 9 episode that results in a brief episode of acute 10 kidney injury does not actually result in durable 11 injury whether you can measure it or not. 12 And what the kidney does very effectively 13 and why I am very anti-creatinine -- I'm in the ABC 14 camp of anything but creatinine because I think that 15 it's old and it needs to be updated -- is what the 16 kidney does is that it says, oh, there's so much 17 creatinine around I can't increase my filtration. 18 I'll just take my tubular reserve and secrete more. 19 And we sit there and see the creatinine go 20 from 1.2 to 1.5 back to 1.2 and we're happy. But the 21 kidney is durably injured. It's managing. And we 22 think everything is fine and nothing is fine. And I</p> |
| <p style="text-align: right;">Page 111</p> <p>1 type of immunosuppression that they are receiving? 2 For example, if they are on a CNI-based 3 regimen because of the constriction, do they have more 4 renal reserve compared to patients on non-CNI 5 regimens? 6 And this also ties to the concept that we've 7 been seeing especially in old papers that while 8 patients had an acute rejection episode, but the 9 creatinine returned back to baseline value or the GFR 10 return. 11 Does that really mean that those patients 12 did not sustain any permanent damage or is it simply 13 because that the remaining nephrons are compensating 14 for the ones that are lost? 15 So if anybody wants to or Dr. Chowla wants 16 to -- 17 DR. CHOWLA: Yeah. So I think that's a 18 really important question. And let me address the 19 first one first which is that I think the medications 20 do matter. If you're on a calcineurin dependent 21 inhibitor I'm sure your ability to alter filtration 22 fraction and increase blood flow, which is the primary</p> | <p style="text-align: right;">Page 113</p> <p>1 think that this is a huge problem in an intellectual 2 approach which is damaging because creatinine is a 3 lousy marker in my view. And our continued dependence 4 on it I think is enormously problematic. 5 I would concede we have nothing better now, 6 but it's a lousy marker. And the fact that we haven't 7 updated it in 60 years I think is enormously 8 problematic. 9 DR. GASTON: So we did those studies. And 10 this is -- seems like ancient history, but it has 11 published in JASN in 1995. And we studied renal 12 functional reserve in patients on and off cyclosporine 13 and transplant recipients. 14 And basically -- and the control group was 15 Imuran treated patients then for those of you who 16 remember Imuran. And the -- there was substantial 17 functional reserve in the patients on Imuran that was 18 related to renal blood flow that was abrogated with 19 cyclosporine. And these were chronically treated 20 patients on stable doses of cyclosporine. 21 To my knowledge it was done with Imulan 22 clearance, with PAH clearance, and so on, very labor</p> |

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| <p style="text-align: right;">Page 114</p> <p>1 intensive. And those studies have not been repeated 2 to my knowledge with tacrolimus. 3 Based on differential impact between 4 cyclosporine, tacrolimus, an renal function, long-term 5 renal function my bias would be that the affect that 6 we saw with cyclosporine would be less with 7 tacrolimus, but I'm not sure of that and that work has 8 not been done. 9 And then I would expect the patients on BELA 10 and not on CNIs to behave much like the Imuran 11 patients even though that's not been done either. So 12 I -- that's always made me suspicious of the GFR as an 13 endpoint because as a nephrologist I know I can 14 manipulate GFR all sorts of ways and so that I think 15 of an endpoint as more of a fixed kind of thing. 16 That said, watching the BELA data evolve and 17 with data out to seven years that shows this 18 differential between CNIs the duration of that effect 19 over time has become more compelling to me in thinking 20 about it. 21 But clearly the patients retain renal 22 functional reserve. And it is affected by the</p> | <p style="text-align: right;">Page 116</p> <p>1 non-invasive and non-toxic. 2 Not our company. I mean us as a community. 3 DR. NICKERSON: So just a follow-up question 4 with the Lasix the furosemide stress and looking at 5 reserve. So can that be done as an out-patient? 6 Is this a requirement that that come in and 7 be clearly monitored? 8 DR. CHAWLA: Oh, yeah. It can certainly be 9 done as an out-patient. It can be done with Gatorade 10 is the ideal replacement solution. And you just have 11 them sit down and you just keep track of them. 12 And there are colleagues of ours who are 13 doing this and they're doing it as a convenient 14 sample. People will come in for a biopsy for whatever 15 reason and they're basically getting furosemide post- 16 biopsy which in some ways is useful to see if they 17 have hematuria and basically wash them out if there's 18 a concern about that. 19 And they're just tracking it as they go and 20 they replace them CC per CC at the bedside with -- 21 with Gatorade which is, you know, a nice, balanced 22 salt solution at the bedside.</p> |
| <p style="text-align: right;">Page 115</p> <p>1 mediations they take or can be affected. 2 DR. WOODLE: So, Bob, is it possible to do 3 these tests when patients are on drug like a CNI that 4 reduces renal blood flow by 30 to 50 percent? Is it 5 applicable test? 6 DR. GASTON: Well, the way you do it is with 7 -- or the way we did it was with a fixed infusion of 8 amino acid that was known in normal people. And 9 basically we used L-arginine and we got all into 10 nitric oxide and so on in the studies. And it was 11 interesting. 12 So that, yeah, it's fairly standardized and 13 very doable I think or reproducible, but it's very 14 labor intensive. And I think you have a difficult 15 time even getting Imulan these days to do that sort of 16 thing so. 17 DR. CHAWLA: I would agree with all that. I 18 think that's very important. I would just point out 19 the one piece of good news is real time GFR in a non- 20 invasive fashion is coming soon. And we will have 21 that at the bedside within the next three to five 22 years in 510(k) and everything quite clean and very</p> | <p style="text-align: right;">Page 117</p> <p>1 And so far I think they've enrolled over 85 2 patients. It's been very safe. As to whether the 3 data are meaningful or not it remains to be seen. 4 That's to come. 5 But it is very straightforward in so long as 6 you have it in a reasonably monitored environment. I 7 don't think this is something you do, you know, 8 without someone checking in on them, you know, but 9 certainly in any kind of reasonable hospitalized 10 setting or a clinic setting would be fine. 11 DR. GASTON: Oh, just the addition that I 12 would say about the CNI effect is if you can look at a 13 myriad of studies from Chris's and Peter's to all 14 sorts of other things and see that those patients in 15 that top curve have very stable GFRs. They're 16 adherent and don't have DSA. 17 They have stable GFRs over 10 to 12 years 18 basically and they're all on CNIs. And so that -- 19 there's a lot to be said for that that there is not 20 built into CNIs a decline in GFR independent of other 21 things. 22 So that to do -- even though CNIs may</p> |

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1 inhibit this renal functional reserve business what
 2 we're after is not preserving renal functional reserve
 3 necessarily. It's preserving kidneys. And I don't
 4 know if Dixon's still here. Dixon taught me that
 5 years ago, Dixon Kaufman, that we're not about
 6 preventing diabetes or maximizing GFR even though
 7 that's -- those are both good things. We're really
 8 about making grafts work for long periods of time for
 9 the patients that we serve.
 10 DR. ALBRECHT: Dr. Colvin?
 11 DR. COLVIN: Yes. Just a follow-up question
 12 to Dr. Chawla on the furosemide test. One of the
 13 things we're not very good at as pathologists and I
 14 think probably also as clinicians is predicting which
 15 patients with acute kidney injury are going to recover
 16 or not.
 17 And does your test allow this distinction to
 18 be made?
 19 DR. CHAWLA: Yeah. So thank you for
 20 referring to it as my test, but it's certainly not my
 21 test. This is a conglomeration of knowledge from
 22 people who are much older than me and a simple step of

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1 standardization.
 2 There's two studies now where they have
 3 looked at this later in the course of acute kidney
 4 injury and it does predict. And, you know, this is
 5 not rocket science. We've all done this clinically.
 6 Someone's sort of in their recovery phase, you give
 7 them a big slug of furosemide, they respond. You sign
 8 off on them Friday and you don't see them ever again
 9 hopefully.
 10 And we do this all the time. This is just a
 11 standardization of bedside practice. But it does
 12 work. It does work with metrics. And the general
 13 metric is that if you make more than 100 CCs an hour
 14 for 1 mg per kg so the math is easy to remember you
 15 tend to be okay. If you're under 100 CCs an hour for
 16 1 mg per kg assessment you don't do as well. And
 17 obviously there's gradations depending on how far or
 18 below that threshold you are.
 19 So it does work. It should not be an
 20 exclusive test because many patients have variable
 21 effects of furosemide based on furosemide itself. And
 22 it doesn't have to be furosemide. If someone wanted

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1 to get very cute they could use probenecid or anything
 2 else that uses human organic transporters. This just
 3 happens to be super cheap and convenient which is why
 4 we selected it, but it does work on both ends. It
 5 works to predict worsening. It works to predict
 6 recovery.
 7 There's no traction in DGF. And given the
 8 cost constraints we're all feeling I think it might be
 9 an opportunity to marry it with other thoughtful
 10 diagnostics that we use and maybe improve fidelity
 11 overall.
 12 DR. NICKERSON: I'd like to move to question
 13 4 which is based on the information on diagnosis,
 14 treatment, what do we know about the ability to select
 15 control therapy?
 16 And I'd like comments on this please because
 17 I think this is a really critical question for us
 18 going forward as we think about clinical trial design.
 19 So what do we -- what are the comments that
 20 we have and do we -- what do we know about the ability
 21 to select control therapy?
 22 DR. MANNON: So, Peter, I was -- you know, I

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1 was not involved in the design of the Alexion
 2 equilizumab trial that Steve showed the data for. But
 3 the way the control arm was allowed was sort of
 4 substantial flex- -- I would say flexibility in the
 5 terms of it was an HLA incompatible living donor study
 6 with central laboratory.
 7 So they wanted you to use relatively high-
 8 risk patients that were both DSA positive and flow
 9 cross match positive. But they used a central lab to
 10 sort of ascertain whether your level of risk was
 11 similar to someone else's.
 12 And then after the enrollment it was
 13 randomized. You could, you know, do the incoming
 14 treatment is whatever, plasmapheresis, whatever the
 15 standard of care of your center was. And not every
 16 center gave pre-transplant immunosuppression and some
 17 centers did.
 18 And so I don't know if that's the kind of
 19 question you're asking, you know, from an acute -- you
 20 know, I mean, we have -- we have three different uses
 21 -- desens, AMR, and CAMR.
 22 And so, you know, from that equilizumab study

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| <p style="text-align: right;">Page 122</p> <p>1 that was a desens application. And so I think there 2 needs to be some standardization because I think it 3 hurt the study in the end.</p> <p>4 From the AMR study, again, there's lots of 5 ways peop- -- you know, I know on the calls we said, 6 oh, this is the standard. But there's -- every center 7 has a little bit of a tweak, you know, whether they're 8 using IDIG or low dose IVIG or cytogam and then the 9 CAMR.</p> <p>10 So I don't want to monopolize the 11 conversation, but I -- because there's other people 12 who are in here that do this work, as well.</p> <p>13 DR. NICKERSON: So maybe make -- just I'll 14 -- before I let you go, though, talk about CAMR and 15 what you would say you would think as a control 16 therapy in CAMR.</p> <p>17 DR. MANNON: So, I mean, I think what we do 18 is, you know, we sometimes give the option about -- we 19 typically will give a one course of IVIG to see if we 20 can make any dent into the DSA because our assessment 21 is that the persistence of DSA is persistence of 22 injury.</p> | <p style="text-align: right;">Page 124</p> <p>1 And but if you take an AMR that's past six 2 months, most of them are going to be mixed rejections 3 that have the molecular signatures of both T-cells and 4 AMR. And I think that because with early AMR the 5 therapeutic results are really good, okay.</p> <p>6 And so based on diagnosis if you're going to 7 allow both early and late into your trial I think you 8 need to stratify and I think you need to control for 9 it both at the entry level and at the endpoint 10 analysis level.</p> <p>11 As far as treatment it's my opinion, and, of 12 course, those opinions are always subject to bias, but 13 I -- my interpretation of literature between IVIG 14 based regimens and proteasome inhibitor based 15 regimens, which I think are the two major options that 16 you have right now, that the results for early AMR are 17 equivalent and the results for late mixed rejection 18 are equivalent. And that's in terms of IDSA 19 reduction, in terms of histologic improvement, and in 20 terms of renal functional outcomes.</p> <p>21 And I think those are the three major 22 endpoints we've looked at and analyzed when we've</p> |
| <p style="text-align: right;">Page 123</p> <p>1 Similar to one of the other speakers 2 yesterday, if we see fairly advanced IFTA, grade 3, we 3 typically reserve that. If the eGFR is below 30 it 4 portends doom and so I think we sometimes use the IVIG 5 just to give patients a sense of hope.</p> <p>6 ACE and ARBs are standard of care for 7 proteinuria unless the eGFR is too low or there's 8 hyperkalemia. Steroids have been used in our group in 9 modest doses and then intensification of 10 immunosuppression is tolerated. And, again, it's 11 based on the eGFR when you try to push tack up.</p> <p>12 And then we get into a debate about 13 rituximab and use of rituximab dosing based in some of 14 the other studies. And it's not used consistently.</p> <p>15 So those are -- those are the things that a 16 standard big center -- and, you know, I'm welcome to 17 hear my other colleagues.</p> <p>18 DR. WOODLE: So I think that very clearly if 19 you're going to do an AMR trial -- so an AMR 20 therapeutic trial you've got to either focus on early 21 or late. And the late by whatever term you define it, 22 you know, has to be carefully defined.</p> | <p style="text-align: right;">Page 125</p> <p>1 looked at our results and then sort of compared them 2 to what the historical literature is.</p> <p>3 That being said, I did not show data at the 4 end of my talk, but, as I mentioned before, IDSA 5 reduction by at least 50 percent in 14 days is the 6 most powerful predictor in our analysis of outcomes of 7 graft survival.</p> <p>8 Death censored graft survival after an 9 episode of AMR treated with a proteasome inhibitor. 10 And that's in a group of about 100 patients with AMR 11 treated with a single proteasome inhibitor based 12 regimen. And that's a pretty big experience.</p> <p>13 DR. NICKERSON: And just to clarify because 14 I think the Banff language is hurting us still. Is 15 this acute AMR where we actually have graft 16 dysfunction that you're talking about?</p> <p>17 DR. WOODLE: Yes. Yeah. So that series was 18 exactly that, Peter. As I mentioned before, we're 19 starting to try to move to where we're treating AMR 20 before we have renal dysfunction.</p> <p>21 And I think that that -- that's an important 22 thing to consider when you're looking at entry</p> |

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| <p style="text-align: right;">Page 126</p> <p>1 criteria.</p> <p>2 DR. NICKERSON: So if -- and maybe just</p> <p>3 going to push you a little bit more. So if you have</p> <p>4 chronic AMR, the smoldering, chronic active AMR where</p> <p>5 you have some early DG and you have some active</p> <p>6 lesions, microvascular inflammation, C4d positive, and</p> <p>7 you're creatinine has really just got this sort of</p> <p>8 niggling rise, what's your approach as standard of</p> <p>9 care in your center?</p> <p>10 DR. WOODLE: Yeah. So our general feeling</p> <p>11 -- so we look at not in terms of trying to put things</p> <p>12 into a basket. We look at the biopsy, we look to see</p> <p>13 if they have proteinuria, we look to see if what their</p> <p>14 renal function is and how much inflammation they have</p> <p>15 in the graft.</p> <p>16 That being said, we treat them all the same.</p> <p>17 We don't have a specific treatment for one of those</p> <p>18 lesions. What we try to do is you try to get rid of</p> <p>19 the antibody as much as possible, okay.</p> <p>20 And we don't -- what we haven't included in</p> <p>21 our therapies is a long-term maintenance concept for</p> <p>22 keeping that antibody suppressed. So we don't have</p> | <p style="text-align: right;">Page 128</p> <p>1 treatment because we didn't know what was the best</p> <p>2 thing to do. And progressively we escalated therapy</p> <p>3 to steroids and steroid IVIG and additional rituximab</p> <p>4 and in some cases (indiscernible) and there was a</p> <p>5 mixed component.</p> <p>6 Given all the limitations of this</p> <p>7 observational study we have come out of it with</p> <p>8 defining our control being steroids and IVIG because</p> <p>9 that was -- after all I just mentioned in multivariate</p> <p>10 the single determining factor in improving outcomes by</p> <p>11 50 percent in terms of graft loss.</p> <p>12 And if there is no significant scoring on</p> <p>13 the biopsy or if serum creatinine is less than 3, then</p> <p>14 we add rituximab. So that has become our new</p> <p>15 standard.</p> <p>16 MR. HAAS: You say chronic antibody mediated</p> <p>17 rejection. Do you mean chronic active antibody</p> <p>18 mediated rejection or just chronic?</p> <p>19 I think it's very important to distinguish</p> <p>20 between the two. I mean, if you have just TG by</p> <p>21 itself, that's just chronic antibody mediated</p> <p>22 rejection at least most of the time and if you have a</p> |
| <p style="text-align: right;">Page 127</p> <p>1 that. We give a two-week course of a proteasome</p> <p>2 inhibitor based regimen.</p> <p>3 Now and so for our outcomes we basically</p> <p>4 look -- we want to see the antibody go down by at</p> <p>5 least 50 percent. If it does that, to me, suggests</p> <p>6 it's a treatable lesion. It may be the biology rather</p> <p>7 than the treatment. It may be not what you treat</p> <p>8 with, but just the fact that patient's particular</p> <p>9 biology is treatable.</p> <p>10 We also like to see proteinuria stabilize.</p> <p>11 We like to see the creatinine come back down to</p> <p>12 baseline. But, as you know, with these chronic</p> <p>13 lesions it's hard to know what the baseline is so.</p> <p>14 DR. DJAMLI: Peter, if you -- oh.</p> <p>15 DR. NICKERSON: Go ahead.</p> <p>16 DR. DJAMLI: I just wanted to say that we</p> <p>17 published last year in human immunology the -- a</p> <p>18 rather large series of chronic rejection. Of course</p> <p>19 this was observational in 126 patients with CAMR just</p> <p>20 to see how we had progressed our management over the</p> <p>21 past 15 years.</p> <p>22 And, in fact, the first round of them got no</p> | <p style="text-align: right;">Page 129</p> <p>1 history of DSA.</p> <p>2 But if you have TG plus active microvascular</p> <p>3 inflammation or C4d, that's chronic active antibody</p> <p>4 mediated rejection. One is just can almost be</p> <p>5 considered a bland scar and the other can be</p> <p>6 considered an inflamed process that is in the process</p> <p>7 of undergoing scarring, but, you know, it's still an</p> <p>8 active process.</p> <p>9 So I think it's important to distinguish.</p> <p>10 So do you know if these also had active inflammation?</p> <p>11 DR. DJAMLI: Yes. The common denominator</p> <p>12 was CG. And the vast majority of them had active</p> <p>13 lesions. And we looked at the independent impact of</p> <p>14 those variables including microvascular injury and so</p> <p>15 forth and the DSA and some of them panned out</p> <p>16 significant in univariates. But in multivariates the</p> <p>17 only variables that were really retained were retox-</p> <p>18 -- not -- is IVIG and the functional value, I'm sorry</p> <p>19 to say, but serum creatinine at the time of biopsy.</p> <p>20 DR. NICKERSON: I'm going to call the</p> <p>21 session to a close. We're about five minutes over</p> <p>22 time. We do want to try and stay on time so we are</p> |

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| <p style="text-align: right;">Page 130</p> <p>1 going to ask people to reconvene in ten minutes at 11. 2 So it'll be a brief break and we'll start up at 11 3 again. Thank you very much. 4 (A brief recess was taken.) 5 DR. BALA: Thank you, Dr. Albrecht. So 6 we'll start with the first talk and our speaker is Dr. 7 Gregory Knoll. And he will be talking about potential 8 primary endpoints in clinical trial of antibody 9 mediated rejection. 10 And he will be covering examples like 11 desensitization, prevention and treatment of acute 12 AMR, and prevention and treatment of cellular 13 rejection -- chronic rejection. Sorry. 14 DR. KNOLL: Thank you. This is my 15 disclosure slide. So allograft survival, and more 16 specifically the one-year allograft survival has 17 really become the main endpoint that we use to 18 evaluate therapies in kidney transplantation. 19 And this figure's from the 1983 landmark 20 trial of cyclosporine and you can see the patients who 21 got cyclosporine clearly had a better one-year graft 22 survival than the comparator Imuran and Prednisone.</p> | <p style="text-align: right;">Page 132</p> <p>1 and harms of any intervention. 2 So what are the advantages of using 3 surrogates? Well, these are usually measured earlier 4 in a trial compared to our clinical endpoints that 5 allow for shorter and cheaper trials. This results in 6 faster decision making about treatment which is very 7 important in this topic area. 8 Also typical surrogates are continuous 9 variables so that all patients in the trial will, in 10 fact, have an event and this greatly reduces sample 11 size, increases power, and reduces cost. 12 So what are the disadvantages? Well, the 13 major thing is that most biomarkers are, in fact, not 14 valid surrogate endpoints. And it's actually quite 15 difficult to properly validate a surrogate outcome. 16 First of all, the surrogate needs to be 17 prognostic for a hard clinical endpoint. Changes in 18 the surrogate with treatment must predict changes in 19 the occurrence of the clinical endpoints. And finally 20 the full effect of the treatment on the clinical 21 endpoint should be captured by the surrogate. And 22 invalid surrogates may misrepresent really the true</p> |
| <p style="text-align: right;">Page 131</p> <p>1 And in the decade following this trial the 2 one-year graft survival I think has really become the 3 most important clinical endpoint we've been using in 4 kidney transplant. 5 So what are some of the other outcome issues 6 we can use? So, first of all, we can use clinical 7 endpoints. These are also called patient important 8 outcomes. This is simply a characteristic that 9 reflects how the patient feels, functions, or how long 10 they survive. And in kidney transplantation examples 11 of this include graft survival, patient survival, and 12 quality of life. 13 We also have biomarkers and these are just 14 characteristics that are objectively measured as an 15 indicator of a normal biologic process, a pathogenic 16 process, or some response to therapy. And typical 17 ones in transplant are creatinine and GFR that we've 18 heard about in the talks. 19 And finally we have surrogate endpoints and 20 these are simply biomarkers that are used as 21 substitutes for our clinical endpoints. And a true 22 surrogate is really expected to predict both benefits</p> | <p style="text-align: right;">Page 133</p> <p>1 consequences of an intervention. 2 And in the literature there's a variety of 3 examples where we've had bad surrogates where in well- 4 done clinical trials the surrogate measures were 5 moving in a favorable direction whereas when we looked 6 at the clinical endpoints -- and many of these are 7 mortality -- they were going in an unfavorable 8 direction. So we just have to be careful when we 9 choose our surrogate endpoints. 10 So what then clinical endpoints would be 11 important to transplant patients? Well, I think 12 obviously patient survival. But I think also 13 allograft survival in my mind perhaps is more 14 important as it accounts for both patient death and 15 graft failure. 16 I think it -- I look at it as marker of 17 quality of life if you think of time off of dialysis 18 with the graft still functioning. It's also a marker 19 of cost given the cost differentials of the treatment. 20 And, as I mentioned, the one-year allograft 21 survival has really been the one that's most commonly 22 used. But as I'm going to show you it's become more</p> |

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| <p style="text-align: right;">Page 134</p> <p>1 difficult to use as our success has improved.</p> <p>2 So if you think of overall now one-year</p> <p>3 graft survival is in the range of about 94 percent.</p> <p>4 And if we think of in the setting of ABMR what's one-</p> <p>5 year graft survival it's not an easy number to find,</p> <p>6 but it's probably in the range of 90 percent as most</p> <p>7 of these grafts fail beyond the first year.</p> <p>8 So if we think of sample sizes needed to try</p> <p>9 and improve on this 90 percent one-year graft survival</p> <p>10 you could see if you just wanted to get them back to</p> <p>11 sort of the average of 94 percent with a new therapy</p> <p>12 this is going to require 1,400 patients in that trial.</p> <p>13 If you had a dramatic -- you know, sort of a</p> <p>14 blockbuster-type drug that you thought might have a</p> <p>15 dramatic improvement from 90 to 98 percent at one</p> <p>16 year, this would only require 276 patients.</p> <p>17 But I've highlighted the reflux era study</p> <p>18 which many of you know about, but this is one of the</p> <p>19 largest published randomized control trial in ABMR.</p> <p>20 And this had only 38 patients and it took 21 centers</p> <p>21 to get those 38 patients. And they didn't even get</p> <p>22 their sample size of 64. So although that sample size</p> | <p style="text-align: right;">Page 136</p> <p>1 but in the context of this condition it may be a trial</p> <p>2 that's just not feasible.</p> <p>3 So I don't think graft survival on its own</p> <p>4 will be a useful endpoint for ABMR trials. It's going</p> <p>5 to be difficult for new interventions to show a</p> <p>6 reasonable treatment of fact using realistic sample</p> <p>7 sizes. And I think most of our interventions are</p> <p>8 likely going to produce more modest incremental</p> <p>9 improvements. And these sample sizes are probably</p> <p>10 just not feasible.</p> <p>11 So what, then, might be the ideal endpoint</p> <p>12 for ABMR trials? Well, as we've discussed over the</p> <p>13 past two days, I think markers of histology are going</p> <p>14 to be very important such as freedom from ABMR or its</p> <p>15 components or perhaps freedom from TG.</p> <p>16 We need to relook at our conventional</p> <p>17 biomarkers. And finally we'll probably need to</p> <p>18 encompass some of the new biomarkers such as DSA and</p> <p>19 gene transcript expressions.</p> <p>20 And I do want to point out that these</p> <p>21 outcomes are all surrogate endpoints. And most kidney</p> <p>22 transplant trials, in fact, do not measure clinical</p> |
| <p style="text-align: right;">Page 135</p> <p>1 of 276 looks fairly reasonable in the context of the</p> <p>2 condition we're talking about it may be very</p> <p>3 unrealistic.</p> <p>4 Now what about late graft survival? Could</p> <p>5 this be a possible endpoint? These are just some</p> <p>6 figures from some different studies. And you can see</p> <p>7 that the outcomes are highly variable. And we know</p> <p>8 this depending on when the ABMR is occurring, is this</p> <p>9 associated with nonadherence, is this an early or a</p> <p>10 late lesion.</p> <p>11 But I think when I looked at it the average</p> <p>12 seemed to be in the range of a five-year survival of</p> <p>13 about 50 percent. So if we took that as an average</p> <p>14 benchmark if we wanted to show a small relative</p> <p>15 increase, say, of 10 percent, so going to 50 to 55</p> <p>16 percent, this is over 3,000 patients in that kind of</p> <p>17 trial.</p> <p>18 A more typical trial might look at an</p> <p>19 increase of the endpoint of 25 percent. This would</p> <p>20 translate into an absolute change of five-year graft</p> <p>21 survival of 63 percent. And this would only require</p> <p>22 456 patients which again seems much more reasonable,</p> | <p style="text-align: right;">Page 137</p> <p>1 endpoints. So this was a systematic review we did a</p> <p>2 number of years ago where we looked at all kidney RCTs</p> <p>3 in a fixed period of time.</p> <p>4 And you can see that the surrogate -- a</p> <p>5 surrogate endpoint was the primary outcome in 78</p> <p>6 percent of these trials. So we're using surrogates a</p> <p>7 lot. I think we just have to be careful in how we</p> <p>8 select them and how we use them.</p> <p>9 So, again, getting back to the candidate</p> <p>10 endpoints for ABMR trials, if we talk about the hard</p> <p>11 endpoints of patient and graft survival I think for</p> <p>12 feasibility issues these are going to be difficult.</p> <p>13 Quality of life is obviously an important endpoint,</p> <p>14 but I think this is going to become much more relevant</p> <p>15 once we have some proven treatments to choose from.</p> <p>16 So I think we are faced with looking at some</p> <p>17 surrogate endpoints. And I think the key ones that</p> <p>18 need to be looked at a little more closely are some</p> <p>19 marker of kidney function, histology, DSA, gene</p> <p>20 expression in the graft, and proteinuria. And I'll</p> <p>21 expand on these in the rest of my talk.</p> <p>22 So, first of all, is kidney function a valid</p> |

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| <p>1 surrogate outcome measure? Well, again, kidney 2 function measurements are used a lot in kidney 3 transplant trials. This was a systematic review that 4 we did awhile back that showed some measure of kidney 5 function was using in trials about 80 percent of the 6 time. 7 And eGFR which has become very commonly used 8 was a primary secondary outcome in 61 percent of these 9 trials. So obviously very common in the field of 10 kidney transplant. 11 So first of all I think the first question 12 you want to ask is reduced kidney function associated 13 with worsening graft survival? And this is one of the 14 oldest papers to look at this where they looked at the 15 one-year serum creatinine and then looked at graft 16 survival over time. And you can see that there was a 17 clear association with a higher serum creatinine at 18 one year with worse graft survival. 19 And the authors of this study concluded that 20 the quality of renal function should be implemented as 21 a newer endpoint for comparative trials. 22 So the rationale for using kidney function</p> | <p>1 can see that the low dose tac arm also had the lowest 2 acute rejection rate. So perhaps it was the pathway 3 of reduced rejection rather than through GFR that was 4 leading to the improvement. 5 And this is just a schematic that you'll see 6 when people are looking at validation of surrogate 7 outcome measures. You have an intervention here low 8 dose tac that led to an improvement in GFR. And 9 what's being hypothesized that less toxicity from this 10 regimen was leading to improved graft survival. 11 But I just showed you that there was a 12 possible alternative pathway for this treatment to 13 work. And that might be better immunosuppression 14 leading to fewer rejections and improvement in graft 15 survival. So in this particular trial it's not clear 16 that GFR is, in fact, a valid surrogate outcome for 17 graft survival. 18 So here's another study that was looking at 19 eGFR and the relationship between graft survival and 20 mortality. And you'll see this a lot in these types 21 of studies where there's a strong association between 22 the outcome and in this case both death and graft</p> |
| Page 139 | Page 141 |
| <p>1 as an endpoint would be that you improve early renal 2 function and you also improve long-term graft 3 survival. And that was clearly true in that 4 observational study, but is that rationale true in the 5 setting of a randomized trial when you have an 6 intervention? 7 So I'll just give you one example. This is 8 from the Symphony trial many years ago where they 9 looked at a variety of immunosuppressive regimens. 10 And the primary outcome of this trial was, in fact, 11 the one-year GFR. And you can see that low dose 12 tacrolimus was, in fact, the best regimen and produced 13 the best one-year GFR. 14 Low dose tac also had the best one year 15 graft survival in that study. And when looking at 16 validation of the endpoint you want to know is this 17 full effect of the treatment on the clinical endpoint. 18 In this case would be graft survival being captured by 19 this surrogate. And in this trial it was not entirely 20 clear. 21 As you can see on the right these are the 22 acute rejection rates from that same trial. And you</p> | <p>1 failure. 2 But then when you look at the discriminating 3 ability how well can this predictor actually tell you 4 who will and will not eventually have graft failure? 5 It doesn't perform as well. 6 In this particular ROC curve this is the 7 six-month eGFR is the predictor looking at three-year 8 censored graft survival. And it doesn't matter how 9 you calculate these eGFR you can see there's a bunch 10 of different formula there that the C statistics are 11 in the range of .5 to .6, so not very good at 12 discriminating who's going to get graft failure. 13 Here's a study from the Mayo Group where 14 they divided the patients into their GFR at one year 15 being above or below 40 mils per minute. And what I 16 wanted to highlight on this first slide was that the 17 patients who had a GFR above 40 mils per minute at one 18 year, 49 percent of them in this series eventually 19 lost their graft, so patients who you thought would do 20 well intuitively at one year. 21 And when they looked at this a little bit 22 further they broke down that group of patients with a</p> |

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| <p style="text-align: right;">Page 142</p> <p>1 high GFR into those that progressed and those who did 2 not progress. And you can see that lower orange brown 3 survival curve. The group that had progressed but had 4 a high GFR at one year actually did worse than the 5 patients who had a low GFR at one year. So although 6 not very intuitive, early renal function tells us 7 little bit -- little about the risk of late graft 8 failure in many of our patients. 9 So why is the GFR at a fixed time point off 10 and poorly predictive of long-term outcomes? Well, 11 perhaps the creatinine may be a poor marker of true 12 GFR as we've heard in some of the earlier talks today. 13 And, two, GFR may also not reflect the 14 severity of the disease that's going on in the graft 15 if we look at the pathology. One serum creatinine 16 value may not reflect true baseline or steady state 17 and that may be an issue with these calculations. 18 And a lot can occur after 6 or 12 months. 19 And a lot of these studies are early measures of 20 function and looking at events well down the road. 21 And we clearly know lots of stuff can happen in that 22 time period contributing to graft loss.</p> | <p style="text-align: right;">Page 144</p> <p>1 of the patients who had a doubling of creatinine. 2 So the author said or certainly suggested 3 that maybe this is a better endpoint because it occurs 4 more frequently, but is also associated with our hard 5 clinical endpoints. 6 Now this exact same study and analysis was 7 done in a large set of transplant patients. This is 8 from Steve Chadban's group in Australia. And you can 9 see whether looking at overall or death censored graft 10 failure that a 30 percent decline in eGFR was strongly 11 associated with these endpoints. 12 And what they also showed was smaller 13 declines in GFR occurred more commonly. So if you see 14 if even you took a cut point of 20 percent, this 15 occurred in 19 percent of the patients. Importantly, 16 the decline in GFR was associated with both death and 17 graft failure. 18 Just highlighting the C statistics this 19 really appears to be no cutoff for different declines 20 in GFR. And finally I do want to point out that the C 21 statistics are in the range of .7 so these are good, 22 but not great in diagnostic performance measures.</p> |
| <p style="text-align: right;">Page 143</p> <p>1 So what about declining kidney function? 2 Could this be more predictive? Well, this was looked 3 at in a very large series of patients. These are non- 4 transplant CKDP patients. And this I'll remind people 5 that in nephrology -- many nephrology trials doubling 6 of serum creatinine has become a standard endpoint and 7 that's equivalent to minus 57 percent decline in GFR. 8 And this is strongly associated with ESRD 9 and that's why this endpoint is used. But the big 10 drawback is that it occurs very infrequently and 11 especially in the short frame of most clinical trials. 12 So in this particular study they wanted to 13 see if they looked at lesser declines in eGFR would 14 this also be associated with ESRD? And you can see 15 here the figure over here that if you have a minus 30 16 percent decline in GFR there was still a five-fold 17 increase risk of ESRD. 18 And you can see the association at ten years 19 64 percent of these patients had ESRD. And really the 20 important thing was that this event occurred in 6.9 21 percent of this population. This study had 1.7 22 million patients in it compared to less than 1 percent</p> | <p style="text-align: right;">Page 145</p> <p>1 But, again, these studies are suggesting that perhaps 2 a decline in GFR is an improvement as a marker of 3 long-term function over a GFR at a fixed time point. 4 Now what about DSA, is this a valid 5 surrogate outcome measure? Well, we've heard from Dr. 6 Woodle about this and this is his -- one of his 7 earlier studies looking at this where he had a group 8 of patients that had DSA measured day zero and day 14 9 following therapy and broke them down into a group of 10 responders and non-responders. 11 And you can see here in the graft survival 12 curve those that had a reduction greater than 50 13 percent there were no grafts lost. This was a small 14 series, but the patients at a less than 50 percent 15 reduction had a significant improvement in graft 16 survival. 17 Here's a second study from Dr. Woodle that 18 was looking at a scoring system -- a histologic-based 19 scoring system following proteasome-based therapy that 20 I'm going to talk about in a little more detail in a 21 minute. 22 But within this trial he also had his DSA</p> |

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| <p style="text-align: right;">Page 146</p> <p>1 data. And, again, if you see a greater than 50 2 percent reduction in DSA, 100 percent one year graft 3 survival compared to only 57 percent for those that 4 did not have a less than 50 percent decline. So these 5 two studies suggesting that decline in DSA may be an 6 important surrogate measure.</p> <p>7 Now what about these histologic markers? 8 Are these valid surrogate outcome measures? Here's 9 the study I just mentioned from Dr. Woodle. So what 10 they did was they created an acute composite score and 11 a chronic composite score based on the components of 12 the Banff scoring system.</p> <p>13 And you can see on the left this is the 14 acute composite score. And it didn't matter if this 15 was earlier or late AMR, you could see that there was 16 a nice decline in the composite score following a 17 treatment.</p> <p>18 And as you might expect on the right -- the 19 figure on the right there didn't appear to be much 20 change in the chronic composite score.</p> <p>21 In looking at this a little closer, again, 22 the acute score is on the left. You can see that most</p> | <p style="text-align: right;">Page 148</p> <p>1 presence of ABMR on a protocol biopsy would be a 2 possible surrogate outcome measure.</p> <p>3 Now here's a trial from Dr. Montgomery's 4 group looking at the C1s raised inhibitor. And in 5 this particular study they developed a score card 6 based on histologic criteria as the primary endpoint.</p> <p>7 And you can see the score card has a 8 glomerularitis score, a vascularitis score, et cetera 9 based on the variety of findings on the light 10 macroscopy.</p> <p>11 And what they did was they measured this -- 12 or used this score card at entry into the trial and on 13 day 20 in the trial. And unfortunately in this 14 particular trial there was no real improvement in any 15 components of this particular score card.</p> <p>16 But what they did show in a subset of the 17 patients who had active therapy on a six-month biopsy 18 none of them had transplant glomerulopathy whereas 43 19 percent of the placebo patients had TG.</p> <p>20 And as has been suggested by others, 21 including Dr. Colvin, that perhaps the presence of TG 22 would be an important surrogate outcome measure.</p> |
| <p style="text-align: right;">Page 147</p> <p>1 components of this acute score fell nicely with 2 treatment. And, again, really in the chronic scores 3 there was really no major effect.</p> <p>4 So perhaps this acute composite score or 5 some type of histologic measure like this could be 6 used as a possible surrogate outcome measure, but 7 obviously we need longer follow up with graft failure 8 data.</p> <p>9 Here's a figure from Loopy's paper that 10 we've seen a few times basically showing that the one- 11 year protocol biopsy if you have evidence of 12 subclinical antibody mediated rejection, that's the 13 figure in the red, you have the worst outcome long 14 term.</p> <p>15 And what they then did was they put the 16 presence of ABMR into their multivariate model. And 17 you can see that there was a three-fold increase risk 18 of graft failure in the presence of subclinical ABR. 19 And it's important to point out that this is also 20 independent of GFR and proteinuria, other strong 21 clinical factors that we use.</p> <p>22 So perhaps the absence of ABMR or the</p> | <p style="text-align: right;">Page 149</p> <p>1 Now here's another study from France looking 2 at the other C1s raised inhibitor and they didn't use 3 a score card, but they looked at components of the 4 Banff scoring system at entry into the trial and then 5 six months later.</p> <p>6 And you can see except for C4d there was 7 really no improvement in any of these histologic 8 components of the score card. But getting back to our 9 discussion on kidney function you can see that there 10 was a significant improvement in GFR despite any real 11 improvement in histology.</p> <p>12 So, again, suggesting that perhaps both of 13 these are using them somehow together would be the 14 better way to go.</p> <p>15 Here's the papers that we've seen from the 16 Mayo Group on the equilizumab trials. And, as you 17 recall, the primary outcome was just the occurrence of 18 ABMR using our standard diagnostic criteria.</p> <p>19 And as been discussed by others, these are 20 the long-term follow up that where maybe viewed as 21 being not as promising as we thought. But if you look 22 the occurrence of TG in the eck treated patients was</p> |

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| <p style="text-align: right;">Page 150</p> <p>1 45 percent and then the control group it was about 64 2 percent. 3 And this was not statistically significant, 4 but these are two also I would say fairly relatively 5 small numbers. And I think the trend anyways might be 6 that this is a promising therapy again suggesting that 7 TG may be a possible surrogate outcome to use. 8 Now what about the molecular microscope Dr. 9 Haas has given us an introduction to this? Are these 10 -- or could these be potentially used as valid 11 surrogate outcome measures? 12 So this is one of the original papers from 13 Phil Halloran's group where they took a bunch of 14 kidney biopsies and gave them conventional a diagnosis 15 using histology. And those are labeled along the X 16 axis. 17 And then they applied the micro array to the 18 biopsy samples and determined a classifier using 19 discriminate analysis which really is just a number 20 reflecting the probability that ABMR is operating in 21 the biopsy. 22 And you can see in this particular study</p> | <p style="text-align: right;">Page 152</p> <p>1 infrequent events together to allow sufficient sample 2 sizes. 3 But there's always caveats with composites. 4 And, first of all, is that the composites are often -- 5 the components are not of importance or the same 6 importance. So in our particular example is the 7 persistence of DSA really the same as graft loss if 8 you had those together in a composite. Probably not. 9 And you see this a lot in other fields of medicine. 10 Also the components may not occur with a 11 similar frequency. And it's often the less serious 12 one that occurs the most often. And this is really 13 common in the cardiology literature. If you look at 14 it there's often, you know, admission to the hospital 15 is the main thing driving it rather than mortality. 16 And then the final issue to think about is 17 this relative risk reduction. So really you want the 18 biology of all your components to be working in the 19 same direction so that they have similar relative risk 20 reductions. And really what the worst thing you want 21 is when they start going in the opposite direction. 22 So keeping that in mind just as we talk</p> |
| <p style="text-align: right;">Page 151</p> <p>1 they've chosen this cutoff of .2. And you can see 2 that the high ABMR scores are nicely clustering around 3 the histology of ABMR. And when using that threshold 4 they've got an excellent AUC in this particular study 5 of .89. 6 And Dr. Haas already showed the study so 7 I'll just go through it briefly. But basically they 8 used that scoring system in a whole new different 9 cohort of patients. And as was pointed out in a 10 previous talk the slides here -- or, sorry, the 11 (indiscernible) curves here of the blue and red one, 12 those are the patients that had the worst outcome. 13 These are the ones that were S positive so they had an 14 ABMR score that was positive and greater than .2. 15 And this was independent really of whether 16 there was histologic evidence of ABMR being present. 17 So perhaps this ABMR score could also be used as a 18 surrogate outcome measure. 19 I just want to touch briefly on composites 20 as I think this will be discussed by Dr. Irish in the 21 next talk. But really why do we use composite 22 endpoints? It's really so that we can combine</p> | <p style="text-align: right;">Page 153</p> <p>1 about composites this was a study that looked at the 2 -- I'll say the composite in a different way. This 3 was not a randomized controlled trial, but looking at 4 combining different areas to see if we can improve 5 prediction. 6 And what they did was they took our typical 7 clinical factors and added on histology data as well 8 as DSA data to see if they could improve prediction of 9 graft survival. 10 So, first of all, what they did was they 11 used this risk calculator on the left which uses GFR 12 and age and gender and typical things we would use 13 clinical factors to predict outcome. And it 14 calculates a five-year graft survival. 15 And what they did was this was created in a 16 different set and then applied. This was a large 17 group of patients from the Mayo Clinic. And you can 18 see that it performed very well in this second group 19 of patients. The AUC for the death censored graft 20 failure was .84 which was very good. 21 And what they then did was they added 22 histology into the model so they added the</p> |

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| <p style="text-align: right;">Page 154</p> <p>1 glomerulitis and chronic interstitial fibrosis scores. 2 And you can see that the C statistic improved quite 3 nicely from .84 to .9. Excuse me. 4 And then finally they added DSA to the model 5 and it really unfortunately didn't add much 6 prediction. But at least started the idea that if you 7 add histology in addition to our clinical factors this 8 may improve our clinical prediction. 9 Here's another paper using the ABMR score 10 from Halloran's group. And you can see here at the 11 time of treatment for ABMR if the score was positive 12 this was associated with a two-fold increase risk of 13 graft failure. 14 And the important thing of this is this is 15 independent of the humeral histologic score. So, 16 again, using the score in conjunction with histology 17 gave a better prediction of outcome and improved model 18 discrimination in this particular study from .77 to 19 .81 again suggesting that this composite of clinical 20 factors, histology, and the ABMR score may be a better 21 predictor of outcome and may be a better way to look 22 at endpoints.</p> | <p style="text-align: right;">Page 156</p> <p>1 within this population would be an important surrogate 2 to consider. 3 So which outcome measures should we use? 4 Well, I think it obviously depends on the type of 5 trial that we've -- we've been talking about different 6 trials, but is this a trial to prevent ABMR or are we 7 talking about a trial once someone already has 8 established ABMR and were going to treat it. Is this 9 an early event or is this in a late event, as well? 10 I've basically been focusing on 11 (indiscernible) what we always have to remember that 12 safety endpoints are going to be crucial in these 13 types of trials such as our overall infection rates 14 and cancer rates. 15 And I'm just going to give a couple of 16 examples really to stimulate discussion in the QA 17 period. And these are just opinions because none of 18 these have really been validated in any trials. 19 So this is a potential composite endpoint 20 that you could consider for a treatment trial. It 21 doesn't have to have all of these components, but 22 certainly these components are what I think are</p> |
| <p style="text-align: right;">Page 155</p> <p>1 Finally, I'm just going to touch on 2 proteinuria. There's a ton of literature in the non- 3 transplant population, but I'll just show you one 4 study recently published in a large cohort of 5 transplant patients where they measured proteinuria at 6 the time of a biopsy. 7 And you can see in that top box that 8 increasing the amounts of proteinuria as we know are 9 strongly associated with graft failure down the road. 10 And important in this trial was this was independent 11 of all the different histologic parameters they saw on 12 the biopsy at that time. 13 And it was also fairly discriminate. You 14 can see the ROC curve on the left with an AUC of .73 15 for the presence of proteinuria at one year and late 16 graft failure. 17 But I think interestingly the figure on the 18 right this is in the cohort of patients who had 19 transplant glomerulopathy. And you can see that 20 increasing the amounts of proteinuria within the 21 patients who had TG was strongly associated with graft 22 survival again suggesting that perhaps proteinuria</p> | <p style="text-align: right;">Page 157</p> <p>1 important. 2 Some functional outcome, histology outcome, 3 a molecular outcome, DSA outcome, and some damage or 4 proteinuria marker. So if we look back at our 5 functional outcome I think perhaps if we looked at a 6 greater than 30 percent eGFR decline and it's always 7 important to know when the start and end point is. 8 And I think it would be obviously the entry into the 9 trial is the start point and I think the convene time 10 would be one year following -- sorry, following 11 therapy to look at the functional decline throughout 12 that time period. 13 If we look at a histology outcome perhaps we 14 may want to look at -- and I'll just call them bad 15 features on the protocol biopsy at one year. And I 16 would let the pathologists work this out in a little 17 more detail, but we could look at persistence of 18 inflammation, persistence of C4d, or the presence of 19 TG. 20 I think the molecular score is very 21 interesting and perhaps the most novel edition to what 22 we've been talking about in the last few days. And</p> |

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| Page 158 | Page 160 |
| <p>1 perhaps the presence or persistence of positive ABMR</p> <p>2 score on a protocol biopsy could be a nice component</p> <p>3 to a composite endpoint.</p> <p>4 As far as DSA less than 50 percent reduction</p> <p>5 of DSA may be a surrogate, but also as was mentioned</p> <p>6 yesterday perhaps a more significant reduction or</p> <p>7 elimination would be something you want to look at.</p> <p>8 And then finally I put in proteinuria and I</p> <p>9 just picked an arbitrary cutoff. But I also stated</p> <p>10 that if TG was present because I think we only want to</p> <p>11 add proteinuria here if we can ascribe it to the TG</p> <p>12 because it doesn't make much sense if it's due to</p> <p>13 something else.</p> <p>14 And I do want to point out again that this</p> <p>15 is just an arbitrary selection of outcomes with a</p> <p>16 bunch of arbitrary cutoffs. But what we need to do as</p> <p>17 a community I think is start measuring similar</p> <p>18 outcomes pre and post-treatment to see what is</p> <p>19 responsive and what is predictive similar to what Dr.</p> <p>20 Woodle's paper did when he looked at the change in</p> <p>21 that composite score following an intervention. I</p> <p>22 think that's where we really need to start measuring</p> | <p>1 measures involving these surrogates in my opinion will</p> <p>2 be necessary for ABMR trials. And likely candidates</p> <p>3 that I've gone through are GFR, histology, molecular</p> <p>4 transcripts, DSA, and proteinuria, and some</p> <p>5 combinations of these.</p> <p>6 Validation of the endpoints will need to</p> <p>7 occur and we need to begin measuring these outcomes</p> <p>8 before and after treatments. And finally long-term</p> <p>9 follow up will be needed for all ABMR trials using</p> <p>10 surrogates to evaluate their eventual effect on hard</p> <p>11 clinical endpoints such as graft survival.</p> <p>12 Thank you for your attention.</p> <p>13 DR. MANNON: Thanks, Greg, in particular for</p> <p>14 putting in so much information in the allotted time.</p> <p>15 Our next speaker is Dr. William Irish will be talking</p> <p>16 about performance of clinical trials and low incidence</p> <p>17 conditions.</p> <p>18 DR. IRISH: So how do you advance this? Oh,</p> <p>19 yeah. Okay. Thank you. So today I'm going to spend</p> <p>20 a little bit of time talking about scientific</p> <p>21 challenges and study design considerations of studies</p> <p>22 in low incidence and rare conditions.</p> |
| Page 159 | Page 161 |
| <p>1 these.</p> <p>2 So here's a potential endpoint that we may</p> <p>3 want to use in a prevention trial and it has a lot of</p> <p>4 the same sort of themes. But I think as far as</p> <p>5 prevention obviously I think just the diagnosis of</p> <p>6 clinical ABMR would be enough as a key part of that</p> <p>7 diagnosis.</p> <p>8 Then we could look at, again, some bad</p> <p>9 features on a protocol biopsy, the molecular score,</p> <p>10 from a DSA perspective perhaps the development of a</p> <p>11 de-novo DSA would be important, and, again, some</p> <p>12 proteinuria or damage marker.</p> <p>13 So to summarize, I think it's difficult to</p> <p>14 use patient-important outcome such as graft survival</p> <p>15 alone in ABMR trials given the sample size required to</p> <p>16 show realistic treatment effects.</p> <p>17 Surrogate endpoints are commonly used in</p> <p>18 renal transplant trials especially measures of GFR.</p> <p>19 And while convenient from a sample size and a power</p> <p>20 perspective most of the surrogates are not well</p> <p>21 validated.</p> <p>22 Surrogate outcomes, though, and composite</p> | <p>1 So just by way of disclosure I'm a full-time</p> <p>2 employee of CTI, and international contract research</p> <p>3 organization. And by way of further disclosure I'm a</p> <p>4 statistician by training. And so I'm going to discuss</p> <p>5 these issues from a statistical perspective.</p> <p>6 And as the cartoon says, statisticians</p> <p>7 aren't always right. And I think my wife would agree</p> <p>8 with that one.</p> <p>9 So scientific challenges. So there are very</p> <p>10 few epidemiologic studies describing the occurrence of</p> <p>11 AMR and reporting incidence varies. And we've seen</p> <p>12 that depending on, for example, different diagnostic</p> <p>13 criteria at the local practice center level, different</p> <p>14 patient populations studied which is really a</p> <p>15 reflection of geographic regions. And this presents a</p> <p>16 challenge when designing a clinical trial.</p> <p>17 Studies of AMR require multicenter, multi-</p> <p>18 country participation that have inherently different</p> <p>19 healthcare systems, treatment options, and management</p> <p>20 approaches.</p> <p>21 And coupled with that is the type of study</p> <p>22 or the intended indication. And Dr. Knoll sort of</p> |

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| <p style="text-align: right;">Page 162</p> <p>1 discussed that whether it's prevention or whether it's 2 for treatment both are potentially hindered unless 3 there's a crystal clear on the diagnosis or resolution 4 following treatment. 5 And there are regulatory challenges. For 6 example, the choice of endpoints, the choice of 7 comparative group. This is a very complex question 8 and it may be an eliminating step. 9 For one, how do you get subjects to 10 participate and enrolled if there's potential for 11 harm? 12 The use of historical controls. This 13 requires access to reliable, valid data. And temporal 14 bias is always an issue especially in a disease area 15 where management practices are constantly evolving. 16 And sample size. We need a sufficient 17 number of subjects to show a treatment effect with a 18 certain level of power. And this is a question I get 19 asked constantly. How many subjects do I need? 20 So looking at the incidence of AMR so this 21 table is based on a brief lit review that I performed. 22 And we see that a lot of this data is investigator-</p> | <p style="text-align: right;">Page 164</p> <p>1 creative ways that we can look at the data 2 analytically, but for the remainder of this talk I'm 3 going to talk about the design stage. 4 And so, for example, there are enrichment 5 strategies. These are used to decrease variability 6 and maximize power. Adaptive designs. Making planned 7 well-defined changes in key clinical trial design 8 parameters as data accumulates. And willingness of 9 the regulatory agency to consider the creative use of 10 surrogate and composite endpoints that were discussed 11 in the previous -- previous talk. 12 And these strategies are not necessarily 13 mutually exclusive. For example, we can use an 14 adapted design to change the enroll- -- the enrichment 15 strategy or we can incorporate phase in methods to 16 help guide decisions. For example, dull selection, 17 sample size re-estimation, futility, or assessment of 18 a biomarker's predicted probability of response. 19 So I'm going to talk about these -- some of 20 these issues in more detail in the next series of 21 slides. 22 So enrichment strategies. Have I picked a</p> |
| <p style="text-align: right;">Page 163</p> <p>1 specific which creates a problem. 2 The best that could be said is that AMR 3 occurs after transplant and the occurrence depends on 4 pre-transplant amino status, post-transplant 5 diagnostic criteria, and type of AMR be investigated. 6 And this is an important issue and this has 7 been discussed at length when designing a study. AMR 8 is not an it, AMR is a they. 9 So let's, for the moment, assume that we're 10 investigating the same AMR. So based on my lit review 11 I calculated the incidence of AMR at one year post- 12 transplant to be approximately 9 percent. This is a 13 weighted average based on sort of a non -- a random 14 effects model. 15 If we assume treatment reduces AMR by 50 16 percent and we need -- we need approximately 478 -- 17 487 subjects for a group with 80 percent power. Now 18 this is a big trial. A study of this magnitude would 19 take years to enroll even with a large number of 20 centers. 21 So to overcome these challenges we need 22 creative strategies at the design stage. There are</p> | <p style="text-align: right;">Page 165</p> <p>1 population that's most likely to be able to show an 2 affect? So this is a very important question. 3 The main reason for enrichment is study 4 efficiency. Increasing the chance of success often 5 with a smaller sample size. 6 So one approach to enrichment is to decrease 7 heterogeneous 80, so include subjects that have 8 certain characteristics that put them at risk. But we 9 need to be careful with this approach. It may require 10 a long time to recruit if the study population is too 11 narrowly defined. And this could potentially impact 12 the type of AMR and subsequently the incidence rate. 13 Exclusion criteria is relatively 14 straightforward, but that depends on whether the 15 indication is for treatment or for prevention. 16 Prognostic enrichment. Here we want to 17 select subjects with a greater likelihood of 18 occurrence of an event like AMR or substantial 19 worsening of a continuous measurement like change in 20 eGFR. 21 So this approach increases the absolute 22 difference between the treatment groups, but will not</p> |

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| <p style="text-align: right;">Page 166</p> <p>1 alter the relative effect. And the characteristic or 2 measurement process, for example, a biomarker, needs 3 to be validated and agreed to by the regulatory 4 agency. 5 So here's an example. Could DSA relative 6 intensity scale be used as a viable prognostic 7 enrichment strategy? So this data's based on results 8 that were published in 2015 in transplantation. 9 So the figure on the right suggests good 10 discrimination with an AUC of 79 percent although the 11 DSA relativity intensity scale is much more variable 12 in patients with AMR based on the figure on the left- 13 hand side. Since this data is based on a single 14 center it's not clear how this association would 15 translate to other centers. 16 What about pre-transplant HLA DSA level? So 17 this figure based on data that was published in 2010 18 suggests a positive correlation of peak pre-transplant 19 DSA level and risk of AMR. Oh, sorry. So here we're 20 looking -- we have this gradient in terms of the DSA 21 and we have this nice linear relationship in terms of 22 the risk of AMR.</p> | <p style="text-align: right;">Page 168</p> <p>1 So this higher event rate, and this is in 2 figure -- figure 1, translates to a lower sample size 3 for a clinical trial depicted in figure 2, which can 4 have both practical and ethical advantages. 5 The benefits of this strategy, however, 6 needs to be weighed against the cost of screening and 7 recruitment, et cetera. And for those that are 8 interested, the simulation was conducted using the 9 bio-PET program Nr. 10 Predictive enrichment is another -- is 11 another option. So with this strategy we choose 12 subjects more likely to respond to treatment. I.E., 13 these are probable responders. 14 So the advantage of predictive enrichment is 15 depicted in this table and this is based on results of 16 a talk by Dr. Temple in 2014. So here if 25 percent 17 of patients have the biomarker that predicts the 18 effect and marker negative patients have no response, 19 an unselected population would need 16 times as many 20 patients. 21 Even if 50 percent of negative marker 22 patients have a response, an unselected population</p> |
| <p style="text-align: right;">Page 167</p> <p>1 So ideally if we have a reliable, validated 2 biomarker that can predict the relevant type of AMR be 3 it DSA relative intensity scale or the pre-transplant 4 DSLA -- DSA level or the Banff CG score, we can have a 5 study with a reasonable number of subjects. 6 For example, to show a 50 percent relative 7 reduction in AMR with treatment if we enrich so that 8 we have a background rate of AMR 50 percent, then all 9 we need is 58 subjects per group as opposed to 487 10 subjects per group without enrichment. So that's an 11 88 percent reduction in the number of subjects 12 required for the same power. 13 So this is a hypothetical example of the 14 potential benefit of a prognostic enrichment strategy 15 using a simulation program Nr. So the idea is to 16 enrich the study population with patients that have 17 increased likelihood of AMR based on a biomarker. 18 So in this example I'm using the peak 19 transplant DSA level. So this enrichment strategy is 20 based on the ability of pre-transplant DSA to 21 distinguish between AMR and no AMR which is summarized 22 by the area under the ROC curve which is .9.</p> | <p style="text-align: right;">Page 169</p> <p>1 would require almost three times as many subjects. 2 And, again, the key issue here is having a valid 3 biomarker. 4 So this is a schematic representation of an 5 adapted two-stage population enrichment design. This 6 was published in the New England Journal of Medicine. 7 So the idea here is the population is stratified 8 before randomization into two sub groups, S and S 9 prime according to some binary biomarker like the 10 presence of DSA pre-transplant. 11 An interim analysis occurs when a specified 12 number of patients -- this is denoted a N-not in this 13 figure -- have been enrolled in each sub group. At 14 that time there'll be a specific number of event in 15 each -- into each group, AMR events in sub group S, 16 for example, AMR events in sub group S prime. 17 So the data are analyzed at this interim 18 juncture and the trial may be terminated for futility, 19 continued as planned, or continued by enrolling 20 patients only in sub group S. 21 In this design there's a biological basis 22 for assuming that the biomarker may have predictive of</p> |

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| <p style="text-align: right;">Page 170</p> <p>1 response in sub group S but not in sub group S prime. 2 And the purpose of the interim analysis is to verify 3 this assumption if it's true. And, if so, to enrich 4 the remainder of the trial with patients with sub 5 group -- with the sub group S only. 6 The randomized withdrawal study this is an 7 example of a predictive enrichment strategy. So in 8 this design all subjects receive active treatment for 9 a specified period of time. All subjects who respond 10 are then randomized to continue treatment or to 11 placebo. So they're withdrawn off treatment. 12 And any difference emerges between the group 13 receiving continued treatment and the group randomized 14 to placebo would demonstrate the effect of the active 15 treatment. So this is sort of the general schematic 16 representation of a randomized withdrawal study. 17 So this is actually a unique design. This 18 is a schematic representation of a three-stage study 19 design that was published in Statistics of Medicine. 20 Not too sure if you can see this clearly. 21 So this unique design has three stages. 22 Stage one consists of an ordinary, randomized,</p> | <p style="text-align: right;">Page 172</p> <p>1 efficacy. So you can -- you can use sort of an 2 adaptive design within this -- within this trial 3 design schematic. 4 So the benefit of this type of design 5 however needs to be weighed with any sort of 6 logistical issues, recruitment, length of follow up, 7 et cetera. 8 And what's nice about this is that the 9 statistical sort of operational characteristic, the 10 validity of this design was studied extensively in 11 this paper. 12 So biomarkers and surrogate endpoints -- and 13 we had a really nice discussion earlier about 14 biomarkers and potential surrogate endpoints. And, as 15 discussed, a surrogate is a biomarker that's used as a 16 substitute for a clinical endpoint and is expected to 17 predict clinical benefit. 18 And there are three key questions one needs 19 to ask. Is the biomarker able to accurately and 20 precisely be accurately and precisely measured? So 21 this is sort of analytical validation. 22 Is the biomarker associated with the</p> |
| <p style="text-align: right;">Page 171</p> <p>1 placebo-controlled trial. Patients who responded to 2 treatment in stage one are subsequently randomized to 3 continue treatment or placebo or withdrawn in stage 4 two. 5 While patients who did not respond to 6 placebo, non-responders in stage one, are placed on 7 after treatment and the responders are then randomly 8 assigned a treatment, continue therapy or placebo 9 withdrawn. 10 So these sort of three-stage study designs 11 are denoted by the rectangular boxes in this figure. 12 And if we take the P values from stage one, the P 13 values from stage two, and the P values from stage 14 three these are combined statistically to test the 15 overall efficacy of treatment. 16 So for studies of rare events like an AMR 17 where patient numbers are limited this three-stage 18 clinical trial design may be a more powerful design 19 option than the traditional randomized trial for 20 conducting a clinical benefit. 21 What's nice about the design you can 22 incorporate stopping rules for futility or for</p> | <p style="text-align: right;">Page 173</p> <p>1 clinical endpoint? This is qualification. 2 And what is the specific context of 3 biomarker use? So this is sort of the utilization of 4 it. 5 And in 2015 an FDA workshop was conducted to 6 discuss surrogate endpoints and biomarkers in kidney 7 transplantation. And Dr. Knoll summarized some of the 8 potential endpoints in his earlier talk. 9 But here is just a few examples of potential 10 surrogate markers in AMR and these can be used for 11 preventative and treatment trials. But, again, more 12 studies are needed to sort of validate their clinical 13 benefit. 14 So what about composite endpoints? What if 15 we combine these composite -- composite surrogate 16 endpoints, would this work? 17 So when planning a trial with a composite 18 endpoint one should ask does the composite endpoint 19 really measure a disease? 20 Does the use of a composite endpoint solve a 21 medical problem or is it just for statistical 22 convenience?</p> |

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| Page 174 | Page 176 |
| <p>1 Are the individual components of the</p> <p>2 composite endpoint valid biologically plausible and of</p> <p>3 importance for patients?</p> <p>4 Are the results clear and clinically</p> <p>5 meaningful?</p> <p>6 Do they provide a basis for therapeutic</p> <p>7 decisions?</p> <p>8 And does each single endpoint support the</p> <p>9 overall result?</p> <p>10 And, importantly, is the statistical</p> <p>11 analysis of the composite endpoint valid? Is it</p> <p>12 adequate?</p> <p>13 So this figure sort of illustrates one</p> <p>14 reason why a biomarker in general could be of</p> <p>15 correlative clinical benefit, yet might not be a valid</p> <p>16 surrogate.</p> <p>17 First, there are usually multiple pathways</p> <p>18 through which the disease process influences the risk</p> <p>19 of the clinical efficacy endpoints. If the proposed</p> <p>20 surrogate endpoint lies in only one of these pathways</p> <p>21 and if the intervention does not affect -- actually</p> <p>22 affect all pathways, then the effective treatment on</p> | <p>1 on the same -- all need to be on the same page.</p> <p>2 An acceptance of biomarkers as well as</p> <p>3 creative or non-traditional endpoints is another</p> <p>4 solution. Alternative trial design such as the</p> <p>5 adapted designs.</p> <p>6 And these designs are complex both</p> <p>7 statistically and logistically so there needs to be a</p> <p>8 certain level of education in the transplant</p> <p>9 community. And perhaps this could be done via the</p> <p>10 ATC.</p> <p>11 Lastly, leveraging existing resources. For</p> <p>12 example, transplant registries or individual level of</p> <p>13 clinical trial data. So pooling individual level of</p> <p>14 data could help inform clinical trial designs into a</p> <p>15 value -- to evaluate and validate potential biomarkers</p> <p>16 and surrogate endpoints. So I'll leave it at that.</p> <p>17 DR. BALA: Thank you, Dr. Irish. Our next</p> <p>18 speaker is Dr. Anita Chong from University of Chicago.</p> <p>19 And she'll talk about animal models in AMR, how can</p> <p>20 they inform clinical studies.</p> <p>21 DR. CHONG: Okay. I want to start by</p> <p>22 thanking the organizers, especially for not putting me</p> |
| Page 175 | Page 177 |
| <p>1 the clinical efficacy standpoint could be over or</p> <p>2 underestimated by the effect on the surrogate</p> <p>3 endpoint.</p> <p>4 Second, the intervention, itself, could have</p> <p>5 mechanism of actions that are independent of its</p> <p>6 intended effects on the disease process. So this was</p> <p>7 discussed in the 2015 workshop and was discussed at</p> <p>8 length by Dr. Flemming.</p> <p>9 So just in summary, the therapeutic</p> <p>10 development AMR presents many challenges. There's a</p> <p>11 need for alternatives to the traditional randomized</p> <p>12 control trial, for example, an adaptive design. Need</p> <p>13 for more creative outcome measures. Perhaps some non-</p> <p>14 biological measures such as quality of life which was</p> <p>15 alluded to or quality adjusted life years.</p> <p>16 Difficulties of recruiting a control group. And this</p> <p>17 may depend in part on the type of study whether it's</p> <p>18 for prevention or for treatment.</p> <p>19 And the solution requires multi-</p> <p>20 collaboration among stakeholders including the</p> <p>21 transplant community, sponsors, regulatory agency, and</p> <p>22 I might add specifically statisticians all need to be</p> | <p>1 as the final speaker. That honor is for Dr. Knechtle.</p> <p>2 Okay. All this work in mice are the work of</p> <p>3 post-doctoral fellows and students in my laboratory.</p> <p>4 And the clinical work is done in collaboration</p> <p>5 actually completely by Dr. Ron Pelletier at Ohio State</p> <p>6 University.</p> <p>7 I have no conflict of interests to declare,</p> <p>8 but there is some off label use from (indiscernible)</p> <p>9 by Dr. Pelletier's studies.</p> <p>10 Okay. As you have heard today and yesterday</p> <p>11 that there has been a lot of work trying to target</p> <p>12 antibody mediated rejection. And I think that these</p> <p>13 strategies can be categorized into those that target</p> <p>14 the early prevention of antibodies using a lot of the</p> <p>15 conventional immunosuppression and also a lot of</p> <p>16 interesting limiting antibody mediated damage that has</p> <p>17 been extensively discussed by Dr. Woodle earlier</p> <p>18 today.</p> <p>19 But I think that there is actually a sweet</p> <p>20 spot and a Goldilocks phase where the ability to</p> <p>21 target and stop ongoing antibody production. And</p> <p>22 there are some approaches that may perhaps be used to</p> |

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| <p style="text-align: right;">Page 178</p> <p>1 be considered as targeting this, but these are pretty 2 I think straightforward. The use of IVIG, depleting 3 B-cells, depleting plasma cells.</p> <p>4 But I think that none of these strategies 5 really leverage the huge amount of information that 6 we're gathering and we're understanding of this phase 7 of this B-cell expansion in the germinal center where 8 B-cells proliferate extensively, undergo class 9 searching, undergo somatic hyper mutation so that they 10 generate high affinity antibody cells, release the 11 cells from the germinal center as antibody secreting 12 cells as well as memory B-cells.</p> <p>13 And so our goal in starting these mouse 14 studies was to develop a therapy at least in mice for 15 treating ongoing B-cell responses and plasma cells 16 responses that result in a rapid depletion of antibody 17 responses and long-term suppression.</p> <p>18 So when we started our studies about five 19 years ago there was a rationale for using and starting 20 with CTLA4 IG. That the high affinity mutant 21 belatecept was approved for kidney transplantation.</p> <p>22 And while we knew that there was a slightly</p> | <p style="text-align: right;">Page 180</p> <p>1 concerned about the antibodies binding to the graft 2 and kind of delaying the appearance of antibodies in 3 the serum.</p> <p>4 And so with CTLA4 IG as we expected if you 5 start treatment continuously twice a week from the day 6 of immunization you saw strong inhibition of the 7 antibody responses.</p> <p>8 If we waited till seven days after 9 immunization when we could already see a significant 10 increase in DSA, we found that when you start 11 treatment within a week the antibody increase is 12 immediately halted.</p> <p>13 And then the third what we did was to treat 14 from day 14. And you can see that this -- when we 15 start treatment on day 14 we could no longer inhibit 16 that antibody response illustrated in blue.</p> <p>17 So there could be two reasons for why this 18 very delayed day 14 CTLA4 treatment fails. Firstly, 19 it's because the late germinal center B-cell response 20 has now become resistant to CTLA4 IG or, secondly, 21 that the germinal center B-cells had already exported 22 antibody secreting cells and that these cells were</p> |
| <p style="text-align: right;">Page 179</p> <p>1 higher rate of acute rejection, the salutary effects 2 on antibody was not apparent at that time. However, 3 in mouse models there were some data to suggest that 4 blocking another co-stimulation pathway with anti-cd- 5 154 can be used and was successfully used to disrupt 6 established germinal center B-cell responses.</p> <p>7 However, because we know that CTLA4 IG not 8 only inhibits the cd-28 co-stimulatory pathway, but it 9 can also inhibit the co-inhibitor or checkpoint 10 pathway. And there was a possibility that the use of 11 CTLA4 IG, especially late in the antibody response, 12 may actually be enhancing the antibody responses as 13 opposed to inhibiting it.</p> <p>14 And so the first series of experiments we 15 did were really simple. We wanted to delay CTLA4 IG 16 and see how late we could -- for what were the effects 17 of delay CTLA4 IG on inhibiting and ongoing antibody 18 responses.</p> <p>19 And so in the mouse, a B6 mouse, what we did 20 was immunized with a BALB/c spleen cell donor-specific 21 transfusion. And this allows the antibody responses 22 to be accurately measured and we didn't have to be</p> | <p style="text-align: right;">Page 181</p> <p>1 then resistant to CTLA4 IF.</p> <p>2 And so to be able to address these two 3 possibilities we develop a technique to track allo- 4 specific B-cells that was described in brief by Dr. 5 Gebel yesterday. And we used a double -- double 6 fluorochrome single tetramer approach because we know 7 from the observations by Mark Jenkin's Group in 8 Minnesota that there is a very large population of B- 9 cells that can actually recognize the fluorochrome.</p> <p>10 And while this does not completely eliminate 11 other components of the tetramer that the B-cells are 12 -- may be recognizing, it's significantly enriched for 13 the MHC-specific B-cells.</p> <p>14 And the flow plots for gating these cells, 15 especially for gating the germinal center B-cells 16 which express fast and GL7 illustrated below.</p> <p>17 So then what we did was a very similar 18 experiment is we -- as I've previously described which 19 was to treat CTLA4 with CTLA4 IG either from day zero 20 to day 7 or from day 7 to day 14 and day 14 to day 21 21 and then the mice were sacked at those indicated days.</p> <p>22 And in each time point that we treated with</p> |

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| <p style="text-align: right;">Page 182</p> <p>1 CTLA4 we observed a significant decrease in the number 2 of tetramer positive, so allo-specific germinal center 3 B-cells whether you treated them from day zero or day 4 21. So the germinal center even at the late stage 5 remains susceptible to collapse in the presence of 6 CTLA4 IG. 7 So which allowed us to conclude that it's 8 likely that the reason for why CTLA4 IG starting on 9 day 14 fails to reduce the DSA levels was because the 10 germinal center had already exported the antibody 11 secreting cells. 12 The other export cells from this germinal 13 center is memory B-cells. And certainly it's clear 14 that if you can inhibit germinal center B-cells it's a 15 good thing for transplant. 16 So what we did was use the same B6 model, 17 however, we were -- we used this -- a mouse that could 18 report on B-cells that had entered the germinal 19 center. And these are B-cells that then activate the 20 enzyme cited in deaminase which is AID cre. 21 And so when the B-cells enter this germinal 22 center they turn on the expression of XYFP and we can</p> | <p style="text-align: right;">Page 184</p> <p>1 CTLA4 IG at least from day 7 post immunization 2 inhibits -- significantly inhibits allo-reactive 3 memory B-cell generation. 4 And more importantly we also show that if 5 you delay CTLA4 treatment till day 6 post-heart 6 transplantation in the model of BALB/c to be six mice, 7 which is the full MHC mismatch system and in which the 8 hearts are completely stopped beating on day 8. 9 And so you can see that by day 6 post- 10 transplantation there is significant C4d deposition as 11 well as T-cell infiltration in the grafts. And in 12 this case we can show again that the delayed treatment 13 of CTLA4 IG can reverse -- or can inhibit and collapse 14 the germinal center response. 15 Such that if you look at the data here which 16 focuses on class one specific germinal center B-cells 17 in the absence of any treatment the germinal center B- 18 cells increases from day 6 to day 14; however, if you 19 treat them from day 6 to day 14 with CTLA4 IG the 20 germinal center B-cell numbers are completely 21 collapsed. 22 Importantly, this is also associated with a</p> |
| <p style="text-align: right;">Page 183</p> <p>1 detect these cells and enumerate these cells. And, in 2 particular, the B-cells that are donor-specific. And 3 in this case instead of using the class one donor- 4 specific tetramer we validated and are using a class- 5 two specific tetramer system. 6 And what we find is that in mice that are 7 sensitized with this BALB/c spleen cells you can see 8 that by day 43 there is a significant increase in the 9 total number of memory B-cells. 10 And when you treat the mice with day 7 with 11 CTLA4 IG you can see that this memory frequency of 12 cells is significantly decreased. Whereas if you 13 treat them on day 14, then the memory numbers are not 14 significantly different from the untreated controls. 15 And these differences in memory B-cells of 16 significant because if you then challenge these mice 17 after stopping CTLA4 IG for two weeks with a secondary 18 challenge of BALB/c spleen cells you can see that the 19 DSA levels that we see in the absence of CTLA4 in this 20 rechallenge mirror the frequencies of these memory B- 21 cells. 22 So allowing us to conclude that the delayed</p> | <p style="text-align: right;">Page 185</p> <p>1 significant prolongation and treatment of acute 2 rejection such that about -- about 60 percent of the 3 grafts go on to survive long term with treatment under 4 CTLA4 IG starting from day 6. 5 And if you look at the hearts that are 6 sacrificed on day 60, you can see that there is a 7 significant reduction in the amount of complement 8 deposition in these grafts. 9 And importantly as an additional control if 10 we add that hyper immune serum to these mice that were 11 treated with CTLA4 IG we abrogate a lot of the effects 12 of CTLA4 IG. 13 Okay. Thank you. Okay. Then the last 14 experiment that we wanted to do was what happens -- 15 what is the effect of CTLA4 in fully-sensitized 16 recipients? 17 And so in these experiments what we first -- 18 what we did was to sensitize the recipients with 19 BALB/c spleen cells and then wait 10 to 20 weeks later 20 and then we transplant these mice with BALB/c hearts. 21 And then we analyze initially the quality of 22 the memory recall response. And if you remember in a</p> |

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| <p style="text-align: right;">Page 186</p> <p>1 primary B-cell response the majority of the B-cells 2 enter a germinal center response. And it's in that 3 reaction where there's significant proliferation of 4 the B-cells in class switching and affinity 5 maturation.</p> <p>6 However, in a memory response we see very 7 little germinal center response as illustrated in this 8 figure. In contrast, what we find is that there is a 9 rapid differentiation of the memory B-cells into 10 antibody secreting cells independently of the germinal 11 -- a strong germinal response.</p> <p>12 And you can see it here in an elispot assay. 13 This is an elispot assay that quantifies the number of 14 antibody secreting cells that are specific to donor 15 class one molecule KD.</p> <p>16 And this is illustrated here in numerically 17 that you see that there is a very strong increase in 18 the total number of antibody secreting cells in -- 19 upon heart transplant in a sensitized animal and that 20 this response is very quick and also very rapidly 21 reduced.</p> <p>22 We show that if you treat these mice,</p> | <p style="text-align: right;">Page 188</p> <p>1 exported short-live antibody secreting cells. And so 2 we reasoned that if we combined CTLA4 IG with 3 bortezomib as you've heard previously that this would 4 be a reasonable protocol to rapidly reduce antibody 5 secretion and sustain long-term inhibition of antibody 6 responses.</p> <p>7 And so to this -- to test this very briefly 8 in a mouse model what we did was to do to indeed 9 immunize mice with BALB/c and then wait before we 10 start treatment with CTLA4 IG 14 days after the 11 immunization either alone or with bortezomib along 12 given two doses or bortezomib in combination with 13 CTLA4 IG.</p> <p>14 And you can see that the combination group 15 was significantly better at reducing antibody titers 16 at 14 days later compared to the monotherapy group.</p> <p>17 And importantly we also what we did was to 18 challenge these mice with a secondary immunization and 19 then in the mice that were treated with CTLA4 IG we 20 continued that treatment.</p> <p>21 And we showed that in the bortezomib group 22 which was only given two doses on day 14 and day 16</p> |
| <p style="text-align: right;">Page 187</p> <p>1 sensitized mice, with CTLA4 IG that it completely 2 abrogates the antibody differentiation and the total 3 number of antibody secreting cells that you can 4 recover from the spleen. It inhibits total DSA 5 responses which is illustrated in the next graph. 6 And, importantly, it prolongs graft survival with 7 CTLA4 IG alone in these sensitized recipients.</p> <p>8 So collectively these mouse studies show us 9 that CTLA4 IG is indeed an unexpectedly potent 10 inhibitor of germinal center and memory B-cell 11 responses. And that it can affect -- it can collapse 12 an ongoing germinal center and importantly it can also 13 inhibit memory B-cell reactivation in differentiating 14 into antibody secreting cells.</p> <p>15 And I think that these data are in 16 retrospect very congruent to the clinical observations 17 reported recently by Vincenti, et al., that despite an 18 increase in the frequency of acute rejection the 19 antibody titers are significantly reduced compared to 20 calcineurin controls.</p> <p>21 But what -- as I mentioned earlier, what 22 CTLA4 cannot do is inhibit antibody production by the</p> | <p style="text-align: right;">Page 189</p> <p>1 these mice responded in the secondary response very 2 comparably to the untreated animals. Whereas mice 3 that were maintained on CTLA4 IG did not respond to 4 the secondary immunization.</p> <p>5 So with this in mind we started a 6 collaboration with Dr. Ron Pelletier who's a 7 transplant surgeon at Ohio State with the hypothesis 8 that belatacept in combination with velcade would be 9 effective at inhibiting or controlling acute AMR.</p> <p>10 And so this is an institution in which the 11 standard of care is ATG induction, everolimus, neural, 12 and a rapid one-week steroid taper.</p> <p>13 So after I visited his institution about a 14 month or so later in 2015 Ron -- Dr. Pelletier 15 encountered this first patient who was a 39-year-old 16 male receiving his third kidney transplantation. So 17 this is a highly sensitized patient, but did not have 18 DSA.</p> <p>19 This patient had graft failure 12 hours 20 after post-transplantation and was -- DSA was detected 21 about 11 days post-transplantation. And then a 22 positive acute AMR biopsy was proven about day 18</p> |

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| <p style="text-align: right;">Page 190</p> <p>1 post-transplantation.</p> <p>2 He started treatment with belatacept about</p> <p>3 day 18 post-transplantation together with velcade</p> <p>4 treatment. Two treatments day 26 and day 35 post-</p> <p>5 transplantation. And what he saw was that there was a</p> <p>6 rapid decrease in donor-specific class one as well as</p> <p>7 class two. And that these titer remain suppressed for</p> <p>8 over a year. I think this particular patient is a</p> <p>9 year and a half post-transplantation.</p> <p>10 So I see that I'm running out of time so I</p> <p>11 won't go -- but the second patient he treated had very</p> <p>12 similar reduction and maintenance in long-term</p> <p>13 survival. And he has now five patients with exactly</p> <p>14 the same course of clinical outcomes.</p> <p>15 So I want to conclude by saying that animal</p> <p>16 models can inform on clinical trials but that there</p> <p>17 are certain limitations and future directions for us.</p> <p>18 We don't know what -- whether the effects of CTLA4 IG</p> <p>19 on B-cells are unique to CTLA4 IG or can be</p> <p>20 recapitulated with other immunosuppressive drugs.</p> <p>21 We don't have a very good model of chronic</p> <p>22 antibody rejection so we don't understand the</p> | <p style="text-align: right;">Page 192</p> <p>1 So that is matched by a new opportunity due</p> <p>2 to many new drugs that target C-cells, plasma cells,</p> <p>3 or cytocons. And what I hope to talk to you about is</p> <p>4 the value of animal models for helping us understand</p> <p>5 mechanisms of the allo B-cell response and antibody</p> <p>6 activation and B-cell maturation.</p> <p>7 Models that hopefully can guide us in</p> <p>8 developing a rational approach toward the application</p> <p>9 of novel drugs to this challenging clinical problem.</p> <p>10 So the goals of the non-human primate models</p> <p>11 that we have used in our laboratory are to try to</p> <p>12 mimic human HLA sensitization and antibody mediated</p> <p>13 rejection. This is a challenging problem.</p> <p>14 We're able to measure it in monkeys a</p> <p>15 positive cross match to class one and class two</p> <p>16 antigen. And the histology of antibody mediated</p> <p>17 rejection in the monkey models closely parallels that</p> <p>18 that is seen in humans.</p> <p>19 And Bob Colvin and the group at Mass General</p> <p>20 also working with cynomolgus monkey models have</p> <p>21 demonstrated very elegantly the very close parallels</p> <p>22 between non-human primate and human renal allograft to</p> |
| <p style="text-align: right;">Page 191</p> <p>1 processes and, therefore, what would be the best drug</p> <p>2 combination for acute versus chronic rejection. And</p> <p>3 certainly I think it's very important we don't have a</p> <p>4 good model for belatacept or CTLA4 resistant T-cell</p> <p>5 mediated rejection.</p> <p>6 So with that thank you for your attention.</p> <p>7 DR. MANNON: We're running a few minutes</p> <p>8 behind, but our last speaker is Dr. Stuart Knechtle</p> <p>9 from Duke University. He'll be talking about animal</p> <p>10 models that are pre-sensitized.</p> <p>11 DR. KNECHTLE: Well, thank you to the</p> <p>12 organizers for including me in the program and thank</p> <p>13 you all. You're either very curious, very polite, or</p> <p>14 adherent to FDA policy for being here so thank you.</p> <p>15 So we've all heard at this excellent</p> <p>16 conference over the last couple of days that we lack a</p> <p>17 reliable, durable therapy for antibody mediated</p> <p>18 rejection. We have difficulty desensitizing patients</p> <p>19 to allow them to be successfully transplanted.</p> <p>20 And although we have some therapies, we</p> <p>21 really don't know how to treat do-novo DSA and how to</p> <p>22 -- what guides our therapy.</p> | <p style="text-align: right;">Page 193</p> <p>1 pathology.</p> <p>2 We want this non-human primate monkey to be</p> <p>3 a robust model that's actually challenging. We don't</p> <p>4 want it to -- the challenge of some of our research,</p> <p>5 of course, in rodent models is that it sometimes</p> <p>6 doesn't translate or predict what happens in humans.</p> <p>7 And since non-human primates are about 97 percent</p> <p>8 identical to humans there tends to be a much greater</p> <p>9 parallelism. And, in addition, many of the human</p> <p>10 drugs and reagents developed only work in either</p> <p>11 humans or, in most cases, non-human primates.</p> <p>12 I actually backed into this area. Antibody</p> <p>13 mediated rejection is a long-standing interest of</p> <p>14 mine, but I backed into this because I spent a fair</p> <p>15 bit of time studying T-cell depletion with either</p> <p>16 alemtuzumab in humans or CD3 immunotoxin in monkeys.</p> <p>17 And we demonstrated and Doug Bloom in</p> <p>18 Wisconsin wrote a paper showing that homeostatic</p> <p>19 repopulation happens when you deplete T-cells</p> <p>20 profoundly and that there is a compensatory activation</p> <p>21 of a B-cell response associated with a high BAFF</p> <p>22 level.</p> |

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| <p style="text-align: right;">Page 194</p> <p>1 And so allo-antibody is an accompanying 2 problem typically when you're using profound T-cell 3 depletion. And Jenny Kim Page is the first author on 4 this first of our models in monkey. And this was to 5 use that T-cell depleting immunotoxin in monkeys 6 intentionally to study de-novo allo-antibody 7 production. 8 And we demonstrated first of all that we 9 reliably develop allo-antibody after four to six weeks 10 post-transplant and that the histology of these 11 kidneys closely parallels antibody mediated rejection 12 as seen in humans. 13 And then we were -- the focus of this work 14 was to study the usefulness of co-stimulation blockade 15 to prevent de-novo allo-antibody development and 16 antibody mediated rejection. 17 And we published this first paper which 18 effectively demonstrated that either a belatacept in 19 blocking CD28 or a 2C10 which is an anti-CD40 blocking 20 the CD40, cd-154 interaction effectively prevented 21 rejection as shown here by the blue and the purple 22 lines which show the monkeys treated with co-</p> | <p style="text-align: right;">Page 196</p> <p>1 at -- on the right side of the slide showing that the 2 treatment severely blunted KI67 or a B-cell 3 proliferation in the follicle. 4 So I think that work effectively 5 demonstrated that co-stimulation blockade could block 6 out any production of B-cell isotype switching, 7 germinal center reconstruction, and t follicular 8 helper cells in the germinal center. 9 And that work served as background work also 10 for the clinical trial that was sponsored by the FDA 11 that Allen Kirk performed carrying this into human 12 kidney transplantation with a cocktail of alemtuzumab 13 induction, sirolimus, and belatacept to maintenance 14 therapy that has turned out to have excellent results 15 without allo-antibody production. And excellent graft 16 function and survival. 17 While we move from that concept of trying to 18 prevent de-novo allo-antibody production in the monkey 19 to trying to model the highly sensitized patient. A 20 different problem, but also related, of course, to 21 allo-antibodies. So how do we take our highly 22 sensitized patients and desensitize them more</p> |
| <p style="text-align: right;">Page 195</p> <p>1 stimulation blockade is that they maintain stable era 2 function without rejection over time. And, as shown 3 here, the treatment effectively blunted a development 4 of allo-antibody which occurred in all controls. 5 Jean Quan at this time really moved us well 6 ahead by suggesting that we should be looking at a 7 lymph node morphology and not just the morphology, but 8 the amino chemistry to look at what's happening in the 9 germinal center as a result of T-cell depletion and B- 10 cell activation and to get a handle on what co- 11 stimulation blockage was doing at the germinal center 12 level. 13 And by a co-staining for B-cells with CD20, 14 T-cells with CD3, and KI67 as a proliferation marker 15 what he demonstrated then was that in the co- 16 stimulation treated monkeys either with bela- -- 17 treated with either belatacept or 2C10 that we were 18 disrupting this proliferation of B-cells in the 19 germinal center. 20 So, in other words, co-stimulation blockage 21 is substantially disrupting the activation of B-cells 22 in the germinal center. And that is shown graphically</p> | <p style="text-align: right;">Page 197</p> <p>1 effectively? 2 And in order to model this in the non-human 3 primate we wanted a difficult model. We wanted to 4 make it tough to succeed. So we exchanged skin grafts 5 between MHC mismatched non-human primate rhesus 6 monkeys and we'd give them two successive skin grafts 7 that reliably results in a very high MHC class one and 8 class two allo-antibody level. And this reaches a 9 peak and then a decay over time. 10 And we wanted to then try to desensitize 11 them when they're on the shoulder of this curve, not 12 when they're at the peak of sensitization because this 13 would be more analogous to our human patients who have 14 relatively stable allo-antibody levels over a long 15 period of time. 16 So we do two phases of the -- or three 17 phases if you will of the experiment. There's the 18 sensitization phase, then we desensitize, and then we 19 do the kidney transplants using the same donor as the 20 recipient is sensitized by skin grafts. 21 That can be argued as an even more difficult 22 situation than we face in the clinic because our</p> |

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| <p style="text-align: right;">Page 198</p> <p>1 patients are usually across sensitized by a third 2 party sensitization or other means of sensitization, 3 but they're usually not sensitized to this high 4 degree. 5 So that is a tough model and I won't tell 6 you about all kinds of things that did not work and 7 how we beat our head against the wall for a long time. 8 But I'll focus instead on a therapy that has looked 9 very promising and that is the combination or 10 proteasome inhibitors and co-stimulation blockade. 11 So what we do is give that therapy over a 12 four-week period when we're on the shoulder of this 13 of the sensitization curve here. And what we found 14 was that the combination of these agents resulted in a 15 reliable decrease in bone marrow plasma cell secreting 16 allo-antibody and about a 50 percent reduction in 17 donor-specific antibody. 18 In contrast, when you give either bortezomib 19 alone or belatacept 2C10 alone we did not see any 20 significant change really in allo-antibody compared to 21 a baseline. 22 So following that triple therapy or what</p> | <p style="text-align: right;">Page 200</p> <p>1 made was that -- and this is published just earlier 2 this year by Jean Quan and really based on his 3 observation of what's happening in the germinal center 4 -- is that if you treat with proteasome inhibition 5 alone we are actually activating the germinal center. 6 And as shown here germinal center B-cells 7 are exposed -- they are expressing BCL4 at higher 8 levels. The follicular helper T-cell is substantially 9 activated as shown in the upper right. And that's 10 shown pictorially here where this quiescent B-cell 11 follicle is activated following bortezomib treatment 12 alone. And this was also associated with an in- -- a 13 significant increase in serum BAFF levels. 14 So now returning to the cohorts treated with 15 the triple therapy as shown pictorially in the upper 16 left, this dual targeting regimen was able to actually 17 substantially lower donor-specific antibody. And 18 mechanistically we've been able to look at bone marrow 19 plasma cells which are substantially reduced in the 20 monkeys, lymph node germinal center B-cells are also 21 substantially reduced as are lymph node follicular 22 helper T-cells and were blunting substantially the</p> |
| <p style="text-align: right;">Page 199</p> <p>1 we're calling now dual targeting desensitization we 2 then went on to perform kidney transplants. And the 3 regimen that we used to immunosuppress the monkeys was 4 a depleting -- a T-cell depleting induction regimen 5 with anti-CD4 and CD8 and conventional maintenance 6 immunosuppression, if you will, with tac MMF and 7 steroid. 8 And this is the overall survival result. 9 You can see that controls reject at a mean of about 27 10 days and the monkeys treated with the desensitization 11 protocol did not succumb to rejection. 12 However, we did see in these longer 13 surviving monkeys a significant issue with CMV 14 infection. Rhesus has their own unique CMV species 15 and it behaves similarly to humans. And despite 16 prophylaxis we had significant challenges. 17 So, in other words, depleting plasma cells 18 targeting co-stimulation molecules and T-cell 19 depletion is profoundly immunosuppressive. And while 20 we were able to prevent graft rejection and AMR, this 21 was a daunting combination of immunosuppression. 22 I think the conceptual breakthrough that we</p> | <p style="text-align: right;">Page 201</p> <p>1 isotypes switched B-cell proliferation. 2 And that is shown a little bit more 3 graphically here. And on the left are the control 4 lymph nodes and the red here is staining for the B- 5 cell follicles. And this is post-treatment on the 6 right here. 7 And you can see that these b-cell follicles 8 are essentially empty on the right. So there is a 9 profound effect of co-stimulation blockade in 10 combination with proteasome inhibition in altering the 11 germinal center morphology. And that is summarized 12 graphically on the lower right for you. 13 In order to aim for a more tolerable 14 immunosuppressive strategy at the time of kidney 15 transplantation we backed off of T-cell depletion 16 induction and gave them basilizimab instead, an anti- 17 CD25. 18 And that was much better tolerated and the 19 overall graft survival is shown in the upper right 20 here with 3 of 3 monkeys having rejection-free 21 survival. And the histology is summarized in the 22 upper right with an absence of antibody mediated</p> |

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| <p style="text-align: right;">Page 202</p> <p>1 rejection. And, again, that is paralleled by complete 2 disruption of the lymph node follicles. 3 So that I think is a clinically applicable 4 strategy that we can take forward into patients. 5 You've just heard from Anita Chong about a very -- a 6 similar strategy minus the anti-CD40. 7 But I think it's encouraging that this works 8 not only in a mouse but in a monkey. And we're 9 working with Steve Woodle to, you know, think about 10 how we will carry this forward in the clinic. 11 I think some of the questions that we're 12 interested in addressing and using the monkey model to 13 try to address is would plasma cell targeting more 14 specifically with monoclonal such as daratumumab or 15 elotuzumab or plerixafor accomplish the same type of 16 donor-specific antibody reduction plasma cell 17 depletion with less toxicity than proteasome 18 inhibitors. 19 We're also interested in looking at whether 20 BAFF or IL-6 receptor targeting in combination with 21 plasma cell depletion could be just as effective in 22 terms of the clinical outcome in the non-human</p> | <p style="text-align: right;">Page 204</p> <p>1 question is the end result would be a couple things. 2 One is do you prevent the formation -- the 3 end result of germinal center is either mature B-cell 4 or plasma blast. And what I didn't see I think in 5 your talks were do your treatments with belatacept 6 blockade or CTLA4 IG prevent the generation of new 7 plasma blasts that are antigen specific? 8 DR. CHONG: So in the mouse studies we know 9 that even if you have memory B-cells or naive B-cells 10 if you introduce antigen in the presence of CTLA4 IG 11 you will inhibit those B-cells from differentiating. 12 So it always requires T-cell help at least for allo- 13 specific antibody responses. 14 And we also show that if you give CTLA4 IG 15 late you can still -- there is a window in which you 16 can inhibit the germinal center output of memory 17 cells. So you can actually inhibit B-cell 18 sensitization or at least in terms of, you know, 19 memory B-cells. 20 So all the outputs that are germinal center 21 dependent, time dependent within the germinal center 22 you can inhibit and you can inhibit the recall.</p> |
| <p style="text-align: right;">Page 203</p> <p>1 primate. 2 Another pressing issue is how durable is 3 this sensitization? The type of strategy that I've 4 just outlined for you would probably apply to 5 desensitizing if you have a living donor, but for 6 deceased donor transplantation you'd have to 7 desensitize in a durable manner that would last three 8 years or so for most programs. 9 So we're interested in considering how 10 durable is that approach and can we extend that by a 11 maintenance phase of desensitization therapy. 12 So in conclusion we have found that the non- 13 human primate model is an invaluable tool for 14 developing better immunosuppressive strategies and 15 drugs for transplantation and can lead us to more 16 appropriate clinical trial design. Thank you. 17 DR. MANNON: Can we go ahead and get the 18 session questions up? Any questions for clarification 19 of the four prior speakers from anyone? 20 DR. WOODLE: I would ask this question to 21 Anita and to Stuart both. I think that if, indeed, 22 you're inhibiting a germinal center response the</p> | <p style="text-align: right;">Page 205</p> <p>1 DR. KENCHTLE: So, Steve, we have not been 2 able to look at allo-specific B-cells, but we do bone 3 marrow aspirates to look at plasma cell that secrete 4 antibody and use an elispot to look at them. And 5 there is a substantial reduction in antibody secreting 6 cells by those bone marrow derived plasma cells. 7 DR. WOODLE: I just wanted to congratulate 8 both of you. I think that there's always been a 9 question in our mind as to why there's resistance to 10 proteasome inhibitor therapy. And it's clear now from 11 your work and it just substantiates a lot of prior 12 work that if you deplete the source of antibodies 13 there are reflexes in place and mechanisms to replace 14 that in the immune system. 15 And now we know how to go after this. And I 16 think this is probably the most significant 17 development in the history of proteasome inhibitor 18 treatment for human responses. And my guess is that 19 this is going to be a big step towards solving the 20 problem. 21 I don't know of a more promising approach in 22 the field right now to treat human responses in</p> |

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| <p style="text-align: right;">Page 206</p> <p>1 transplant recipients other than what you guys are 2 proposing.</p> <p>3 DR. ALLOWAY: I'd like to kind of compare 4 and contrast the toxicities that you reported in the 5 monkeys compared to what we've seen in the humans. 6 We've used T-cell depleting induction in 7 combination with tacrolimus and MMF for a long time 8 and treated a lot of people with velcade. Knock on 9 wood, essentially we -- although we have prophylaxed 10 effectively for the viral effects we have not paid the 11 price of infectious complications in that regard.</p> <p>12 However, as we move onto treating with 13 belatacept despite the prophylaxis we do -- we are 14 paying the price in terms of toxicity and being able 15 to handle and manage the viral infections that do 16 occur.</p> <p>17 So I guess I'm interested in your -- you 18 essentially assigned the over immunosuppression that 19 was related in your monkey model to your -- your 20 induction -- potent induction depletion and 21 potentially the PI.</p> <p>22 But I would kind of offer an alternative</p> | <p style="text-align: right;">Page 208</p> <p>1 transplantation of sensitized patients. That's one of 2 our better tools besides tac.</p> <p>3 So we were surprised that giving simulect we 4 didn't see more rejection early on. So I suspect that 5 the combination of bortezomib is not only -- and a co- 6 stimulation blockade is also affecting the T-cell, of 7 course.</p> <p>8 In fact, we've also shown that the naive T- 9 cell component is enhanced by this therapy.</p> <p>10 DR. ALLOWAY: In humans a similar story that 11 we saw when we had EBV mismatch I think we're seeing a 12 similar story when we have CMV mismatch. I mean, 13 maybe this is oversimplification, but what is the 14 serial status of the monkeys? Are they all positive?</p> <p>15 DR. KNECHTLE: Yes. All the monkeys are 16 positive.</p> <p>17 DR. ALLOWAY: Okay.</p> <p>18 DR. KNECHTLE: Yeah.</p> <p>19 DR. MANNON: Any other comments about the 20 clarification? Otherwise we'll turn to the questions. 21 And Shukal indicated she'd like us to walk through 22 them. We don't have to be -- some of this may be</p> |
| <p style="text-align: right;">Page 207</p> <p>1 reason for that.</p> <p>2 DR. KNECHTLE: In other words, you're 3 suggesting that it's the co-stimulation blockade --</p> <p>4 DR. ALLOWAY: Yeah.</p> <p>5 DR. KNECHTLE: -- that may be responsible? 6 Okay. That's fair enough. So since I'm giving all 7 these drugs I can't tease them apart. However, I can 8 tell you that the CD4 -- the depleting Cd4 monoclonal 9 that we give that comes from Keith Ryman (phonetic) 10 that is a profound deplete and those monkeys don't 11 reconstitute their Cd4 cells for many months. The CD8 12 is also very effective.</p> <p>13 There's some variability by lot for this 14 CD4, but in general we have significant problems in 15 our monkeys when we get profound T-cell depletion. I 16 mean, we've had -- we've learned that from previous 17 experiments.</p> <p>18 Of course, the -- you may be correct, 19 though, that co-stimulation blockade is a significant 20 cofactor in that issue. So we addressed it by backing 21 off. And, frankly, as you know, a T-cell depletion 22 plays a very important role in successful</p> | <p style="text-align: right;">Page 209</p> <p>1 rhetorical because -- I'm sorry, Steve.</p> <p>2 MR. WOODLE: Just one more comment. I think 3 this highlights -- so one of the reasons why we wanted 4 to get away from IVIG is so that you start to 5 specifically target known biologic pathways. And 6 that's what's happening here.</p> <p>7 And I think to further emphasize to the FDA 8 we're going to be coming with combination regimens 9 both of them off label. They may be actually outside 10 of the field of transplant. And this is where I think 11 the field is moving and agency should be considering 12 this and be prepared for it.</p> <p>13 DR. MANNON: No. I think that's an 14 excellent point, Steve. And, you know, based on you 15 have rodent data and non-human primate data mimicking 16 each other and I know we've been sort of honestly let 17 down sometimes by those models not coming through, but 18 I think in this case the biology is mimicking what 19 we're seeing in people.</p> <p>20 And there are differences in depletion. We 21 can't use ATG. Rabbit ATG is ineffective in NPH. So 22 I think that they're trying to adopt those agents, but</p> |

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| <p style="text-align: right;">Page 210</p> <p>1 I do think that, you know, a number of us in the room 2 have seen these data and they're very interesting. 3 And, you know, people looking at an agent which 4 unfortunately commercially is difficult to get now, 5 you know, and I wish -- I don't know if there's 6 anybody from BMS here, but I'd hope they'd be 7 encouraged by these kind of data. 8 And the sad fact that they may not be here 9 is unfortunate. They may be listening in, but I hope 10 that they're encouraged by some of these 11 presentations. 12 DR. WOODLE: You know, sometimes you get 13 market share through the back door, you know. And 14 this is sort of an end around approach to getting that 15 but certainly, you know, if this works out, I mean, 16 this means that patients are developing humeral 17 responses post-transplant will be converted to bela. 18 That's what I think. 19 DR. MANNON: And I have my own conversion 20 stories of people, but I'll get in trouble. But I 21 have no stock options, blah, blah, blah. I have 22 nothing to do.</p> | <p style="text-align: right;">Page 212</p> <p>1 in outcomes as we saw in some of the talks this 2 morning. 3 So I think we -- as Bob suggested, we 4 probably need a more granular assessment of CG. And, 5 you know, this is something that Bob and Michael 6 Mangel are working on and to look to see if this is 7 adopt -- adaptable to a clinical trial. 8 And ultimately if it is this'll have to be 9 incorporated into BANFF. I must say, though, BANFF is 10 a consensus, it moves very slowly. Watching BANFF 11 move is kind of like watching the grass grow. 12 We had evidence for C4d negative antibody 13 mediated rejection in 2009 and it took until 2013 to 14 incorporate it into the classification. 15 We've had evidence that IFTA is bad since 16 2010 and it still hasn't been incorporated into the 17 classification. So admittedly these things take time. 18 One thing that I would perhaps suggest and 19 advise is that although BANFF is the consensus maybe 20 for the purposes of clinical trials to try and develop 21 and validate histologic endpoints outside of BANFF is 22 not necessarily a bad idea. And this is coming from</p> |
| <p style="text-align: right;">Page 211</p> <p>1 So if you guys are okay we'll move onto the 2 first question in terms of what we know about 3 endpoints and using them. And the one comment I feel 4 comfortable making is in terms of histopathology. 5 So Mark Haas presented a lot of information 6 and there's been comments about this. I think one of 7 the challenges I think for the BANFF working group is 8 some clarification of some of the definitions to be 9 clear that there are clinical entities associated with 10 the pathology. 11 But also that maybe one of the working 12 groups has to really redefine the CG TG -- you know, 13 CG as a potential endpoint because, as you point out, 14 it's the worst glomerulus of the number of glomeruli 15 you see. 16 DR. HAAS: Yeah. I mean, the glomerular 17 lesions as a whole do not have great inter-observer 18 reproducibility. So, I mean, that's a problem. The 19 -- the current -- the current definition of CG is a 20 very low threshold kind of defi- -- definition. 21 And so I think we need -- and clearly 22 increasing amounts of CG have association with changes</p> | <p style="text-align: right;">Page 213</p> <p>1 somebody who is heavy invested in BANFF. 2 But, you know, in order to make the field 3 move faster, move faster we can't really depend on 4 something that moves very slowly. And if we have data 5 then that might give a push to BANFF to try and move 6 its process along at a little bit faster rate, too. 7 DR. MANNON: And an alternative strategy 8 with this transplant therapeutic consortium 9 investigating biomarkers, histo- -- you know, having 10 -- I mean, part of the issue is that BANFF is a 11 voluntary organization. You don't get paid and in 12 your spare time of the thousand other things you're 13 doing, you know, you have to do it. 14 So and that's kind of why I sort of don't 15 want to throw stones because I know how long it takes 16 me to look at things. But I think that that might be 17 an opportunity for the liaison between a private 18 public partnership and the BANFF working groups are 19 individuals interested that want to look at this 20 because now they obviously realize -- if the group 21 doesn't realize that, I think these histological 22 endpoints are really quite critical. And some of the</p> |

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| <p style="text-align: right;">Page 214</p> <p>1 definitions have been really improved.</p> <p>2 I think along the same lines the molecular</p> <p>3 endpoints group has to come up with. You know, it's</p> <p>4 more than the indats and the intercomex. There's</p> <p>5 other things that people are working on in this room</p> <p>6 that haven't been published yet that look quite</p> <p>7 promising.</p> <p>8 DR. HAAS: Yeah. And certainly, you know, I</p> <p>9 mean, the ABMR classifier is a massive improvement</p> <p>10 over the indats. And I think the slides that were</p> <p>11 shown, you know, that Greg showed this morning really</p> <p>12 show that quite well.</p> <p>13 And the onus is very much to try and</p> <p>14 incorporate some of the molecular diagnostics into the</p> <p>15 classification. There was a very early attempt to do</p> <p>16 this back in '13. Excuse me. But I think it really</p> <p>17 sort of needs to be moved along at a little bit faster</p> <p>18 rate.</p> <p>19 But, again, it's the -- you know, it's a</p> <p>20 consensus. It moves slowly. And it'll ultimately be</p> <p>21 done and I expect that BANFF 2019 will have an ABMR</p> <p>22 classifier in the classification. But I actually</p> | <p style="text-align: right;">Page 216</p> <p>1 heard yesterday, I mean, how one measures DSA in terms</p> <p>2 of what constitutes a 50 percent drop is important.</p> <p>3 There are limitations to MFI which seems to be the</p> <p>4 current standard, but we've heard that MFI has its own</p> <p>5 limitations.</p> <p>6 And also all DSAs are not created equal.</p> <p>7 And some DSAs are harder to get rid of than others and</p> <p>8 we've seen this in desensitization. So that you may</p> <p>9 have -- for example, I mean, it's easy enough if you</p> <p>10 have a single DSA, but many of these patients will</p> <p>11 have more than one donor-specific antibody. And one</p> <p>12 of them might be quite amenable to current therapies</p> <p>13 to lower DSA and the other might be, you know, a DR51</p> <p>14 that's harder to get rid of.</p> <p>15 So a 50 percent reduction per se might be a</p> <p>16 good start, but I'm not sure that's necessarily the</p> <p>17 gold standard. And I think we really need to go</p> <p>18 farther than just, you know, lumping all DSAs</p> <p>19 together.</p> <p>20 DR. WOODLE: Mark, I was wondering if I</p> <p>21 could just take a -- make a general observation on</p> <p>22 that. So our drop in DSA is using the immune dominant</p> |
| <p style="text-align: right;">Page 215</p> <p>1 proposed at the 2017 meeting just a few weeks ago that</p> <p>2 we try and do it this year, but it kind of met, you</p> <p>3 know, a great deal of resistance.</p> <p>4 And so but we need to really I think see</p> <p>5 studies that use this as perhaps an alternative</p> <p>6 endpoint. And if this is found to be valid as an</p> <p>7 alternative endpoint then that will facilitate its</p> <p>8 incorporation into BANFF.</p> <p>9 DR. MANNON: I guess the only other comment</p> <p>10 I wanted to make is five years ago we tore each other</p> <p>11 alive. Not us necessarily, but some of the labs tore</p> <p>12 each other alive about donor-specific antibody and the</p> <p>13 validation using that as an endpoint.</p> <p>14 And I think we've heard a lot of clinical</p> <p>15 data that's encouraging in terms of seeing drops in</p> <p>16 DSA or the most immunogenic. And, again, that might</p> <p>17 be another TTC project where the HLA labs, you know,</p> <p>18 in conjunction with all the ongoing issues of</p> <p>19 monitoring might be interested. I'll just throw that</p> <p>20 out there. I'm not, you know -- anyway.</p> <p>21 DR. HAAS: And just one, you know, sort of</p> <p>22 point of caution about DSAs again is that I think we</p> | <p style="text-align: right;">Page 217</p> <p>1 DSA. And that is defined as being either class one or</p> <p>2 class two and it's the highest in the five level,</p> <p>3 okay.</p> <p>4 And so what we find in both desensitization</p> <p>5 and in antibody mediated rejection is that if that</p> <p>6 antibody drops almost all other antibodies drop with</p> <p>7 bortezomib.</p> <p>8 The old history about the public epitopes of</p> <p>9 DR Beta 3, 4, and 5, that is DR51, 52, and 53, they</p> <p>10 are more -- they seem to react quite well to</p> <p>11 proteasome inhibitor therapy.</p> <p>12 Your point is well taken though that in</p> <p>13 general class two doesn't respond as well as class</p> <p>14 one. So those are the caveats that I would just add</p> <p>15 to your comments.</p> <p>16 DR. GEBEL: I'd like to add one thing to</p> <p>17 your comment, too. And that is with DSA -- we've been</p> <p>18 talking this entire time looking at one half of the</p> <p>19 equation.</p> <p>20 In order for DSA to have any effect there</p> <p>21 has to also be a target. And what we don't know --</p> <p>22 it's just unknown at this point -- is what is the</p> |

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| <p style="text-align: right;">Page 218</p> <p>1 level of target expression especially for things like 2 HLADQ which we know at the onset at least on 3 peripheral blood is expressed at a ten-fold lower 4 concentration than HLADR. 5 In vasculature I just don't think we have 6 enough information. I think there needs to be more 7 dedication towards looking towards what that target 8 is. 9 DR. TAMBUR: I'm sorry that I'm going to 10 bring you back again, but we are talking about MFIs 11 that are close to 20,000 and we're outside of our 12 scale to be able to differentiate which of them is 13 stronger than the other. 14 We're lumping them together and I believe I 15 am the only one who's currently doing titrations. And 16 I can tell you DQ titers are significantly higher than 17 class one titers. And maybe everything that we're 18 seeing right now is a result of this. 19 So obviously it's only my data, but I think 20 we need to start looking at antibodies in a little 21 better resolution of how we quantify them. And right 22 now we're looking at this range and we have patients</p> | <p style="text-align: right;">Page 220</p> <p>1 I know we got to find something that works. 2 That works towards improving for patients. In my 3 opinion there's three pieces. Longevity, which I 4 think we talked about; health, health outcomes, 5 decrease cardiovascular disease, all sort of the side 6 effects that actually affect the medical aspect 7 management of the patient; as well as the quality of 8 life. And quality of life came up briefly here. 9 But what's the value of these treatments 10 that we're proposing and what's really the cost here? 11 To me there's two parts of the value equation and 12 right now we're looking at does it work. And 13 ultimately we've got to find something that does work. 14 But then the other side is going to be what 15 are the costs? Is there healthcare utilization 16 measures? Are there pieces that from a patient 17 perspective this is more -- you know, this is from me 18 adherence simplifies or makes harder adherence. It 19 does -- makes me feel cruddy the day I get it, et 20 cetera, et cetera. 21 So just a push that as we work on trying to 22 find something that works clinically and meets either</p> |
| <p style="text-align: right;">Page 219</p> <p>1 have antibodies some were up there and we're totally 2 missing that. 3 So I think before we jump into conclusions 4 we owe it to ourselves to test whether that might be 5 the case. And I challenge the centers -- and this is 6 why I approached Montgomery at the time -- that had 7 differential responses to treatment to look at how 8 strong that antibody truly was prior to treatment, not 9 by MFI but something else that they can truly quantify 10 the antibody. 11 DR. HAAS: And that was actually the point I 12 was trying to make, but not nearly as elegantly 13 because I'm a pathologist. 14 DR. MANNON: Uh-oh, somebody leaning in the 15 back. So any comments about question 2, the pros and 16 cons of composite endpoints? 17 Is everybody just like burnt out? Maybe the 18 presentations were -- 19 DR. LENNON: Yeah. So one question or more 20 comment towards these composite endpoints. One of the 21 ques- -- words that keeps running around in my head is 22 value here.</p> | <p style="text-align: right;">Page 221</p> <p>1 our surrogate or our clinical endpoints that maybe we 2 look at some of the sort of process measures of how is 3 this actually interacting with the patient and the 4 provider as they interact to make it work so. 5 DR. MITTELMAN: I also have a question on 6 composite endpoints because I know we've talked a lot 7 -- you've talked about it today. But don't people 8 kind of just cheat to use composite endpoints? 9 I mean, I've been around the clinical trials 10 a lot and you kind of do it to just get your study 11 properly powered basically. And -- and then you end 12 up combining a lot of events that are of different 13 importance levels to patients and then it kind of 14 screws up your data the way I understand composite 15 endpoints. 16 I'm kind of confused why people are still 17 looking at them. So I guess I would challenge you 18 guys, I mean, to think about this. I've planned a lot 19 of trials in my day. I used to do pricing and market 20 access at some point so I'm confused why there's -- 21 why it's on the board. 22 DR. WOODLE: Composite endpoints doesn't</p> |

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| <p style="text-align: right;">Page 222</p> <p>1 necessarily mean that you introduce a degree of 2 subjectivity. You can have composite endpoints in 3 which the individual components are objective and 4 measurable and verifiable.</p> <p>5 And I think that those are always preferable 6 to an endpoint that's subjective.</p> <p>7 DR. BALA: Dr. Knoll, do you want to -- 8 DR. KNOLL: No. I was just -- I mean, 9 that's very good points. Obviously we -- in this 10 field we're using them because we're struggling to get 11 enough patients, enough endpoints to show any meaning 12 effect to some of the therapy.</p> <p>13 So as I did point out, you have to be very 14 careful about what you put into the composite. And 15 one of the key issues is relevant importance to the 16 outcome. And you just can't have things that are 17 small.</p> <p>18 I mean, there used to be a phase in industry 19 trials and some of the trials we did many years ago 20 where loss to follow up was part of a composite which 21 like made no sense to me with graft and patient 22 survival being part of it.</p> | <p style="text-align: right;">Page 224</p> <p>1 DR. ALBRECHT: So there is actually a group 2 at FDA that's involved with patient reporting outcome. 3 And one of the challenges is that developing those 4 kind of patient reported outcome measurement scoring 5 systems is very challenging.</p> <p>6 It does involve -- just like many of the 7 biomarkers that you're hearing about today it does 8 involve working with patients. It's important, but, 9 again, it's time consuming. It involves working with 10 patients, having groups of patients discuss what is 11 and isn't relevant to their health and their -- the 12 benefit that they gained from the treatment that's 13 being proposed.</p> <p>14 And then again the same thing validating it 15 and assuring that other groups of patients can use 16 that same score to score whatever the parameters are 17 that are objectively determined to be of importance.</p> <p>18 So, again, just to summarize there's a group 19 and certainly I think in the field of transplant we 20 could start talking about that.</p> <p>21 MR. MITTELMAN: Yeah. But what about the 22 other point that Jack mentioned which is value, right?</p> |
| <p style="text-align: right;">Page 223</p> <p>1 So I think we've thought about it a little 2 more and I just brought up -- no. I don't think 3 anyone has the answer of what the endpoints should 4 look like for the trials yet, but I think we're going 5 to have to have a few things in there. And we do have 6 to realize that they have to be important for 7 everyone, patients and providers.</p> <p>8 DR. MITTELMAN: Yeah. And, I mean, so Jack 9 mentioned this value point, right. And I've been to a 10 lot of conferences recently where, you know, people 11 are trying to understand what are important outcomes 12 to patients without necessarily looking at these 13 intermediary secondary endpoints.</p> <p>14 And so I guess one of the challenges I would 15 ask you guys is is where are you in thinking about 16 some of those things particularly around something 17 Jack mentioned, quality adjusted life years which I 18 know they do in the UK and other countries. And I 19 used to do it also for planning for purposes.</p> <p>20 So does the FDA and do you guys ever think 21 you'll begin looking at that more, those kinds of 22 metrics, endpoints?</p> | <p style="text-align: right;">Page 225</p> <p>1 So icers and those kinds of things that people look 2 at. So this value based which is where in the 3 hospital work that I do, you know, it's value-based 4 models are all the realm now. And, I mean, I remember 5 pricing drugs that you guys passed that were 6 ridiculously expensive. I feel bad about it.</p> <p>7 DR. BALA: Dr. Irish? 8 DR. ALBRECHT: From the agency we look at 9 the benefit and risk to patient. Actually the FDA 10 does not involve itself in the pricing, although that 11 has been a topic recently.</p> <p>12 MR. MITTELMAN: Yeah. I just mean can it -- 13 can it become one? I mean, we're talking about it, 14 right? So is it something the FDA's going to 15 consider, start looking at? 16 I mean, why not? 17 DR. ALBRECHT: So the FDA follows the laws 18 passed by Congress and so if that's in that equation 19 then obviously the FDA would participate. But that's 20 the scope of where we get our authority.</p> <p>21 DR. ALLOWAY: I would like to use that 22 opportunity to make a comment about PROs, however. So</p> |

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| <p style="text-align: right;">Page 226</p> <p>1 we all have used the common toxicity criteria for 2 adverse event reporting that has been developed in 3 oncology. And they are attempting to develop a 4 similar strategy for PROs. 5 So I hope that we can get closer to using a 6 PRO in a way we use the common toxicity criteria for 7 importing adverse events because historically, as you 8 know, the price of validating a PRO has been more 9 expensive than the price of developing the new drug. 10 So I think that if we could come to that 11 agreement with adverse event reporting, hopefully 12 we'll be able to do the same with patient-reported 13 outcomes. 14 DR. ALBRECHT: Well, and as I mentioned, the 15 21st Century Act does include patient-focused drug 16 development. And I think we're still, you know, 17 taking the first baby steps, if you will. 18 But it's true that when the FDA is looking 19 at products and saying, well, here are the benefits, 20 here are the risks and someone says based on whose 21 criteria. And the important point is it's got to be 22 on the patient's criteria.</p> | <p style="text-align: right;">Page 228</p> <p>1 Sorry. If I could make a comment about your question 2 on value. I'm sure you recognize this entire two-day 3 discussion involves exceptionally expensive therapies. 4 So the denominator in the value equation is going way 5 up, right, so the value is coming down. 6 And I think for that reason it's interesting 7 to me that you were the one that made the comment 8 because certainly as money is sucked out of the 9 healthcare sector it's going to be harder and harder 10 to do this type of work. 11 And transplant centers are evaluated on 12 their overall outcomes. So if you do a higher-risk 13 patient, you're potentially hurting your results and 14 your program. So I think there's a real premium on 15 coming up with affordable strategies that work and 16 applying them very carefully in a way that not only 17 preserves a reasonableness to the cost of the therapy 18 but also reasonableness to the risk and the side 19 effects to the patient. 20 DR. WOODLE: In terms of overall long-term 21 healthcare cost the drug costs are only a part of 22 that. One of the major advantages if you do economic</p> |
| <p style="text-align: right;">Page 227</p> <p>1 So not someone else deciding what's 2 important to patients, but actually having those 3 public types of for -- where that information can be 4 gathered and then studies where it's tested and so 5 forth. 6 So, no, I agree with what you're saying. 7 It's just the scope of FDA is the risk benefit of the 8 product and how the patient then ultimately feels, 9 functions, and survives. 10 DR. BALA: Dr. Irish? 11 DR. IRISH: Yeah. I just wanted to -- you 12 alluded an important issue with respect to a composite 13 endpoint. You have these individual components and 14 when we do analysis we -- we equally weight them. 15 And this is -- this is a challenge. And 16 there's a lot of research now that's being done using 17 composite endpoints, but providing sort of a clinical 18 utility value to the -- that's not equal. And that's 19 a really important area for research in terms of the 20 composite endpoint. 21 DR. BALA: Dr. Knechtle? 22 DR. KNECHTLE: If I could make a comment,</p> | <p style="text-align: right;">Page 229</p> <p>1 advantages of these approaches, if you do salvage a 2 graft and keep a patient off dialysis there are huge 3 cost savings overall to the industry. So that's a 4 major factor. 5 But I think knowing that that saves a lot of 6 money to the healthcare system in the long term 7 combined with the fact that this is a small population 8 when drug companies go to do their calculations to 9 determine what the market price will be those are 10 factors that are going to wind up being higher prices 11 for these drugs rather than lower prices. 12 DR. BALA: Dr. Knoll? 13 DR. KNOLL: Yeah. I just wanted to say, 14 again, just a follow-up to your question about the 15 endpoints is there's another initiative called the 16 song initiative which is a standardized outcomes in 17 nephrology that myself and Dr. Nickerson, Dr. Mannon 18 have been at some meetings. 19 They're looking at developing a core set of 20 endpoints for all kidney transplant trials. And it's 21 an international group. Half of the people involved 22 are patients so it's a very -- it's a true partnership</p> |

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| <p style="text-align: right;">Page 230</p> <p>1 with patients and providers.</p> <p>2 And there is a meeting that's going to be</p> <p>3 held at the ATC coming up so if you are interested in</p> <p>4 that I can certainly get you linked up with that</p> <p>5 group.</p> <p>6 DR. MITTELMAN: That'd be cool. I know</p> <p>7 nothing about it so that'd be -- that'd be cool.</p> <p>8 Thanks.</p> <p>9 DR. BALA: Okay. So if we could just spent</p> <p>10 couple of minutes -- couple of minutes on the last</p> <p>11 question. What are the major limitations to the</p> <p>12 applicability of the animal models of AMR to clinical</p> <p>13 transplantation?</p> <p>14 DR. KNECHTLE: Well, I'll try to answer that</p> <p>15 I guess. Certainly the non-human primate experiments</p> <p>16 are extraordinarily expensive so funding is a major</p> <p>17 limitation. Then there's always the question of how</p> <p>18 translatable is the animal data to humans.</p> <p>19 There's been a trend toward disbelieving</p> <p>20 rodent data in the last five years I think that's fair</p> <p>21 to say. I'm not trying to say that in any way</p> <p>22 disparaging the value of rodent data. It's -- there</p> | <p style="text-align: right;">Page 232</p> <p>1 and peripheral blood.</p> <p>2 And so if you just -- my take from the last</p> <p>3 two days is that if you just monitor without</p> <p>4 underlying hypothesis you -- it's very difficult to</p> <p>5 separate the chance -- especially with limited numbers</p> <p>6 the chance correlations from something that actually</p> <p>7 makes some sense.</p> <p>8 And if you have a hypothesis then perhaps</p> <p>9 the design to either prove or disprove that hypothesis</p> <p>10 that you have formulated and nailed down in a mouse</p> <p>11 model I think makes it perhaps a little bit more</p> <p>12 powerful than just randomly monitoring as many</p> <p>13 parameters as you can.</p> <p>14 DR. MANNON: I know these non-human primate</p> <p>15 studies how expensive they are and painful. I think</p> <p>16 the very positive aspect of them is that they do</p> <p>17 develop transplant glomerulopathy. It's harder to see</p> <p>18 that in the mouse.</p> <p>19 We have our old MHC mismatch model that's</p> <p>20 un-immunosuppressed. And those we got terrible IFTA</p> <p>21 and vasculopathy and glomerulitis we never were able</p> <p>22 to really pull up glomerulopathy.</p> |
| <p style="text-align: right;">Page 231</p> <p>1 are obvious benefits that we do not realize in outbred</p> <p>2 models that are available in the rodent data.</p> <p>3 On the other hand, non-human primate data is</p> <p>4 presumably more applicable. But even some non-human</p> <p>5 primate data has not translated into human so there</p> <p>6 are inherent disadvantages of course of modeling.</p> <p>7 The obvious advantages of the animal data is</p> <p>8 that you can do much more in-depth mechanistic</p> <p>9 analysis and have more rational design of human</p> <p>10 clinical trials.</p> <p>11 DR. CHONG: Yeah. I think, you know, in</p> <p>12 defense of the mouse model I think that there are just</p> <p>13 so many reagents that allow us -- and also in terms of</p> <p>14 cost -- to really nail down on fundamental mechanisms</p> <p>15 that hopefully will translate in large part in terms</p> <p>16 of the immunology of the B-cell development, plasma</p> <p>17 cells, and at least set a framework of a hypothesis</p> <p>18 that can then be selectively tested in humans given</p> <p>19 their limitations or in non-human primates given the</p> <p>20 limitations of especially in humans the access to the</p> <p>21 lymphoid organs which is very, very difficult and the</p> <p>22 only the access to either a limited number of biopsies</p> | <p style="text-align: right;">Page 233</p> <p>1 So I'm positive that a -- and, you know, all</p> <p>2 the old tolerance studies that, you know, when the</p> <p>3 kidneys failed in the primates they do develop it.</p> <p>4 And, again, understanding the transition from</p> <p>5 glomerulitis to glomerulopathy to me is like a</p> <p>6 complete unknown of why that happens.</p> <p>7 I mean, we've been looking in in vitro and</p> <p>8 looking at, you know, co-stimulation -- I mean,</p> <p>9 stimulation of antibody and glomerular endothelium and</p> <p>10 cannot get -- you know, we can get cell activation,</p> <p>11 but we don't see that kind of pattern.</p> <p>12 So I think that animal mod- -- you know,</p> <p>13 though it's a lot of money and very tedious. It's got</p> <p>14 a lot of merit to being more human-like than, you</p> <p>15 know, than we know -- than we realize.</p> <p>16 DR. WOODLE: I think one of the things</p> <p>17 that's important is you're exactly right, Ros,</p> <p>18 complement in the mouse is not worth studying if you</p> <p>19 want to translate to human.</p> <p>20 OKT3 or NECU3 that model was beautiful,</p> <p>21 recapitulated what happened in humans tremendously.</p> <p>22 CTLA4 IG is very translatable from the rodent to human</p> |

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1 as is it looks like the proteasome inhibitor work may
 2 also be very translatable to human.
 3 But what's really exciting now is for the
 4 first time in transplantation with this proteasome
 5 inhibitor work we have mouse models directly relating
 6 to human therapies. We have primate models directly
 7 related.
 8 We didn't describe it today, but Jim
 9 Driscoll at our institution now has an in vitro model
 10 that keeps human plasma cells alive for 14 days or
 11 longer which is the first time people have been able
 12 to keep human plasma cells alive long enough to study
 13 them.
 14 So much of the drug interactions in future
 15 synergistic studies of drugs we can now do in vitro in
 16 humans. And you also saw our data today we're
 17 actually taking plasma cells from humans treated with
 18 these trials and studying them with modern approaches.
 19 And so now we have all of those models
 20 directly focused on a mechanistic way to develop
 21 these. And so that's what's -- that's the exciting
 22 development in the last couple years that exists.


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1 DR. MANNON: So I'm going to have to -- oh,
 2 I was going to cut everybody off to let Renata finish
 3 us up.
 4 DR. ALBRECHT: Well, I was just going to say
 5 that at the FDA part of drug development we look at in
 6 vitro data, we look at non-clinical data, and then we
 7 formulate how to do the clinical studies.
 8 And so I think we value when there is
 9 information both in vitro and from animal models.
 10 That actually helps inform how to take a product into
 11 human.
 12 So although there is a cost I think there's
 13 also clear benefit in being able to design better
 14 studies, better understanding process. And I don't
 15 know if Dr. Bala who reviews a lot of these wants to
 16 add, but we invariably have those discussions of
 17 where's the proof of concept and what's informing our
 18 clinical studies.
 19 DR. BALA: I think we are -- we can close
 20 this session and return it back to you right on time.
 21 DR. ALBRECHT: Okay. Well, we're just past
 22 1:00 so let me keep it very brief. I want to thank

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1 all the speakers. Thank you. Very excellent
 2 presentations, very informative hearing the latest
 3 science.
 4 Again as I said yesterday we are so pleased
 5 that the patients were able to join us. And thank you
 6 so much for your comments. I think it helps us keep
 7 -- you know, helps keep us honest and realize that the
 8 work that this whole group is doing is to benefit the
 9 patients that have transplantation.
 10 I want to thank my FDA colleagues who made
 11 sure things ran smoothly. And, again, to the
 12 audience. Thank you for joining us.
 13 And with that, thank you very much. Have a
 14 safe trip back.
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1 CERTIFICATE OF NOTARY PUBLIC
 2
 3 I, MICHAEL FARKAS, the officer before
 4 whom the foregoing proceeding was taken, do hereby
 5 certify that the proceedings were recorded by me
 6 and thereafter reduced to typewriting under my
 7 direction; that said proceedings are a true and
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 12 and, further, that I am not a relative or employee
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 15 the outcome of this action.
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