

1 we increase the levels within the complete liver or the
2 tumor by giving histamine injections.

3 So, I think actually we have an environment that
4 has the possibility to be inhibited, the H2 receptors are
5 being blocked by histamine, and this hypothesis would work.

6 If we do the experiments with tumors in the liver
7 at sub-Q, the potential of giving histamine in preclinical
8 experiments, we have a larger growth rate reduction in the
9 liver than in other tissues.

10 DR. GEHLSON: I did have an answer for Dr.
11 Dutcher's question. According to our database, we had no
12 patients in either arm that had performance status of 2
13 either in the intent-to-treat population or in the
14 population with liver metastases.

15 DR. NERENSTONE: Dr. Albain.

16 DR. ALBAIN: I have two questions directed toward
17 Dr. Atkins, please. In your very nice review, Mike, you
18 mentioned the lack of real efficacy data for the low dose
19 IL-2 regimens.

20 Could you comment and your thoughts as to what
21 could be going on here since it was a low dose outpatient
22 regimen, could this potentially be histamine effect alone if
23 indeed there is an effect? That is my first question. I
24 will let you do that one first.

25 DR. ATKINS: I think the low dose IL-2 control

1 arms in this particular study supports the data that I
2 showed with low dose IL-2 on that particular table with the
3 response rate in the 2 or 3 percent arm.

4 I think from listening to this presentation, I
5 wasn't involved in the study, that the theory behind
6 histamine is that it might take an immune reaction that is
7 being inhibited by some other factors like oxygen free
8 radicals, and allow it to go on even with less immune
9 stimulation than is typically used with high dose IL-2.

10 DR. ALBAIN: The other question to you is are you
11 aware of any multivariate analyses done specifically for
12 patients with liver metastases in the various historical
13 databases from the large groups? In other words, are there
14 indeed other independent factors present predicting adverse
15 outcome in the face of known liver metastases?

16 DR. ATKINS: I wouldn't be able to comment on that
17 definitely although I know that these are multivariate
18 analyses and I assume that means when you look at patients
19 with liver metastases, and it comes out as an independent
20 predictor, it takes into account all the other variables.

21 DR. ALBAIN: I am just trying to get at the
22 possible explanation. What is puzzling me the most here so
23 far is that at least if you look at the FDA analysis, there
24 is neither a response or a time to progression benefit yet
25 there is a survival benefit.

1 I wonder if either of you could comment on the FDA
2 analysis that was presented in the briefing documents for
3 time to progression because you did address the response
4 issues in your presentation.

5 DR. NERENSTONE: Kathy, I think I would like to
6 hold that question until after FDA has a chance to present
7 their data.

8 DR. ALBAIN: The reason I asked is because he did
9 some rebuttal of the response analysis and stated that the
10 reason there was a survival advantage was perhaps because a
11 response would not bear out with stable disease as another
12 important outcome.

13 DR. NERENSTONE: I think it is going to be
14 important for us to hear the entire FDA presentation and
15 then open it back up, and if it is appropriate for the
16 sponsor to react to that, I would like to save it for that
17 time.

18 Dr. Taylor.

19 DR. TAYLOR: I have several questions. Number
20 one, all of this is done at home. Has anybody counted
21 bottles, do you keep diaries, how do you know how compliant
22 they were and how much drug was actually given by the
23 patients?

24 Number two, did you control for other drugs that
25 they might be taking, such as antihistamines that might

1 interfere with your histamine, and if you did so, did you
2 control so in both arms?

3 Number three, on your quality of life study, a
4 common problem that we have is that as people get further
5 along in their disease, they answer fewer and fewer of the
6 questions, and that is a lot of questions. What percent of
7 people actually completed your Quality of Life studies?

8 DR. GEHLSON: Thank you for those questions.

9 Yes, in the beginning of the study there weren't
10 injection logs. There was certainly a lot of drug
11 accountability that went on as the patients received their
12 drugs each week, they were evaluated each week in the clinic
13 with their physician and their nurse.

14 As the study progressed, we included injection
15 logs that actually would allow the patients to document, and
16 we also had, in many of the patients, home health care was
17 provided, so the home health care nurse could actually, in
18 fact, administer the drugs and fill in the injection logs.

19 Then, there was a lot of accountability. They had
20 to return all the syringes and the vials each week, so it is
21 an at-home treatment. We would hope that these patients
22 were sufficiently motivated to administer their treatment at
23 home, and we had the best reliable information we could have
24 by their injection logs.

25 For the Quality of Life for the number of patients

1 who actually completed all of the forms, as they progress
2 and drop off the study, they aren't going to be filling out
3 any more forms, and I will actually ask the statistical
4 group who put together the Quality of Life analysis to
5 address that question.

6 But on your second question, can you ask me that?

7 DR. TAYLOR: What about concomitant drugs?

8 DR. GEHLSON: Oh, yes, a very good question. Of
9 course, we didn't want our patients to have H2 receptor
10 blockers because we know that this is an H2 receptor
11 phenomenon.

12 They could have had H1 antihistamines for very
13 short periods of time, but we know that the effect on the
14 phagocytic cells H2, so they were not allowed to take any of
15 the antacids that are H2 blockers, but instead we asked them
16 to take the proton pump blockers, which is Prilosec and
17 Prevacid, and then we also listed the other concomitant
18 medications that they could have had in the protocol, and
19 all that was monitored in great detail.

20 If I could have the people who worked on the
21 Quality of Well-Being, they can actually better address that
22 question than I can.

23 DR. ACKERMAN: I am Stacy Ackerman from Covance
24 and I am a consultant to Maxim. I would like to help
25 address the question about the amount of missing data.

1 Overall, in the histamine plus IL-2 group, there
2 was 33.4 percent missing data in terms of the QWB self-
3 administered questionnaire. In the IL-2 alone group, there
4 was 34.9 percent, and tests for difference in terms of
5 missing data, the chi-square value was 0.4, suggesting that
6 there wasn't a statistical difference in terms of the degree
7 of missing data between treatment groups.

8 Does that sufficiently address? Okay. Thank you.

9 DR. NERENSTONE: Dr. Santana.

10 DR. SANTANA: I, too, like Dr. Lippman, don't
11 quite understand whether there has been clinical proof of
12 principle of how this drug works, particularly in the group
13 of patients in which it would appear that it works, but
14 having said that, I also recognize--and this is a comment
15 that there are a lot of drugs I don't understand how they
16 work, but I still use them--my comment is primarily to
17 safety.

18 Does histamine cause a tachyphylaxis both in terms
19 of side effects with repeated dosing, and a correlate to
20 that, translated to its potential physiologic activity as it
21 relates to this combination with IL-2?

22 DR. GEHLSON: Thank you for that question.

23 I am going to ask Dr. Agarwala to actually address
24 that question since he is one of the investigators that
25 treated more patients in this study than anyone else.

1 DR. AGARWALA: Clinically, patients who would
2 react to the histamine would start off at a 20-minute
3 injection or so and modify that time based upon how they
4 reacted. So that is one variable that came into that from a
5 clinical standpoint as to their flushing and headache, and
6 so on.

7 In general, patients tend to tolerate the
8 treatment better as they go along. I am not exactly sure if
9 that is from tachyphylaxis or is it from just them getting
10 used to finding the right timing for administration of the
11 drug.

12 However, there really wasn't a situation where
13 patients would have a severe reaction on the first day of
14 treatment and then by the third cycle were not having any
15 reaction at all. They would all tell us they were having
16 some flushing, some redness of the skin.

17 My feeling is that it got a little bit less, but
18 did not completely disappear, if that helps to answer that,
19 but I don't know of any biologic way of measuring that.

20 DR. SANTANA: Do you know if there is any
21 preclinical data that would carry that further in terms of
22 the effect of histamine on its reported physiologic effect
23 and how it interacts with IL-2?

24 DR. AGARWALA: I am not aware of any. Peter, do
25 you know of any preclinical data that would suggest

1 tachyphylaxis?

2 DR. GEHLSON: We have actually done in humans some
3 pharmacokinetic studies looking at the administration of
4 histamine before or after interleukin-2, and there is no
5 interaction between the two drugs. So, we don't change the
6 pharmacokinetic profile of interleukin-2, nor does it change
7 the pharmacokinetic profile of histamine in patients.

8 DR. NERENSTONE: Dr. Simon.

9 DR. SIMON: One final clarification. Could you
10 clarify was there a formal independent data monitoring
11 committee? Your terminology and your description of the
12 safety monitoring seems a little ambiguous to me. Was this
13 something that was done by the CRO or was there an
14 independent data monitoring committee?

15 DR. GEHLSON: That is an excellent question. Yes,
16 we actually had a disinterested independent Data Safety
17 Monitoring Board comprised of three clinicians in the United
18 States plus one statistician that were not at all involved
19 with the CRO or in the conduct of this study.

20 They independently evaluated safety on a monthly
21 basis, and they did, as per the protocol, did one interim
22 efficacy evaluation. That was a closed evaluation that we
23 actually have not had access to. So, there was, in fact, a
24 disinterested Data Safety Monitoring Board.

25 DR. SIMON: I didn't see in the protocol a clear

1 statement of when the final analysis would be done. How was
2 it decided, was that decided by the independent Data Safety
3 Monitoring Board or what? We heard Dr. Whitman mention in
4 his statement before the presentation that he had analyzed
5 the data from his clinic independently and noticed what he
6 thought was a difference in outcome for the patients.

7 Timewise, when were those kinds of analyses being
8 done by individual investigators?

9 DR. GEHLSON: Thank you. That is also a very good
10 question. Relating to the DSMB, they actually had developed
11 a very specific charter for when they would actually do an
12 interim efficacy evaluation, and that charter is actually
13 also included in our statistical analysis plan. So, they
14 prespecified the time that they would do it and how they
15 would do it.

16 As far as other people analyzing their data, I do
17 not believe that Dr. Whitman analyzed his data before the
18 study was complete or reported in aggregate, and I would
19 have to ask--I mean I would hope that he hadn't, and I am
20 sure that he did not, because we don't know of any other
21 investigator who did.

22 DR. SIMON: But in terms of the final analysis,
23 you were addressing the interim analysis, what about the
24 timing of the final analysis or the analysis leading to the
25 NDA submission?

1 DR. GEHLSON: That is a very good question. We
2 had actually specified that we would analyze the data 12
3 months after the last patient was enrolled. We could have
4 looked at a number of events that would have also given us a
5 guide, and we assumed that 240 events or 12 months after the
6 last patient enrolled would actually give us the level of
7 significance we needed to show between the two groups, but
8 we ended up with 238 events at the 12-month mark, so that is
9 exactly when we specified.

10 DR. NERENSTONE: Dr. Przepiorka.

11 DR. PRZEPIORKA: You showed two slides which
12 indicated that the majority of Grade 4 adverse events and
13 deaths within 28 days were due to tumor, but when you do the
14 subtraction it appears that there are still more events in
15 the histamine arm than in the control arm.

16 Could you go through the nontumor-related deaths
17 in the study, please?

18 DR. GEHLSON: Sure. I think we actually have
19 those patient narratives, so I can go through those.

20 There were 4 deaths in the histamine group versus
21 2 in the intent-to-treat population, and 2 in the liver met
22 population versus 1.

23 If it is okay, I will just give you some quick
24 highlights on those patients. Is that what you would like?

25 DR. PRZEPIORKA: Just the causes of death.

1 DR. GEHLSON: The first patient in the IL-2 group
2 died of influenza and respiratory failure, and it was
3 considered not related to study drug.

4 One patient in the histamine/IL-2 group was
5 considered to have liver failure, and that was considered
6 not related to study drug.

7 Another patient in the IL-2 group had an upper GI
8 bleed with cardiopulmonary arrest, and it was considered not
9 related to study drug.

10 For those that were considered related to study
11 drugs, we had one patient in the histamine group that it was
12 considered a seizure leading to death, and that was
13 considered related to the study drugs.

14 We had one patient in the histamine group with
15 liver failure that was considered related to study drugs.

16 We had one patient with myocardial cerebral
17 infarction that was also considered related to study drugs.

18 Those are the patients.

19 DR. NERENSTONE: Just to take the Chair's
20 prerogative for a moment and to continue with this, the
21 FDA's analysis actually, they gave us descriptions of 10
22 patients of whom they said there were 30 patients who died
23 within 28 days from the last dose of study medication.

24 The thing that concerned me in terms of safety is
25 that there seemed to be a significant number of patient

1 deaths in patients who had poor performance status, who by
2 your own admission criteria should not have been treated on
3 study. There is another patient who died who had received
4 prior IL-2, again who should never have gone on study.

5 So, I guess the devil is in the detail, and this
6 may be addressed by FDA in their presentation as to what
7 exactly is disease progression and what is toxicity of the
8 drug.

9 Would you comment on the number of ineligible
10 patients who were actually on study, who had major
11 violations of the entry protocol out of your study?

12 DR. GEHLSON: Yes, we can do that. I think we
13 have a slide that will summarize the types of exclusions
14 that were granted for patients on this study.

15 The medical monitor, just so you know, we had a
16 medical monitor that was independent from the sponsor, and
17 so the investigators, if they felt that they had an
18 exception or a patient that they wanted to enroll, that may
19 not have met all the criteria, they were to go through the
20 medical monitor and it was the decision of the medical
21 monitor, together with the investigator, that would allow
22 such patients on.

23 I apologize for not having a slide for this
24 particular one.

25 In the IL-2 alone group, there were a total of 42

1 patients that were granted exclusion or they were granted
2 the eligibility into the trial, and there were 45 patients
3 in the histamine arm.

4 Two patients in the histamine arm had received
5 prior adjuvant IL-2 at some point in time in their course.
6 There were 3 patients in the IL-2 alone arm and 1 patient in
7 the Maxamine arm that did not meet the measurable disease
8 criteria.

9 There were 10 patients in the IL-2 group and 11
10 patients in the histamine group that had scans that were
11 greater than 3 weeks from study entry, but usually that was
12 about a day or so.

13 There was 1 patient in each group that had a CT
14 head scan in place of the MRI brain scan. There was 1
15 patient in the histamine group that actually did not meet
16 adequate marrow, kidney, cardiac, or liver function
17 criteria.

18 There were 10 patients in the IL-2 group and 2
19 patients in the histamine group that had PT or PTT
20 abnormalities, 3 patients in the IL-2 group had hemoglobin
21 abnormalities, 1 patient in the histamine group had a
22 platelet abnormality.

23 There are some that are characterized as Other,
24 and I might have to ask, do you know what is in the Other?

25 DR. NERENSTONE: Could you come to a microphone,

1 please, and identify yourself.

2 MS. WOOD: Diana Wood. Basically, in the Other
3 category, contained general items that really couldn't be
4 classified according to the protocol itself for which
5 exceptions were granted. There were situations where an
6 exception was granted, quote, unquote, however, that wasn't
7 necessarily an exception that was required, and that was
8 typically falling in that category.

9 DR. NERENSTONE: And so performance status,
10 according to your records, was not an exception that was
11 granted on the basis of performance status.

12 MS. WOOD: Not in our review of the data, no.

13 DR. NERENSTONE: Have you looked to correlate
14 patients' own reporting of their performance status and
15 correlating it with the investigators, because there at
16 least seems to be some discrepancy in the patients who died,
17 that performance status was not accurately assessed
18 certainly in some patients.

19 I think this is a very important point because we
20 are going to have to talk about the safety of this
21 medication especially in patients who are at home, and the
22 argument is that this is safer than high dose IL-2 and this
23 is tolerable in the community.

24 I am very concerned that that may not be true.

25 MS. WOOD: I think that one of the things that we

1 can show is that the patients did have multiple therapies
2 before they came into the study. Many patients were rapid
3 progressers, and we did allow patients into the study that
4 had brain metastases that were controlled.

5 I would assume that there are patients during the
6 prestudy period, which is three weeks in length, that during
7 that time, they may have had a lot of their work done within
8 that two- to three-week prior to first dose.

9 Once they were randomized, they had two weeks
10 before they start study drug, so it could be during the
11 prestudy period, yes, the performance status was adequate
12 and it met the inclusion criteria for the protocol, however,
13 once they came into the protocol prior to the first
14 evaluation, they would have deteriorated very quickly.

15 DR. NERENSTONE: Dr. Lippman.

16 DR. LIPPMAN: I would just like to follow up on a
17 comment that Dr. Santana made on one of my comments. The
18 reason I was focused on the biologic plausibility, I mean
19 there are a lot of drugs that we don't know how they work,
20 but they work, and in a large randomized study that is
21 acceptable even though we do work to try to improve on that.

22 In this case, since we are being asked to consider
23 as a primary indication a drug based on a subgroup analysis.
24 In my opinion, the issue of biologic plausibility becomes
25 much more important, and that is really the context that I

1 raised, and we will discuss obviously more about this, the
2 whole issue of the subgroup finding even preplanned.

3 DR. NERENSTONE: Dr. Redman.

4 DR. REDMAN: Back to the issue of safety and
5 tolerability, one-third of your patients dropped out before
6 first analysis. How many of those patients had documented
7 progressive disease?

8 DR. GEHLSON: Do you have a slide that can address
9 that question? These are patients that had documented
10 progressive disease, but were continued on therapy. That is
11 not the question that he is asking. He is asking of the
12 patients that were not evaluable at 12 weeks, how many of
13 those were not evaluable due to progressive disease.

14 DR. REDMAN: Documented progressive disease.

15 DR. GEHLSON: Documented progressive disease.

16 DR. REDMAN: I guess while you are looking for
17 that, I have another question regarding this endpoint of
18 biology, because the information is confusing.

19 You have a treatment at least in the median number
20 of cycles that you gave me per therapy were no different
21 between the two arms, and I am assuming that that is the
22 same for intent-to-treat liver metastases also, that the
23 number of cycles between IL-2, IL-2/histamine are not
24 different.

25 DR. GEHLSON: That is correct.

1 DR. REDMAN: The time to progression is not
2 different using standard criteria for time to progression,
3 the response rate is not different, it's inactive in both
4 arms using response rate.

5 Why do you think other than data that is going to
6 come out with the FDA review, patients lived longer with IL-
7 2 and histamine?

8 DR. GEHLSON: I think it is a very reasonable and
9 fair question. As you have heard earlier, there have been a
10 number of studies that have improved the response rate
11 without any improvement in survival, and so there really
12 isn't a direct correlation between the improvement in
13 survival and response rate to date, at least in this
14 population, however, the opposite could be true.

15 We made survival the primary endpoint in this
16 study because we knew that we could not reliably document
17 responses. We did not set up a tumor board to look at
18 responses in progressive disease because if we really are
19 having lymphocyte infiltration in the tumor, can you
20 determine a tumor that is actually progressing or one that
21 is actually being attacked by the immune system. You can't
22 do it.

23 So, we have always said that we could possibly
24 better design a trial if we did survival as the primary
25 endpoint. Of course, we have to look at response rates as a

1 secondary endpoint and look at time to disease progression,
2 but if it can't be absolutely reliably measured in the
3 patient population, we are left with survival, and we are.

4 We are asking you to think somewhat differently.
5 I think the reason that there is an improvement in survival
6 is the number of patients who have stabilized disease, and
7 stable disease is a clinically meaningful benefit for the
8 patient especially if you can do it in a setting like we
9 have done. It may also allow them to get other additional
10 treatments down the road if we could stabilize the rapid
11 progresser.

12 I don't know if Sanjiv or Dr. Glaspy want to add
13 to that. John, would you like to add a little bit?

14 DR. GLASPY: I am John Glaspy from UCLA. I think
15 we need to add one more thing in terms of the delivery
16 subset question, which we all have, because we want to know
17 why if it works, it works in liver.

18 There is a second mathematical explanation which
19 would be that the liver metastases patients represent a much
20 more homogeneous group of patients, and where you have the
21 power in a much smaller number of people to detect survival
22 differences.

23 It may be that the biology isn't different, we
24 just don't have the power in the intent-to-treat analysis,
25 and that is another way I think about this.

1 DR. REDMAN: John, the converse could also be
2 true, though. It is not a homogeneous population, but the
3 population itself in the trial is heterogeneous.

4 DR. GLASPY: Yes, I agree.

5 DR. NERENSTONE: Dr. Taylor, did you have a
6 question?

7 DR. TAYLOR: Well, I wanted to clarify the numbers
8 you gave her were 42 and 45. Are those ineligible patients?

9 DR. GEHLSON: No, those are patients that were
10 granted protocol exceptions for the reasons that I listed.

11 DR. NERENSTONE: Dr. Simon.

12 DR. SIMON: One last clarification. You indicated
13 that the patients who were not evaluable for response or
14 progression evaluation were included in the survival
15 analysis. So, how many patients either died or you have
16 follow-up information on, say, up to within six months of
17 either the September update or the previous? I am trying to
18 get an idea.

19 I mean it is one thing to say that the patients
20 were included in the analysis, but if they were sort of
21 included but censored a long time because you lost track of
22 them, that is including them, but, you know, you can't
23 really have confidence in the results.

24 So, I want to get an idea for the patients who
25 have not been indicated as having died, how up to date the

1 follow-up is on those patients and what proportion of them
2 you sort of lost contact with.

3 DR. GEHLSON: That is another excellent question.
4 All patients that were randomized have been followed up for
5 survival regardless of when they died, and those patients
6 that were still alive on the data cutoff date, were actually
7 identified and followed. There were no patients that were
8 censored or lost to follow-up.

9 So, the same thing happened on September 8th, on
10 the reanalysis, every single patient who had died between
11 the previous analysis and the new analysis were actually
12 followed, and all patients alive today will continue to be
13 followed for survival, and we have no patients lost to
14 follow-up in either one of those analyses.

15 DR. NERENSTONE: Dr. Przepiorka.

16 DR. PRZEPIORKA: It appeared from some of the
17 tables that a substantial proportion of the patients had
18 been treated before coming on the study, so there was an
19 opportunity to observe them prior to study entry.

20 Could you tell us--and I don't know if you have
21 collected this information either at the time of
22 randomization or start of drug--the proportion of patients
23 in each of the arms who had progressive disease versus
24 stable disease?

25 DR. GEHLSON: That is a very good question, but

1 our entry criteria specified that they had to have
2 progressive disease upon entry, so we assumed that all
3 patients that entered this study had actually had
4 progressive disease, and they had to have discontinued their
5 prior therapy 14 or 30 days prior before being eligible for
6 this study.

7 DR. NERENSTONE: Dr. Redman.

8 DR. REDMAN: Did you find an answer to the
9 question about the third of patients who are not evaluable?

10 DR. GEHLSON: They are looking and we will find
11 that answer, I promise.

12 DR. NERENSTONE: Dr. Albain.

13 DR. ALBAIN: You had just mentioned no patients
14 had been lost to your follow-up, so what happened in that
15 first three months is really critical to understand. The
16 same question.

17 DR. GEHLSON: You mean the first three months
18 before they were in the study?

19 DR. ALBAIN: No, the first three months from time
20 zero to month 3, those who went off study.

21 DR. GEHLSON: Yes, and all those patients, of
22 course, are included in the survival analysis as we
23 mentioned, but we will find out if they have discontinued.
24 I would imagine the majority of them discontinued for
25 progressive disease, not for an adverse event.

1 DR. ALBAIN: And were they then scored as
2 progressive disease--

3 DR. GEHLSON: Yes.

4 DR. ALBAIN: --if they had done so, even though
5 they hadn't reached the first evaluation point?

6 DR. GEHLSON: Yes. In fact, I think that is
7 evident here because if here is the first scheduled
8 evaluation, you can see that--all patients, of course, are
9 included in the analysis unless they were, well, in fact, in
10 time to disease progression, all patients are included, so
11 if they had progressed here or died, or died, then, they are
12 included in here.

13 I think the majority of those patients actually
14 progressed and died before the first scheduled evaluation.
15 I think this is also why you see this artifact because the
16 first scheduled evaluation was after two cycles, and you see
17 the majority of the patients actually had the diagnosis of
18 progressive disease at that first evaluation, but the
19 patients were allowed to continue if they did have
20 progressive disease, and we can tell you that there was no
21 investigator bias because those patients that were continued
22 with what might be progressive disease, and were allowed to
23 continue on therapy, is essentially identical to the group,
24 in fact, favors the IL-2 group.

25 More patients were continued on IL-2 with the

1 first diagnosis of progressive disease than on the
2 histamine/IL-2 group. They were equally distributed between
3 the two groups, so we can show you those data.

4 Actually, you could also just tell me the number
5 of deaths before 12 weeks, because the number of patients
6 are on the slide.

7 DR. DUTCHER: Just help me with this. The not
8 evaluables are a subset, I mean are included in the
9 progressive disease, some of them, or not some of them?

10 DR. GEHLSON: No.

11 DR. DUTCHER: They are not evaluated because they
12 didn't reach the 12 weeks.

13 DR. GEHLSON: Yes, they didn't get their first
14 response evaluation.

15 DR. DUTCHER: But you are saying they came off
16 study because they progressed, most of them, or you think
17 that most of them did.

18 DR. GEHLSON: You have to have a scan to know if
19 the patients had progressive disease, if they are rapidly
20 deteriorating and then they die before they actually get to
21 the first evaluation, but that is why we need to know.

22 MS. WOOD: This is Diana Wood. When the patients
23 are removed from study, they are required to fill out a
24 study completion page. On that page, the reason for study
25 discontinuation must be checked. If the patient was removed

1 from study due to progression of disease, that check box
2 would be ticked.

3 Does that answer the question?

4 DR. REDMAN: And you don't have the raw data, you
5 don't have the documentation of their x-rays and scans
6 showing that.

7 MS. WOOD: That would be monitored by the site
8 monitors as part of the monitoring conventions to ensure
9 that if progression of disease was checked, that there
10 should be some documentation either in the form of a scan,
11 physical exam, or some other portion within the case report
12 form that the patient is indeed progressing.

13 DR. REDMAN: So, you do have that data.

14 MS. WOOD: That data would be located within the
15 case report form.

16 DR. REDMAN: It is an important issue if it comes
17 down to safety, because metastatic melanoma patients with
18 performance statuses of zero to 1, dying within 12 weeks of
19 going on trial sort of negates the fact that performance
20 status is an important criteria.

21 MS. WOOD: I think what we would like to do, if
22 it's acceptable, is to provide you with that 12-week data of
23 the patients that died and the patients that died due to
24 progression of disease after the break, if that is
25 acceptable.

1 DR. REDMAN: Yes.

2 DR. NERENSTONE: Dr. Sledge.

3 DR. SLEDGE: A question about the eligibility.

4 This is a fairly astoundingly high rate of patients with
5 enrollment violations, I mean in excess of 40 percent. I
6 saw the listing of why they were granted exceptions, but I
7 guess my question would be if you have such poor control
8 over who enters the study, why should we have any great deal
9 of confidence about the conduct of the study past that
10 point.

11 DR. GEHLSON: Well, it is a fair question. I mean
12 I can't directly answer that. I know that U.S. clinicians
13 are very compassionate people, and when you identify a
14 patient who may benefit from this particular treatment, if
15 their scan is one day out of the three-week window, I don't
16 think granting an exception for a patient like that is much
17 of a problem.

18 Many of these patients had failed all prior
19 therapy, so we found that our medical monitors and our
20 clinicians were rather compassionate and wanted to include
21 these patients, but I don't know if we should be penalized
22 for those because if we would have had more forethought on
23 the types of inclusion criterias, we could have broadened
24 those earlier on, but we allowed all patients into the study
25 that met the criteria if they were granted an exception by

1 the medical monitor, and it appeared to be appropriate by
2 the medical monitor and the investigator, these patients are
3 included in the intent-to-treat analysis.

4 DR. SLEDGE: I can understand why your physicians
5 were being compassionate for their patients. I don't quite
6 understand why your medical monitors were. I mean this is a
7 truly extraordinarily high rate of ineligible patients by
8 cooperative group standards.

9 DR. GEHLSON: Yes, but the reasons for, though,
10 are relatively insignificant I would say clinically. If
11 they missed a scan by a day or so, which is the majority of
12 those ineligibility criteria, or they have one lab value
13 off, I think that those things don't represent looseness of
14 the medical monitor, but actually working together with the
15 investigator to identify and try to help these patients and
16 put them onto the study. We weren't afraid of having them
17 in our study.

18 DR. NERENSTONE: Dr. Temple.

19 DR. TEMPLE: I suppose ideally, your medical
20 monitor would have told you this was happening, so you
21 could, if necessary, adjust the entry criteria. I mean you
22 may be right, that being a day off is no big deal, but it
23 sort of could suggest no one was watching closely.

24 DR. GEHLSON: I think you are absolutely right,
25 and, in fact, we actually have seven amendments to the

1 protocol, and most of the majority of the amendments were
2 related to criteria that the medical monitor and the
3 investigators identified that needed to be changed.

4 So, during the course of the study, we made
5 adjustments to the eligibility criteria to allow for these
6 particular changes, and you would see that most of these
7 patients who may have been granted exceptions were granted
8 early on in the study before many of these changes took
9 place. So, in fact, we were in direct communication with
10 our medical monitor at all times.

11 DR. NERENSTONE: There being no more questions
12 from the committee, I would like to call a break. Please be
13 back at 3:50 to start the last part of the afternoon. Thank
14 you.

15 [Recess.]

16 **FDA Presentation**

17 DR. CHIAO: Good afternoon. Dr. Nerenstone,
18 members of ODAC, ladies and gentlemen, it is my pleasure
19 here today to be part of the members of the FDA team
20 presenting to you the FDA review of the New Drug Application
21 of histamine dihydrochloride.

22 [Slide.]

23 I will review the clinical studies in the NDA.
24 Following my presentation, FDA statistician Dr. Sridhara
25 will go over some important statistical issues in the major

1 study. Finally, Dr. Donna Griebel, medical team leader,
2 will address the regulatory standard for using a single
3 study to support an NDA.

4 This slide lists the members of the FDA review
5 team.

6 [Slide.]

7 The applicant is seeking marketing approval of the
8 histamine/IL-2 combination for the treatment of patients
9 with melanoma that has metastasized to the liver.

10 [Slide.]

11 This slide outlines the FDA presentation. The FDA
12 review of the major study MP-US-MO1 will focus on the
13 following three issues: Is survival difference in the
14 intent-to-treat population a persuasive finding? Is
15 survival difference in the liver subgroup a persuasive
16 finding? Is the histamine/IL-2 combination a well tolerated
17 regimen?

18 [Slide.]

19 As we have heard earlier, metastatic melanoma is a
20 relatively chemo-resistant disease with very limited
21 treatment options. This disease is known to have a very
22 variable clinical course.

23 Publications over the past 20 years have
24 consistently demonstrated that survival in this disease is
25 influenced by prognostic factors as the ECOG investigators

1 pointed out in the recent analyses of 1,362 patients on ECOG
2 melanoma trials. The prognosis for patients with Stage IV
3 melanoma still seems to be influenced by disease factors
4 than any particular therapy.

5 [Slide.]

6 This slide lists the major prognostic factors.
7 Although patients with liver metastases have poor prognosis,
8 the literature suggests that these patients also have a
9 variable clinical course.

10 Two studies, one from Memorial Sloan-Kettering and
11 one from ECOG, showed that the presence of liver metastases
12 at study entry is not a significant predictor for poor
13 survival in multivariate analyses.

14 [Slide.]

15 The Division met with the applicant in April 1997
16 to discuss the design of registration study for the
17 histamine/IL-2 combination. The dose and schedule of
18 histamine/IL-2 combination in the proposed MP-US-MO1 has
19 never been tested in Phase I/II setting.

20 The Division felt there was a lack of safety data
21 on the tolerability of the proposed treatment regimen and a
22 lack of efficacy data to support the estimates for the
23 proposed sample size.

24 Not convinced that the results of MP-US-MO1 alone
25 would be compelling to support an efficacy claim, the

1 Division asked for two trials stating that additional
2 studies might provide supporting evidence in case the
3 results of MP-US-MO1 was weak.

4 The Division emphasized that the registration
5 studies should be stratified by key prognostic factors to
6 ensure the two arms were balanced in patient characteristics
7 that might affect survival.

8 [Slide.]

9 Regarding the design of a second well-controlled
10 study, the applicant proposed to do an international Phase
11 III study which uses a different treatment regimen, that is,
12 histamine/IL-2 plus alpha-interferon versus DTIC alone.

13 The Division stated that this trial could not
14 support MP-US-MO1 because the treatment regimen was
15 different. The Division also stated that the single arm
16 study MA-O103 could not be used as second well-controlled
17 trial because the added benefit of histamine to IL-2 could
18 not be demonstrated and survival data would be difficult to
19 interpret in the absence of a control arm.

20 [Slide.]

21 This slide shows the study design for MP-US-MO1.
22 It is an open-label, randomized study which was not
23 stratified by any prognostic factors. There was no
24 stratification based on the presence of liver metastases at
25 study entry and therefore, randomization within a stratum,

1 that is, in the liver subgroup was not carried out. The
2 primary endpoint of this study was survival.

3 With 300 patients, the study had an 80 percent
4 power to detect a 50 percent increase in median survival
5 from 7.8 months to 11.3 months.

6 The following three slides summarize the
7 statistical analysis plan concerning the liver subgroup.

8 [Slide.]

9 The original protocol dated July the 1st, 1997,
10 stated the primary objective of the study is to evaluate the
11 efficacy and safety of the histamine/IL-2 combination in
12 patients with metastatic melanoma who have not been treated
13 or have failed other first-line therapies.

14 Patients will be stratified in subgroup analyses,
15 liver versus no liver mets; prior treatment with DTIC or no
16 DTIC.

17 [Slide.]

18 The last patient was randomized on March 26, 1999.
19 Revised statistical analysis plan in June 24, 1999, still
20 stated that the intent-to-treat subset will be used as the
21 primary subset. All efficacy endpoints will be summarized
22 for non-exploratory subgroup of patients with liver
23 metastases at study entry.

24 [Slide.]

25 The null hypothesis testing for the liver subgroup

1 was introduced in the final statistical analysis plan dated
2 November 18, 1999, which was about a month after the study
3 finished accrual and five months before the data was
4 analyzed.

5 It is our view that survival analysis in the liver
6 subgroup is not a prospectively defined primary analysis.

7 [Slide.]

8 The FDA review of study MP-US-MO1 will focus on
9 three issues. The first one is whether survival difference
10 between the two arms in the intent-to-treat population is a
11 persuasive finding.

12 [Slide.]

13 Two cutoff dates were used for survival analyses.
14 None of these dates were prespecified in the protocol. The
15 update survival data using September 8th cutoff date was
16 submitted about three weeks ago before this meeting.

17 Forty patients were alive on September the 8th.
18 Thirty-three of these 40 patients had last follow-up date 30
19 days or more beyond the cutoff date. Four deaths occurred
20 after the cutoff date, and three were on the histamine/IL-2
21 arm.

22 [Slide.]

23 This slide shows median survival at different
24 times. The first two days were used by the applicant, and
25 the last one was by FDA only. At March 8, 2000, cutoff

1 date, 243 patients have died. That is, 80 percent of the
2 events have occurred. By September 8th, 2000, an additional
3 22 patients have died, an increase of 7 percent events.
4 Four more patients died if the last follow-up date of all
5 patients were used. Regardless of what dates were used, the
6 difference in median survival between the two arms is about
7 one month.

8 [Slide.]

9 This slide shows the hazard ratio and log-rank p-
10 value of the three survival analyses. Hazard ratio is the
11 risk of death on the treatment arm in this trial is the
12 histamine/IL-2 arm divided by the risk of death on the
13 control arm, a measure of relative treatment efficacy of the
14 histamine/IL-2 combination.

15 A lower hazard ratio indicated a lower risk of
16 death on histamine/IL-2 arm. As you can see, the hazard
17 ratio from all three studies are around 0.8. That is,
18 patients on histamine/IL-2 arm had about 20 percent less
19 chance of dying when compared to patients on IL-2 alone arm.

20 It is interesting to note that the log-rank p-
21 value is the smallest at the September 8th cutoff date.
22 Overall, these hazard ratios were very similar indicating
23 that there was no significant change in the survival
24 difference between the two arms with longer follow-up.

25 [Slide.]

1 This is the Kaplan-Meier curve of survival
2 analyses using the March 8th cutoff date.

3 [Slide.]

4 This is the survival curves using the September
5 8th cutoff date.

6 [Slide.]

7 This is the survival curve using the most recent
8 follow-up data.

9 There is not much difference between these three
10 analyses in terms of Kaplan-Meier curves.

11 [Slide.]

12 All these p-values I just showed you are not
13 adjusted for multiple comparisons.

14 [Slide.]

15 We performed subgroup analysis to look for
16 consistency, which we did not find.

17 [Slide.]

18 We looked at three subgroups which are listed on
19 this slide. 129 patients had liver metastases at study
20 entry. These patients represent 42 percent of the study
21 population. Median survival is 5 months on IL-2 arm and 9.2
22 months on histamine/IL-2 arm, strongly favoring the
23 histamine/IL-2 arm with p equals 0.0033.

24 176 patients had no liver metastases at study
25 entry. These patients represent 58 percent of the study

1 population. Median survival is 10.3 months on the IL-2 arm
2 and 8.7 months on the histamine/IL-2 arm, favoring the IL-2
3 arm, but this does not reach statistical significance.

4 We then look at the subgroup of patients with
5 skin/lymph node/lung only disease. These patients are
6 considered to have good prognoses. The median survival of
7 patients with skin/lymph node only disease is about 7 months
8 although there is wide variability. Median survival for
9 patients with lung involvement in the literature is about 11
10 months.

11 82 patients, that is, about 27 percent of the
12 study population have skin/lymph node/lung only disease.
13 Median survival is 12 months on IL-2 arm, and 10.4 months on
14 histamine/IL-2 arm favoring the IL-2 arm, but this does not
15 reach statistical significance.

16 [Slide.]

17 This is the survival curves in the liver
18 metastases subgroup, 129 patients.

19 [Slide.]

20 This slide shows the survival curves in 176
21 patients with no liver metastases.

22 [Slide.]

23 This is the survival curves in 82 patients with
24 skin/lymph node/lung only disease.

25 [Slide.]

1 We looked for supporting evidence from tumor
2 response rate and time to progression, but did not find any.

3 [Slide.]

4 The overall tumor response is very low, 3 percent
5 on each arm. By FDA assessment, here was only one CR, which
6 is on IL-2 arm. The other two CR's reported by the
7 applicants were not confirmed by appropriate imaging
8 studies.

9 [Slide.]

10 FDA assessment of time to tumor progression
11 differed from the applicant's in 223 patients out of 305.
12 Sixty-two patients had no follow-up scans after baseline
13 studies, 34 were on IL-2 and 20, histamine/IL-2. These
14 patients were not included in the FDA time to tumor
15 progression analyses.

16 Other differences in the methods used to determine
17 time to progression are listed here. FDA censored time to
18 progression on the date of the last imaging studies
19 submitted in the dataset. The applicant censored time to
20 progression on the last day when the patients were known to
21 be alive, which in some cases was the cutoff date for
22 survival analyses.

23 FDA did not count death as progression unless
24 progression was documented. All deaths were counted as
25 progression by the applicant.

1 For patients who progressed, FDA based the
2 question date on the date of the imaging studies documenting
3 the progression. The applicant based progression on the
4 date when the imaging study was read.

5 [Slide.]

6 This slide shows the FDA analysis of time to
7 progression in 243 patients. There is no difference between
8 the two arms.

9 [Slide.]

10 In summary, we have the following comments on the
11 efficacy results in the intent-to-treat population.
12 Survival difference in the ITT population did not reach
13 statistical significance.

14 P-value dependent upon cutoff dates, which were
15 not prespecified in the protocol.

16 Lack of internal consistency across subgroups.

17 No supporting evidence from tumor response or time
18 to tumor progression.

19 [Slide.]

20 The applicant is seeking marketing approval of the
21 histamine/IL-2 combination in patients with melanoma that
22 has metastasized to the liver. The efficacy claimed is
23 based on results in a subgroup of 129 patients with liver
24 metastases at study entry.

25 The second issue is whether survival difference in

1 this subgroup of patients represent persuasive evidence of
2 efficacy.

3 [Slide.]

4 MP-US-MO1 is not stratified by the presence of
5 liver metastases at study entry. Therefore, no stratified
6 randomization was performed in the liver subgroup. There
7 were many imbalances in prognostic factors consistently
8 favor the histamine/IL-2 arm.

9 [Slide.]

10 This slide listed the major imbalances between the
11 two arms in this subgroup. Except elevation of LDH, the
12 imbalances consistently favors the histamine/IL-2 arm.
13 There is a striking imbalance in a number of metastasis
14 sites between the two arms. The histamine/IL-2 arm has
15 almost twice as many patients with one site of disease as
16 compared to the IL-2 alone arm.

17 Having one metastasis at a site is considered a
18 favorable prognostic sign. In the series from University of
19 Alabama reported by Dr. Balch, et al., median survival of
20 patients with one single distant metastasis site was 7
21 months, with two sites, 4 months, and with three sites, 2
22 months.

23 Recent publication from M.D. Anderson by Ethan, et
24 al., emphasizes that single visceral organ involvement does
25 not have the same poor prognosis as multiple visceral organs

1 were involved even when the most favorable group of
2 patients, that is, those with lung metastases alone, are
3 excluded.

4 [Slide.]

5 We don't have complete information on prognostic
6 factors. For example, preceding stage of tumor is a
7 prognostic factor, but the study did not collect this
8 information. Information was collected on metastases
9 evaluable at the study entry, but not on those at first
10 diagnosis except the diagnosis date.

11 When we compared the baseline performance status,
12 which was obtained prior to randomization to that on the
13 first day of treatment, that is, cycle 1, day 1, we found
14 that 58 patients had a decrease in performance status, 33 on
15 IL-2 arm and 25 on histamine arm including 18 patients who
16 had a deterioration to performance status 2 or worse.

17 Within the liver subgroup, 28 patients had a
18 decrease in performance status including WHO-4, who had a PS
19 2 or worse on the first day of treatment.

20 [Slide.]

21 Using what we had, we performed adjusted analysis
22 to account for the detected imbalances. The performance
23 status using a model is based on performance status because
24 47 patients did not have performance status on cycle 1, day
25 1.

1 The FDA statistician, Dr. Sridhara, will go into
2 more details on this later, but briefly, the covariates
3 included in FDA models are slightly different than those
4 included as sponsor's model, and the details will be
5 addressed later.

6 After adjusting for these imbalances, both hazard
7 ratios and the p-values shifted indicating that these
8 imbalances contributed to the observed survival difference
9 in the liver subgroup.

10 [Slide.]

11 This slide showed the hazard ratio and p-value in
12 the FDA adjusted analyses. It is our view that because of
13 the large shifts in hazard ratio and p-value, one cannot
14 reliably estimate the magnitude of treatment effect by the
15 histamine/IL-2 combination in this subgroup of patients.

16 [Slide.]

17 A closer look at the liver subgroup revealed that
18 the overall survival difference is the most apparent in a
19 small group of 20 patients with only one site of metastases,
20 that is, liver only disease.

21 [Slide.]

22 As shown on this slide, there was a very large
23 difference in median survival favoring the histamine/IL-2
24 arm in 20 patients with liver only disease.

25 However, we must note that there were twice as

1 many patients on histamine/IL-2 arm as compared to IL-2 arm.
2 As I mentioned earlier, metastasis is a prognostic sign and
3 there were more patients with this prognostic sign on the
4 histamine/IL-2 arm making it impossible to assess. With
5 patients with disease both inside and outside the liver, the
6 treatment effect of histamine/IL-2 combination is less
7 apparent.

8 [Slide.]

9 Again, we looked for supportive evidence of tumor
10 response and time to tumor progression, but did not find
11 any. There were two partial responses occurred on the
12 histamine/IL-2 arm with a response rate about 4 percent.

13 [Slide.]

14 Follow-up available in 96 patients, about 74
15 percent of the liver subgroup, by FDA analysis there is no
16 statistically significant difference in time to progression
17 between the two arms in the liver subgroup.

18 [Slide.]

19 Our comments on efficacy in the liver group are
20 listed on this slide. Imbalances in prognostic factors
21 consistently favor the histamine/IL-2 arm. These imbalances
22 contributed to the observed survival difference between the
23 two arms by FDA adjusted analysis.

24 Treatment effect of the histamine/IL-2 combination
25 is most apparent in the small group of patients with liver

1 only disease.

2 No supporting evidence from tumor response and
3 time to tumor progression.

4 [Slide.]

5 The third issue that we are going to address, is
6 the histamine/IL-2 combination a well tolerated treatment
7 regimen?

8 [Slide.]

9 As shown on this slide, the majority of patients
10 completed no more than three cycles of therapy. Most of the
11 patients dropped out because of progression of disease.

12 [Slide.]

13 The histamine/IL-2 regimens are administered in
14 the outpatient setting except the first two doses of IL-2,
15 which was given in the clinic. Patients on IL-2 arm need to
16 self-administer subcutaneous injections twice a day for two
17 days during week 1 and week 3, and twice a day for five days
18 during week 2 and week 4.

19 [Slide.]

20 Patients on histamine arms must self-administer
21 subcutaneous injection of histamine twice a day for five
22 days for four weeks in addition to the IL-2 injections.

23 [Slide.]

24 According to the applicant, vials or pre-filled
25 syringes were not returned to study sites to check for

1 compliance. Patient compliance was assessed by diary. But
2 a lot of patients didn't complete diary because the diary
3 was implemented during the middle of the trial. Dosing
4 information was available in some patients by other source
5 such as home care records.

6 Overall, we do not believe that patient compliance
7 with medication was adequately assessed in this trial.

8 [Slide.]

9 This slide listed safety information on MP-US-MO1.
10 Based on the applicant's dataset, about 14 percent of
11 patients required dose reduction for adverse events. We
12 could not tell from the database whether the dose reduction
13 was for IL-2 or for histamine or for both.

14 Fifty-four to 60 percent of patients experienced
15 Grade 3 to 4 toxicity, and 11 percent died within 30 days of
16 the last dose of study medication. The numbers are slightly
17 higher in patients with liver metastases.

18 [Slide.]

19 Thirty-three patients died within 30 days of last
20 dose of study medication. Three deaths were attributed to
21 study medication by the applicant and all three were on the
22 histamine/IL-2 arm. We could not exclude toxicity-related
23 death in 12 patients based on review of the patient
24 narratives.

25 [Slide.]

1 Specific types of Grade 3 toxicities are listed on
2 this slide. There toxicities have been described in IL-2
3 trials. More patients on histamine arm had Grade 3
4 headaches. Otherwise, there was no excessive Grade 3
5 toxicities on the histamine/IL-2 arm.

6 [Slide.]

7 About 5 to 7 percent of patients suffered Grade 4
8 toxicity. The incidence of any specific type of Grade 4
9 toxicity is rare. Again, these toxicities have been
10 described in IL-2 trials.

11 [Slide.]

12 MA-0103 is an ongoing single arm study using the
13 same histamine/IL-2 regimen as in the major trial MP-US-MO1.
14 The applicant submitted updated adverse events data on 90
15 patients. Of these 90 patients, 16 died within 30 days of
16 the last dose of study medication, and 8 of these 16 deaths
17 were in patients with liver metastases at study entry with
18 an incidence rate of 23 percent.

19 The incidence of death is higher than what was
20 reported in MP-US-MO1.

21 [Slide.]

22 Grade 3 toxicity occurred in 54 percent of
23 patients, very similar to what was observed in MP-US-MO1.
24 No Grade 4 toxicity was reported. Incidence of specific
25 type of Grade 3 toxicity was also very similar to what was

1 reported in the MP-US-MO1 except chest pain, which was
2 higher in the single arm trial.

3 [Slide.]

4 The next few slides listed FDA overall summary.
5 Only one randomized study was submitted in this NDA to
6 support the marketing approval. The efficacy of the IL-2
7 regimen used in this trial is not known.

8 [Slide.]

9 The survival difference in the intent-to-treat
10 population did not reach statistical significance.

11 Survival difference in the subgroup of patients
12 with liver metastases should be interpreted with caution.
13 Imbalances in prognostic factors favor the histamine/IL-2
14 arm.

15 It is our view that effect of these imbalances
16 precludes the reliable assessment of the efficacy of the
17 histamine/IL-2 combination, and there is no supportive
18 evidence from tumor response rate or time to tumor
19 progression.

20 [Slide.]

21 Safety review showed that 58 percent of the
22 patients suffered Grade 3-4 toxicities and 11 percent died
23 within 30 days of the last dose of study medications.

24 I included here the reported safety data in the
25 most recent DTIC trial to show that incidence of Grade 3 and

1 4 toxicities could be as high as 36 percent in patients who
2 were treated with this drug which is considered to be well
3 tolerated.

4 I mean this is to make a point that it is not
5 possible to adequately assess the incidence of drug-related
6 toxicity in the absence of a non-IL-2 arm.

7 This concludes my presentation, and I think Dr.
8 Sridhara will come up here and to address some important
9 statistical issues in a major study MP-US-M01.

10 DR. SRIDHARA: Good afternoon. I am Rajeshwari
11 Sridhara, statistical reviewer of the study being presented
12 here.

13 [Slide.]

14 I am going to talk about the major statistical
15 concerns in the randomized M01 study focusing on the
16 efficacy aspect of the study. The major concerns can be
17 categorized into two broad areas, namely, the overall
18 finding in the ITT population, and the second one, liver
19 metastasis subgroup finding.

20 [Slide.]

21 There are three specific problems in the overall
22 finding. Problem 1 is regarding evidence of efficacy.
23 Problem 2 is regarding multiple survival analyses. Problem
24 3 is internal consistency. I will be focusing on problems 1
25 and 2 as problem 3 has already been addressed by Dr. Chiao.

1 [Slide.]

2 Let us look at the problem of evidence of
3 efficacy. First, the original protocol did not specify time
4 of final analysis date done even on a specific data cutoff
5 date. However, in the statistical plan submitted by the
6 sponsor in November of '99, an arbitrary cutoff date of
7 March 8, 2000 was chosen for final analysis. As for this
8 date and NDA submission, there is no difference between the
9 two treatment arms with a p of 0.1255 and a difference in
10 median survival of 0.9 months.

11 Note that the data by this March date was
12 reasonably mature with approximately 80 percent occurrence
13 of even. Even in subsequent analysis with updated data,
14 unadjusted p-value has remained above 0.05 level with 88
15 percent of even already occurred.

16 [Slide.]

17 The second problem refers to multiplicity issues.
18 This graph illustrates that repeated analysis result in
19 different p-values. This emphasizes the importance of prior
20 specification of time of final analysis based on number of
21 even.

22 Per sponsor's statistical plan, March 8th should
23 be technically considered as the final analysis date. It
24 appears that the nadir p-value was reached with September
25 8th data cutoff date.

1 The red line represents the 0.05 alpha level and
2 the green line represents 0.042 alpha level, which was the
3 alpha allocated for final analysis in ITT population per
4 protocol. Note that all p-values, that is, the blue
5 diamonds, are above 0.05. The x axis here is not to be
6 scaled by time, and the main point of this illustration is
7 that these p-values are not reliable.

8 [Slide.]

9 Regarding covariate adjusted analysis in the ITT
10 population, the International Conference on Harmonization
11 Guidelines states that, "When the potential value of an
12 adjustment is in doubt, it is often advisable to nominate
13 the unadjusted analysis as the one for primary attention,
14 the adjusted analysis being supportive."

15 It further continues to state that, "In most
16 cases, however, subgroup and interaction analyses are
17 exploratory and should be clearly identified as such; they
18 should explore the uniformity of any treatment effects found
19 overall."

20 We believe that the ITT population was randomized
21 and therefore we base our conclusion on unadjusted analysis,
22 and the adjusted analysis are used only to check for
23 internal uniformity and consistency of results in the ITT
24 population.

25 [Slide.]

1 In summary, the one randomized MO1 study conducted
2 by the sponsor in metastatic melanoma patients does not
3 demonstrate convincing evidence of survival benefit with
4 histamine plus IL-2 treatment in the overall ITT population.

5 [Slide.]

6 Moving to liver metastasis subgroup finding, there
7 are two major problems in the liver metastasis subgroup
8 finding. Problem 1 is the absence of overall survival
9 benefit, and problem 2 is imbalances and multiplicity
10 issues.

11 [Slide.]

12 In the absence of overall survival benefit, any
13 subgroup advantage is questionable. Again, the ICH
14 Guideline states that, "These analyses are not intended to
15 salvage an otherwise non-supportive study but may suggest
16 hypotheses worth examining in other studies or be helpful in
17 refining labelling information, patient selection, dose
18 selection, et cetera."

19 The common standard for strength of efficacy used
20 is p-value of less than 0.05 in two, well-controlled,
21 randomized studies. If the result of the single study
22 considered here is acceptable as sufficient evidence, then,
23 we should evaluate an interaction effect between treatment
24 and covariate. If the interaction is found to be
25 statistically significant, then, the overall results are not

1 interpretable and subgroups have to be studied individually.

2 In such a case, one can consider subgroup
3 analysis. Since the sponsor presented Table 11b of my
4 review, I would like to clarify that this model was
5 considered to test for interaction and find a rationale for
6 further subgroup testing.

7 This model was not intended to evaluate the
8 treatment effect in either of the subgroups, that is, either
9 the liver met subgroup or the non-liver met subgroup. A
10 subgroup analysis was further performed in my review, as
11 well.

12 [Slide.]

13 However, in the study, stratified randomization
14 within liver subgroup was not done. Imbalances favoring
15 histamine plus IL-2 arm in the distribution of patients are
16 observed. Furthermore, liver metastasis subgroup hypothesis
17 testing was added on to the original protocol after the
18 study had completed enrollment.

19 No allocation of alpha for testing liver
20 metastasis subgroup hypothesis was planned prior to the
21 start of the study. A statistical plan was submitted by the
22 sponsor prior to NDA submission with a plan for post-hoc
23 adjustment of type 1 error for testing liver metastasis
24 subgroup hypothesis.

25 [Slide.]

1 In this graph, red bars represent histamine arm
2 and blue bars represent IL-2 arm. The message to be taken
3 from this bar graph is that the red bars, which represent
4 the histamine arm, have higher percentage of patients in all
5 the better prognostic subgroups. For example, patients with
6 less than 65 years of age, female, performance status of
7 zero, no prior chemotherapy, et cetera.

8 Thus, this bar graph illustrates that the
9 imbalances observed favors the histamine arm. It should
10 also be noted that of the 14 characteristics presented in
11 this graph, 13 of them favored histamine arm.

12 [Slide.]

13 Because of these imbalances in the liver subgroup,
14 it is appropriate to further evaluate treatment, in fact,
15 using covariate adjusted analysis. Sponsor has submitted
16 models which are different models with different data cutoff
17 dates. They are also different from protocol specified
18 covariate and covariate specified in the statistical plan.

19 FDA has used consistent model at all times and no
20 selection was considered, that is, all characteristics
21 identifiable with imbalances were included in the model.

22 [Slide.]

23 In the original model, only two factors were
24 prespecified, presence or absence of liver metastasis, and
25 secondly, whether the patients received prior chemotherapy

1 or not. However, subsequently, an amended statistical plan
2 was submitted in November of '99 with the covariates listed
3 in column 1, namely, treatment, age as continuous variable,
4 sex, race, number of prior anti-cancer therapy, metastatic
5 disease sites categorized as skin, lymph, non-visceral
6 versus lung, GI, kidneys, adrenals versus liver, bone
7 disease, number of metastatic sites, LDH as a continuous
8 variable, prior chemotherapy as a continuous variable,
9 baseline performance status, and centers grouped into
10 Midwest, North, West, and South, and each region being
11 compared to South, not sure of reason behind this particular
12 comparison.

13 In the model submitted by the sponsor in the NDA
14 application, with the follow-up data up to March 8th, only
15 6--this is the second column I am talking now--only 6 of the
16 11 specified covariates were considered.

17 The covariates with asterisks were not
18 prespecified in the statistical plan or were not as
19 prespecified in the statistical plan. For example, the
20 number of prior anti-cancer therapy and LDH were used as
21 categorical variables instead of continuous variables as
22 specified in the plan.

23 Also, only bone metastatic disease site was used
24 in the model. The model submitted by the sponsor
25 subsequently in November with updated data considered all

1 factors although some of the continuous factors were
2 categorized.

3 The last column lists the factors included in the
4 FDA exploratory model. All factors with imbalances are
5 included in this model. Notice that three more additional
6 factors - baseline albumin, disease-free survival from
7 initial diagnosis to primary metastasis, and time from
8 primary metastasis to randomization were considered because
9 of the imbalances identified in these characteristics.

10 [Slide.]

11 Survival analysis adjusted for all covariates with
12 imbalances illustrated in the earlier bar graph were
13 included in these analysis. In this table, I am not listing
14 the covariates which went into the model because I have
15 included all the covariates that had imbalances, and only
16 giving the treatment effect here.

17 With the follow-up data up to March 8th, the p-
18 value for treatment effect for adjusting for factors for
19 imbalances was 0.1070 with updated follow-up data up to
20 September 8th using the same model, the treatment effect
21 after adjustment for imbalances was 0.0573.

22 Note that the p-value has dramatically increased
23 compared to the corresponding unadjusted p-value of 0.0033.
24 It should also be noted that this model does not include all
25 known prognostic factors in malignant melanoma.

1 Furthermore, the p-values presented in the table are not
2 adjusted for multiplicity, meaning multiple hypotheses or
3 multiple analysis.

4 For example, adjusting only for two hypotheses,
5 one in the ITT population and one in liver metastasis
6 subgroup, the p-value is 0.1146 with the updated data.

7 [Slide.]

8 Therefore, the take-home message is that the
9 adjusted model results are sensitive to inclusion and
10 exclusion of a covariate. They are also sensitive to
11 whether a covariate is used as a continuous variable or a
12 categorical variable.

13 More importantly, it should be kept in mind that
14 these p-values are not adjusted for multiplicity either for
15 multiple subgroups or multiple analyses.

16 Thus, there is no robustness in the liver
17 metastasis subgroup finding, and it is not possible to
18 assess the true treatment effect in this subgroup given the
19 imbalances from one single open label study.

20 Dr. Griebel will continue the presentation
21 addressing further the single study shift.

22 DR. GRIEBEL: Good afternoon. My name is Donna
23 Griebel and I am the medical team leader. We are here today
24 considering an application that has as its foundation a
25 single randomized controlled trial, and my job on behalf of

1 the FDA is to briefly introduce the perspective on how
2 important it is to keep in mind the limitations a single
3 trial has for allowing us to draw efficacy conclusions.

4 [Slide.]

5 It was not until the Federal Food, Drug, and
6 Cosmetic Act of 1962 that applicants were even required to
7 demonstrate that their product was effective as claimed. In
8 this Act, Congress required that applicants provide
9 substantial evidence of effectiveness, and they defined that
10 substantial evidence in the Act as data that came from
11 adequate and well-controlled investigations, and
12 importantly, the word "investigations" is plural, and the
13 Agency required from that time on that sponsors submit more
14 than one randomized controlled trial in support of the
15 effectiveness claim.

16 However, in 1997, the Modernization Act, Congress
17 gave the FDA some leeway to in some circumstances consider
18 data from an adequate and well-controlled single trial as
19 substantial evidence.

20 [Slide.]

21 The reasons why a single study has generally not
22 been considered adequate are listed in the Agency's guidance
23 to industry for establishing clinical effectiveness, and
24 these include any trial may be subject to unanticipated,
25 undetected, systematic biases that could lead to flawed

1 conclusions.

2 There is inherent variability within biological
3 systems that may produce a positive result by chance alone.
4 So, a positive result that may be thought due to treatment
5 effect may have occurred because of variability in the
6 disease across the study population or variability in
7 baseline characteristics of the participants in the study.

8 Applying the traditional p-value of 0.05 with a
9 two-tailed test, 1 in 40 studies of ineffective drugs will
10 be positive. One in 40 does not sound like a very alarming
11 proportion, but if you evaluate this proportion in view of
12 just looking at positive trials and looking at the
13 proportion of a group of positive trials that could actually
14 be false positive, factoring in the background probability
15 that you are actually testing an effective drug, you can
16 come up with a more hypothetical situation where you end up
17 with a more alarming proportion, where you could have as
18 much as one-third of those positive trials actually being
19 false positive trials.

20 [Slide.]

21 This concept has been described both by Dr. Simon
22 in his chapter in DeVita's Textbook of Oncology and recently
23 in a paper by Dr. Ian Tannock in a supplement to JCO just
24 last month.

25 In this paper, Dr. Tannock listed the causes of

1 false positive trials. They include mere chance alone,
2 prognostic factor imbalances that can happen just by mere
3 chance alone, multiple analyses of multiple endpoints, and
4 the concept that I just mentioned, low prior probability
5 that a new treatment will be a therapeutic advance.

6 [Slide.]

7 This situation is where you are testing many
8 drugs, very few of which are actually effective, and this
9 seems like a situation which is applicable to the field of
10 oncology today.

11 The example to clarify this in the paper that Dr.
12 Tannock gave is very similar to the one that Dr. Simon gave
13 in the chapter in DeVita. If you start with 200 trials and
14 you assume that you are testing in 10 percent of those
15 trials a truly effective drug, 20 of those trials will be
16 true positive trials.

17 In the remaining 90 percent of the trials that you
18 are conducting, you are testing ineffective drugs, so you
19 have 180 of the 200 trials that are true negative trials.

20 If you go back to your column of the 20 true
21 positive trials, and you have powered your trials 90 percent
22 power to detect the effect, you are going to miss the true
23 effect in two of those trials, 10 percent.

24 So, you are left with what is down in the lefthand
25 corner, 18 true positive trials where you actually detected

1 the effect. Going back up to your 180 true negative trials,
2 if you apply the 5 percent p-value of 0.05 in a single tail
3 this time, you come up with 9 trials that are false
4 positive.

5 So, in the end you have 18 plus 9, or 27 positive
6 trials, but 9 of those 27 trials are false positive. Nine
7 into 27 is one-third. One-third of your trials are false
8 positive, and that is a more alarming proportion than 1 in
9 40 that we just mentioned.

10 You can see from this that if you bump up the
11 testing of the truly effective side to, say, 50 percent, you
12 will bring down that proportion. So, if you use 50 percent
13 true positive trials, you will end up with approximately 5
14 percent of your positive trials being false positive.

15 [Slide.]

16 Well, unreproducible positive trials do happen in
17 the area of oncology and have occurred in the setting of
18 metastatic melanoma. Dr. Atkins brought up the tamoxifen
19 history in his presentation for the applicant, and in 1992,
20 an Italian oncologist group presented in a New England
21 Journal article the data from a trial that examined the
22 introduction of addition of tamoxifen to dacarbazine, and
23 they found a survival benefit that was statistically
24 significant favoring the tamoxifen arm.

25 There was a more striking survival benefit in the

1 subgroup analysis of that study in the female population of
2 the study. Subsequent trials examining the addition of
3 tamoxifen to chemotherapy or biochemotherapy have not
4 reproduced that statistically significant survival benefit.

5 [Slide.]

6 So, what does the FDA's guidance on establishing
7 clinical effectiveness say about relying on a single trial?
8 Well, it says that if you do this, it leaves little room for
9 study imperfections or non-supportive information. It
10 should be limited to situations where it is either
11 impractical or ethically impossible to repeat the study to
12 confirm the result.

13 [Slide.]

14 The guidance says that the characteristics of a
15 single trial that can stand a substantial evidence is a
16 large multicenter study, a trial whose design is
17 appropriate, the conduct is flawless, and there is minimal
18 possibility of bias due to baseline imbalances, unblinding,
19 and post hoc changes in analysis.

20 [Slide.]

21 The results should reflect a hypothesis that has
22 been documented in the protocol and the results should be
23 statistically persuasive.

24 [Slide.]

25 So, I return to the single randomized, controlled

1 trial that is the foundation of this application and ask has
2 this trial met the bars that have been set in the guidance.

3 [Slide.]

4 Well, this study was a randomized, controlled
5 trial, it was a multicenter trial, but it is a single trial.
6 The intent-to-treat analysis of the primary endpoint was not
7 statistically significant.

8 [Slide.]

9 There appeared to be a survival benefit in a
10 subset analysis of the patients with liver metastases, but
11 there were imbalances in prognostic factors in this subgroup
12 that favored the histamine/IL-2 arm, and the FDA's adjusted
13 analyses showed that imbalances influenced the observed
14 treatment effect.

15 [Slide.]

16 So, I would like to briefly review our questions.
17 We have five questions. The last two are approvability
18 questions. We have the safety question and we have two on
19 whether the study can stand a substantial evidence, and when
20 we refer to substantial evidence, we are talking about
21 whether the single trial can stand alone as substantial
22 evidence or whether it should be, if it is not substantial
23 evidence, that infers that it needs support of a second
24 trial.

25 So, the first question is a question about the

1 intent-to-treat analysis of the entire study population.

2 Does the survival difference in the planned
3 primary analysis of the study, the intent-to-treat analysis
4 of survival, represent substantial evidence of the efficacy
5 of histamine as an adjunctive treatment for IL-2 for
6 patients with metastatic melanoma?

7 [Slide.]

8 The second question again asks the question about
9 substantial evidence, but this time in reference to the
10 subgroup of patients with liver metastases in the single
11 study and whether it represents substantial evidence of
12 efficacy as an adjunctive treatment to IL-2 for patients
13 with melanoma that has metastasized to the liver.

14 [Slide.]

15 Finally, I will end with our safety question. We
16 ask whether the safety profile is acceptable.

17 We would be happy to answer questions, but I would
18 like to rest of the review team to come up and join me.

19 **Questions from the Committee**

20 DR. NERENSTONE: Does the ODAC Committee have any
21 questions specifically for the FDA reviewers?

22 [No response.]

23 DR. NERENSTONE: Thank you.

24 I would like to then open the discussion up to
25 ODAC. Dr. Pelusi has a question.

1 **Committee Discussion and Vote**

2 DR. PELUSI: I realize we are going to be talking
3 about some of our significant concerns regarding the design,
4 the implementation, and the evaluation of this study. One
5 aspect that I don't want to get lost, when we look at trials
6 especially for metastatic melanoma, is this whole issue of
7 quality of life.

8 I think that it is very difficult to pick an
9 appropriate scale, but the problem is, is if we pick scales
10 that we know probably will never be completed or that we
11 only have maybe some baseline, that doesn't tell us a lot.

12 We also already know that one of the biggest
13 impacts of this disease is on the family members, and we
14 expect the family members to provide a lot of that care
15 whether it is with this drug or with others.

16 So, the question is, as from the very beginning,
17 do we look at quality of life of the family and in
18 relationship to what happens when we put them on these
19 particular studies, because as providers, when we have to
20 look at offering treatment or not, the question is, is the
21 safety, is it safe in that home and what goes into making
22 that judgment, and do we have that kind of information, and
23 obviously we didn't see that here, but I think that that
24 becomes very important.

25 Also, the issue of many of these patients seem to

1 have home health support, as well as wonderful education
2 from nurses, and I think that this is a very important part
3 is again when we look at safety, we have to think about what
4 is the real world use of medications that are approved, and
5 the question again becomes do people have the ability to
6 always have a home health person go in, how do we look at
7 the compliance of how often the drug is actually taken or
8 documented in terms of side effects at home versus what just
9 happens in the office.

10 Again, not in relationship to this study, but
11 these are the issues that I think we really need to address
12 on every particular drug because this is a disease, it is a
13 disease that not only affects the patient, but the entire
14 family, and sometimes when we say let's offer something just
15 to offer it, again, what is it that we are offering, and
16 then I think that again the drug design and stuff will take
17 us in that direction.

18 DR. NERENSTONE: Dr. Dutcher and Dr. Redman were
19 asked to review and I wanted to perhaps ask if they wanted
20 to start with some comments.

21 DR. DUTCHER: Before we start that, I wonder if
22 there is any more information on those patients in the first
23 three months of treatment that fell off the curve before the
24 12-week evaluation.

25 DR. NERENSTONE: We are asking the sponsor to go

1 back to those patients, Dr. Redman's question from earlier
2 this afternoon.

3 DR. GEHLSON: Yes. Before cycle 2, there were 37
4 deaths, 27 were due to progressive disease, 17 on IL-2 and
5 10 on the histamine and IL-2 group. Ten of those deaths
6 were due to other causes, 7 on histamine/IL-2 and 3 on IL-2,
7 and we have discussed those.

8 That leaves the remainder of those patients.
9 There were a number of patients who withdrew consent or
10 withdrew for any other reason and for progressive disease,
11 and that is where we are today on that.

12 DR. NERENSTONE: Dr. Albain also had a question
13 for the sponsor.

14 DR. ALBAIN: I wondered if you could comment on
15 the reversal, so to speak, of the significant p-value
16 between your assessment of time to progression and the FDA
17 assessment of time to progression.

18 DR. GEHLSON: Yes. We can never anticipate what
19 the FDA has done. Because we didn't have a first evaluation
20 until 12 weeks of patients, did not have an evaluation or a
21 scan within that period of time, but they died due to their
22 melanoma, we considered death due to melanoma as progressive
23 disease, because their previous scan may have actually been
24 all the way back to baseline at that point, so there could
25 be 15 some-off weeks before they had a scan, so that would

1 make a big difference in the data because ours was actually
2 the date of death or the data of a confirmed progressive
3 disease.

4 Those are really the only differences that I could
5 identify. We haven't had a lot of time to discuss all of
6 the patients that they have included or excluded or all of
7 the fine details, but we certainly will do that with them
8 when this is done, but that is one I know for sure.

9 DR. NERENSTONE: I am going to open it up for
10 discussion then for anyone with any other comments or
11 questions.

12 DR. DUTCHER: And then to comment on the
13 statistical issues that were raised by FDA.

14 DR. SIMON: Well, I believe very strongly in the
15 importance usually of two clinical trials, and the basic
16 reason being I mean most of the clinical trials in cancer
17 that are done turn out to be negative even the large ones,
18 and so consequently, of the ones that are statistically
19 significant, a high proportion of them are false positives.

20 If we are not going to be making available to the
21 public a lot of ineffective and toxic treatments, then, the
22 only way really to guard against that is to have the two
23 trial rule. I think the situation is even more extreme when
24 you start talking about subset analyses.

25 Regardless of whether the subset was defined in

1 advance or not defined in advance or whether defining it
2 after accrual is completed is far enough in advance, it is
3 still a subset, and it wasn't really the primary focus of
4 this study. Had it been the primary focus of the study, the
5 study would have been on patients just with liver disease
6 and it would have been sized appropriately.

7 Consequently, I think if you approve drugs based
8 on one trial and significance in a subset, even with
9 adjustment for the multiple comparisons, you would be
10 approving a tremendous number of false positives.

11 I think for this particular trial, I personally
12 find it very hard to have any credibility in my mind in the
13 results. There is just too many imbalances that I just
14 don't understand.

15 I would like to believe the results and I hope the
16 results are true, and I really hope that a second trial can
17 be done and we can find out really whether it is true, but
18 given all of the imbalances and ineligible patients and
19 inevaluable patients and large numbers of patients dying in
20 the first two months, I certainly don't find this even
21 approaches convincing evidence of effectiveness overall or
22 for the subset.

23 DR. NERENSTONE: Dr. Redman.

24 DR. REDMAN: I agree with your comments especially
25 regarding the subset analysis. I know of no other drug--and

1 I am open for comments on it--cytotoxic, biologic, hormonal,
2 that is approved for a specific disease site, and not a
3 disease itself.

4 I know there have been multiple trials and subset
5 analysis that have found benefit for certain patient
6 populations for treatment, but overall, patient population
7 did not derive a benefit from that intervention, and I don't
8 know of any drug again that is approved for that.

9 I think the study that was done overall and the
10 primary analysis, the intent-to-treat showed no benefit or
11 no difference between the two treatment arms. It is hard to
12 say that there is any benefit even from the IL-2 arm itself.

13 If we want to address this, I think regarding
14 approving something for a single disease site, I think we
15 have to have an excellently controlled trial to answer that
16 question before we start going down that slope of approving
17 drugs for specific disease sites.

18 I don't think this trial met that criteria.

19 DR. NERENSTONE: There being no further comments,
20 maybe we can address the question.

21 Just to briefly review, we have talked about the
22 study MP-US-MO1 with the summary table, summarizes the FDA's
23 analysis of efficacy.

24 The first column, the ITT IL-2 survival of 8
25 months median versus the histamine/IL-2. 8.9 months with a

1 p-value of 0.0526. The subgroup liver metastasis IL-2, 5
2 month median survival.

3 The next box is the subgroup with the
4 histamine/IL-2 with the median survival of 9.2 with a p-
5 value of 0.0033. The non-liver metastasis subgroup, IL-2
6 alone of 10.3 versus histamine/IL-2 of 8.7 median with a p-
7 value of 0.7808. With the FDA response rate between zero
8 and 5 percent across the six categories.

9 The time to progression, the FDA, a p-value of
10 0.4108 in the entire group. The subgroup analysis, the
11 liver metastasis 0.1315, and the non-liver metastasis
12 0.9075.

13 The FDA's analysis of safety have been reviewed
14 with the IL-2, 10 percent death within 30 days of the study
15 medication; the histamine/IL-2, 11 percent death within 30
16 days of study medication with a 5 versus 7 percent Grade 4
17 and 59 versus 52 percent Grade 3 toxicities.

18 In addition, there are subgroup analysis in the
19 liver metastasis, IL-2 versus histamine/IL-2.

20 Discussion. Metastatic melanoma can have a
21 variable clinical course influenced by prognostic factors.
22 As they outlined, there were many imbalances in the known
23 prognostic factors and other patient characteristics between
24 the two treatment arms in a subgroup of patients with liver
25 metastasis because there is no stratified randomization.

1 substantial evidence of the efficacy of histamine
2 dihydrochloride as an adjunctive treatment with IL-2 for
3 patients with melanoma that has metastasized to the liver?
4 In other words, the subgroup with liver metastasis.

5 Discussion?

6 [No response.]

7 DR. NERENSTONE: All those people who think it
8 does represent substantial evidence of efficacy in that
9 subgroup?

10 [No response.]

11 DR. NERENSTONE: Opposed?

12 [Show of hands.]

13 DR. NERENSTONE: No abstentions.

14 We haven't concluded that efficacy has been shown,
15 so we don't need that one.

16 In view of the efficacy and safety data presented,
17 should histamine dihydrochloride be approved for adjunctive
18 use with IL-2 in the treatment of patients with metastatic
19 melanoma?

20 Discussion?

21 [No response.]

22 DR. NERENSTONE: All those who think it should be
23 approved, please raise your hand.

24 [No response.]

25 DR. NERENSTONE: Opposed?

1 [Show of hands.]

2 DR. NERENSTONE: And the last question. In view
3 of the efficacy and safety data presented, should histamine
4 dihydrochloride be approved for adjunctive use with IL-2 in
5 the treatment of patients with melanoma that has
6 metastasized to the liver?

7 All those in favor?

8 [No response.]

9 DR. NERENSTONE: All those opposed?

10 [Show of hands.]

11 DR. NERENSTONE: Does the FDA have any further
12 questions from the group?

13 [No response.]

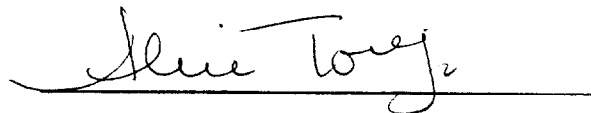
14 DR. NERENSTONE: Then, we stand adjourned, and we
15 will reconvene tomorrow at 8:00 a.m. no matter what the
16 weather.

17 [Whereupon, at 5:00 p.m., the proceedings were
18 recessed to be resumed at 8:00 a.m., Thursday, December 14,
19 2000.]

20

C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script, reading "Alice Toigo", is written over a horizontal line.**ALICE TOIGO**

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0.0001 51:23; 52:8;
53:12; 117:6
0.0003 117:3
0.0006 52:15
0.001 52:20; 55:4; 59:16;
65:19; 147:2
0.0015 81:20
0.003 42:6
0.0033 234:23; 253:23;
268:5
0.01 65:20; 195:5
0.022 59:21
0.042 248:2
0.049 110:22
0.05 247:14; 248:1, 5;
249:20; 256:8; 258:2
0.0526 185:18; 268:1
0.0573 253:21
0.07 55:24
0.08 55:25
0.1 175:2
0.1070 253:19
0.1146 254:6
0.1255 247:9
0.1315 268:11
0.25 89:5
0.4 206:5
0.4108 268:10
0.5 88:25; 89:5, 12
0.70 51:22
0.71 52:7
0.7808 268:7
0.8 233:17
0.9 247:10
0.9075 268:12
01 68:22
0103 187:12
024 76:11
025 86:21

1

1 32:16; 41:3, 13, 15;
53:23, 24, 25; 55:15, 15;
60:19; 116:25; 141:13;
143:25; 144:2; 147:17;
150:21; 152:1; 153:24;
154:3; 168:3, 3, 6, 8, 8;
169:15, 21, 23; 170:14;
172:19; 184:5; 193:21;
210:22; 213:6, 13, 14, 21;
224:18; 239:13, 13, 24, 25;
242:17; 246:22, 24; 249:8;
250:23; 252:3; 256:9;
258:8
1,000 14:3; 29:13;
180:22, 23
1,200 144:16
1,253 160:7
1,362 148:6; 229:1

1,521 145:19
1.1 73:12
1.44 146:12
1.8 89:11
1.89 147:7
1/2 130:13; 132:25
10 37:19; 40:17; 46:23;
51:7; 60:10; 93:24; 97:19;
24; 98:16; 131:24; 134:24;
144:11; 149:21; 150:23;
152:8; 187:16; 188:17;
211:21; 213:9, 18; 257:14,
23; 264:5; 268:14
10,000-fold 29:13
10.3 96:20; 235:1; 268:6
10.4 235:13
10.6 148:7
10.8 161:25; 188:6
100 29:13; 41:20, 24;
68:23; 72:23
100,000 159:15
10:55 88:9
10th 65:2; 68:12; 100:21
11 14:13; 95:15; 99:20;
146:5; 151:1; 152:9;
160:1; 213:9; 235:9;
243:15; 245:22; 252:16;
268:15
11.3 231:5
11.5 96:20
117 176:20
11:55 123:11
11b 174:10; 185:25;
250:3
12 45:21; 95:5; 149:24;
151:1; 152:9; 169:6;
170:17; 187:9; 191:20;
210:2, 5; 216:12; 223:5,
12; 224:18; 235:13;
243:23; 264:20
12-month 81:3; 210:8
12-week 224:22; 263:24
12.8 148:8
125 186:22
129 234:19; 235:18;
237:23
12A-30 7:15; 126:14
13 50:12; 95:5; 98:15;
176:10; 191:12; 251:11
14 48:10; 49:7; 80:22;
191:10; 221:5; 243:10;
251:10; 271:18
15 58:4; 81:9; 85:18;
152:8; 160:6; 182:24;
188:5; 191:9; 264:25
15-minute 149:21
150 58:13
16 58:16; 98:16; 150:3;
182:24; 244:15, 16
16-month 161:11
16.6 176:10
162 58:18; 160:10
17 174:10; 264:4
175 58:18

175,000 17:20
176 234:24; 235:20
17th 166:12
18 51:2; 78:8; 94:17; 96:5;
98:15; 99:9, 21; 105:18;
112:14; 155:21; 158:25;
172:4; 185:11, 17, 21;
187:19, 20; 232:2; 239:15;
257:25; 258:5
18-month 143:10;
185:25; 187:21
180 257:19; 258:1
18th 166:11
19 50:25; 94:17; 98:5;
100:19; 152:23
1962 255:6
1970's 148:17
1977 11:16; 12:22
1983 144:22
1992 258:19
1996 17:10; 35:19; 36:25;
48:8; 93:18
1997 17:13; 18:10; 169:5;
229:15; 231:9; 255:16
1998 58:15; 148:18
1999 48:9; 58:15; 93:19;
166:12; 169:5; 231:18, 19;
232:2
1:15 123:9, 12; 124:2
1:30 123:8
1st 231:9

2

2 40:11; 41:14, 23; 60:19;
74:13; 117:9; 130:13;
132:25; 148:25; 154:3;
162:11; 164:13; 168:3, 5,
5; 169:21; 172:20, 20, 20;
193:19; 194:2; 201:12;
202:3; 210:21, 21; 213:18;
217:7; 238:21; 239:16, 19;
242:18; 246:23, 25; 249:9;
264:3
2.3 51:6
2.4 188:11
2.5 17:3, 21; 18:21; 31:9;
41:2; 44:2; 88:25
2.8 50:21; 51:5; 194:16
20 11:21; 32:17; 44:3;
47:12; 52:13, 25; 71:17;
98:16; 99:9; 132:1;
145:24; 148:22; 228:23;
233:18; 236:13; 240:19,
24; 257:15, 20
20-726/S-006 8:12
20-minute 207:2
200 134:11; 144:21;
161:10; 257:13, 19
2000 46:23; 48:10; 65:24;
74:17; 78:10; 113:12;
143:23; 167:3; 169:7, 9;
185:11; 232:25; 233:2;
247:7; 271:19
201 48:8

208(b)(3 7:11; 126:7
21 48:13; 76:6; 96:5, 8;
100:16; 128:4
21-240 141:13
22 97:11; 233:3
223 236:11
23 81:8; 244:18
238 210:8
23rd 166:1
24 18:6; 20:9; 44:9; 46:7;
56:20; 57:1, 12; 59:23, 25;
60:11; 61:25; 72:8; 96:3;
231:19
240 210:5
243 233:1; 237:7
245 171:15
25 18:4, 11, 18; 20:6;
44:6, 14, 16; 45:4, 11;
51:11; 56:6, 10; 60:11, 17;
61:11, 14; 63:4; 81:9;
86:13; 134:23; 151:11;
239:15
26 49:14; 59:11; 99:8;
231:18
27 49:20; 161:20; 235:11;
258:5, 6, 7; 264:4
270 151:5, 16
272 171:15
28 76:6; 182:22; 183:3;
210:13; 211:23; 239:17
29 48:8; 52:6
2A6 105:25

3

3 49:21; 59:4; 60:18; 96:4;
112:11; 143:25; 152:20;
162:11; 168:3; 181:16, 22;
182:8, 17, 18; 202:3;
213:6, 11, 20; 221:20;
236:4; 242:17; 243:15;
244:1, 3, 4, 22, 25; 245:25;
246:24, 25; 264:6; 268:17
3-4 245:22
3.0 194:17
3.8 176:9
30 22:21; 51:22; 52:12,
25; 54:9; 85:24; 88:16;
98:17; 131:24; 181:3;
187:2; 211:22; 221:5;
232:18; 243:15, 19;
244:15; 245:23; 268:14,
15
30-month 150:10
300 68:18; 231:3
305 169:4; 236:11
31 112:14; 152:24; 184:23
32 81:8; 96:4; 98:3;
100:15, 19
324 58:21
33 49:6; 95:4; 97:10;
165:13; 187:22; 188:17;
239:14
33.4 206:2

337 58:16
34 236:13
34.9 206:4
35 59:21
36 59:15; 246:1
3690 149:9
37 50:24; 264:3
38 52:19; 53:2; 94:12
39 114:5; 186:18; 187:11
3:50 227:13
3A4 105:25, 25; 106:5,
12, 19; 121:1, 3

4

4 48:23; 60:18; 94:3;
98:17; 145:20; 147:15;
148:23; 162:9, 12; 168:5,
8; 176:10; 181:16, 22;
182:8, 13, 13, 15; 200:15;
210:12, 20; 238:21;
241:12; 242:18; 243:15;
244:7, 8, 24; 246:1; 268:16
4.7 188:11
40 22:22; 49:13; 79:16;
94:13; 96:10; 152:7;
225:5; 232:18; 256:9, 10;
258:9
413 160:9
42 95:4; 212:25; 219:8;
234:20
43 48:17
44 50:11; 85:20
45 59:20; 130:12; 144:11;
213:2; 219:8
45,000 143:23
450 47:17
453 94:6
454 94:6
458 94:2
47 239:24
49 52:18; 53:1

5

5 14:13; 47:16; 48:21;
58:11; 60:20; 84:4; 94:5;
144:12; 149:21, 23; 151:2;
162:6, 7, 8, 9; 168:7, 9, 11;
188:8; 234:21; 244:7;
258:2, 13; 268:1, 8, 16
5-year 154:3
5.0 148:7
5.5 176:15
5.7 52:9
50 45:17; 49:7; 98:10;
134:12; 144:11; 151:9, 12;
152:7; 177:10; 185:1;
231:4; 258:11, 12
508 176:21
51 112:11
52 268:17
54 244:22

55 27:20; 52:19; 58:16;
59:14; 85:15; 100:8;
174:21; 188:14
43:1; 51:19; 59:5;
100:8; 169:4
58 112:14; 234:25;
239:14; 245:21
59 268:17
5:00 271:17

6

6 50:18; 51:16; 81:13;
94:10; 18; 95:16; 98:16,
17; 112:12; 144:11;
147:16; 148:24; 150:4;
151:16; 162:9, 11; 166:1;
168:11, 11; 252:15
6--this 252:15
6-year 148:24
6.15 95:23; 100:18
60 22:21; 79:2, 9, 14;
85:15; 158:20; 181:3;
243:14
600,000 149:20
64 165:15
649 146:5
65 49:6; 58:6; 94:23;
172:11; 251:6
67 59:3
51:17
100:8

7

7 149:21; 233:3; 235:7;
238:20; 244:7; 264:6;
268:16
7,700 143:24
7.7 176:15
7.8 148:9; 231:5
70 49:6, 9, 19; 83:23;
84:5; 98:10; 100:9; 109:18
71 52:14
720,000 149:20
74 144:2; 174:21; 188:7;
241:14
75 17:12; 78:10
76-item 183:25
77 51:17
79 48:15; 98:14

8

8 83:21; 149:20, 23;
169:7, 9; 185:11; 186:2;
27:25; 244:16; 247:7;
24
8.7 235:2; 268:6
8.9 150:7; 267:25
80 47:13; 58:5; 72:14;
111:23; 231:3; 233:1;
247:12

817 160:7
82 235:11, 23
83 98:13
84 86:3; 171:18
85 94:24
86 49:9
88 76:5; 186:20; 187:23;
247:14
8:00 271:15, 18
8th 167:3; 186:19; 220:9;
232:15, 17; 233:2, 21;
234:2, 5; 247:22, 25;
252:14; 253:17, 20

9

9 58:24; 96:3; 148:24;
168:3; 258:3, 5, 6
9.1 52:8; 188:15
9.2 234:21; 268:4
9.4 51:15; 73:11
9.87 95:23; 100:18
90 95:1; 112:1; 152:25;
158:21; 200:15; 244:14,
15; 257:17, 21
907 48:20
916 14:5; 48:7, 13
92 49:8
939 93:19
95 53:21; 55:12; 152:1
96 241:14
97 72:22
98 193:1
99 193:1; 247:6; 252:2

A

a.m 123:11; 271:15, 18
abilities 42:3
ability 38:22; 40:21;
42:13; 157:4; 263:5
ablation 23:16
able 12:13; 40:4; 68:10;
75:23; 85:21; 128:22;
129:7, 9, 9, 13; 132:1, 14;
136:13, 17; 139:14; 140:1,
3, 22; 161:16; 166:14;
197:18; 202:16
abnormal 174:7
abnormalities 213:20,
21
abnormality 213:22
above 147:19; 148:14;
247:14; 248:5
absence 120:20; 166:4;
230:19; 246:6; 249:8, 12;
251:24
absolute 8:20; 200:14
absolutely 75:4; 135:2,
14; 161:5; 190:7; 218:2;
226:24
abstentions 269:21;
270:13

abundant 163:15; 199:3
accelerated 9:13, 17
accept 107:10, 21
acceptable 18:15; 74:17;
118:19; 119:24; 215:21;
224:22, 25; 249:22;
261:16
accepted 9:9; 18:25;
127:10; 135:8; 166:11
access 64:20; 68:5;
167:1; 208:23
accomplish 135:23
accordance 7:11; 126:7
according 85:18;
201:11; 214:4, 10; 242:24
accordingly 165:14
account 83:7; 147:21;
202:20; 239:22
accountability 204:11,
19
accrual 232:3; 266:2
accruers 93:21
accruing 107:24, 25
accurately 214:17
acetate 13:19; 31:4, 6, 9,
11, 16; 89:1
achieve 170:20
achieved 11:3; 98:4;
106:2
achieving 67:5
ACKERMAN 205:23, 23
acknowledge 165:25
acquire 34:18
across 34:3; 54:17; 56:2;
61:20; 237:16; 256:6;
268:8
Act 255:6, 8, 10, 16
action 30:7; 35:11, 12;
36:16
activated 156:7; 163:16;
199:8
activation 156:4, 18;
199:9
active 48:22; 58:23;
71:13, 15; 88:25; 94:5
actively 136:12
activities 114:23; 140:2
activity 28:15; 151:20;
156:20; 157:24, 25; 158:2;
198:14; 206:20
Actually 12:10, 25;
13:12; 16:2; 65:1; 70:12;
72:4; 74:16; 75:19; 76:24;
82:23; 85:13; 86:7, 14;
89:17; 111:21; 112:16, 18;
120:24; 132:14; 134:9;
138:23; 139:2, 18; 140:11,
21; 142:10, 13, 13; 155:24;
156:2, 8, 16; 158:9, 23, 25;
159:18; 160:1, 11; 163:16;
165:12, 20, 25; 166:8, 9;
168:10, 17; 169:9; 170:6,
8, 12; 171:17, 22, 24;
172:10, 17; 173:3, 10;
174:5, 13, 14; 178:10, 19;

180:1, 20; 181:5, 11, 17;
183:1, 23; 184:20; 185:10;
186:13, 20, 22; 187:3;
188:3; 189:3; 191:18, 22;
192:2, 5; 193:4, 24;
194:15; 195:4; 196:4, 16,
23; 197:22; 198:3, 5;
199:8; 200:1, 1; 201:3;
203:22; 204:7, 15, 17;
205:1, 3, 21; 206:23;
208:2, 16, 23; 209:10, 11,
12; 210:2, 6, 18; 211:21;
212:10; 213:15; 217:20,
21; 220:6, 11; 221:3;
222:13, 17; 223:4, 20;
226:14, 25; 256:13, 15, 18;
257:8, 25; 263:7; 264:23;
265:1
acute 160:4
add 30:18; 121:25;
127:13; 156:18; 157:2;
174:12; 175:16; 176:1;
198:4, 25; 218:12, 13, 15
added 68:25; 84:25;
158:10; 164:14; 182:3;
185:6; 230:17; 250:17
adding 149:3; 190:8
addition 12:15; 20:1;
29:12; 37:15; 57:23;
59:19; 61:25; 93:6; 120:4;
121:15; 126:9; 136:19;
142:16; 149:9; 151:16;
154:5, 15; 158:5, 14;
164:10; 171:16; 177:2;
181:20; 182:9; 183:10, 17;
184:9, 16; 185:4; 187:4;
190:2; 242:22; 258:22;
259:2; 268:18
additional 11:21, 23;
57:7; 68:20, 20, 23; 218:9;
230:1; 233:2; 253:5
address 7:24; 8:8; 63:24;
75:15; 77:2; 86:25;
126:22; 129:20; 195:7;
203:3; 205:5, 21, 25;
206:8, 23; 216:8; 228:2;
242:5; 246:8; 263:11;
267:13, 20
addressed 139:24, 25;
189:6; 212:6; 240:5;
246:25
addresses 7:1; 125:23
addressing 128:12;
209:23; 254:21
adds 91:21
adequate 9:12, 13, 17,
18; 10:13; 39:19, 23; 56:7;
59:24; 61:10; 120:17, 18;
122:21; 213:16; 215:11;
255:11, 18, 22
adequately 243:7; 246:5
adipose 28:11; 38:20;
39:13
adjourned 271:14
Adjunct 155:5; 163:18;
167:14; 190:12
adjunctive 261:5, 12;
269:13; 270:2, 17; 271:4

adjust 166:18; 171:3;
172:23; 226:21
Adjusted 47:23; 53:10;
55:2; 165:6; 185:1, 23;
234:13; 239:21; 240:12;
241:23; 248:9, 14, 22;
251:15; 253:11; 254:7, 9,
14; 260:12; 269:4
adjusting 47:24; 48:4;
177:5; 195:22; 240:6;
253:18; 254:4
adjustment 248:12;
250:23; 253:21; 266:9
adjustments 82:10;
227:5
adjusts 195:23
adjuvant 12:9; 26:17;
34:9; 45:21, 22; 48:1;
50:25; 51:2, 4, 5; 53:7;
54:11, 23; 56:3; 61:21;
63:5; 90:1; 92:11, 13;
94:14, 15; 110:11, 20;
111:24; 112:2, 7, 13, 19;
116:12, 18, 20; 122:3, 9;
213:5
administer 140:19;
204:18, 22
administered 128:24;
149:20, 23; 162:18; 184:1;
206:3; 242:13
administration 207:10;
208:3
admission 212:2
admit 79:22
admitted 139:21
adopt 23:7; 75:8
adrenal 17:9; 28:8; 39:1
adrenals 252:6
adult 190:13
advance 65:2; 257:5;
266:1, 1, 2
advanced 8:19; 9:7, 22;
10:8, 24; 11:7, 15; 16:12,
25; 17:5, 11, 15; 18:16, 19;
19:2, 6, 10, 13, 22; 20:21;
26:15; 31:24; 43:23; 44:7;
45:12, 24; 50:19; 51:8;
56:9; 61:12; 62:5, 10, 18;
79:8; 87:2; 90:18; 91:2;
92:12; 94:19; 96:14;
101:19; 102:2; 117:12;
118:2; 119:6; 135:4;
137:5, 8; 160:9, 25;
164:19; 168:15, 25;
183:11; 188:10; 189:9;
190:13
advantage 31:22; 66:3;
150:2; 154:21; 199:11;
203:10; 249:13
advantages 56:13; 75:14
adverse 17:22; 47:7;
60:9, 12, 13, 15, 18, 23;
61:6; 98:20; 99:15; 100:7,
9, 11; 101:1, 6; 108:25;
180:24; 181:2, 15, 22;
182:1, 2, 2, 8; 183:6;
202:14; 210:12; 221:25;

243:11; 244:14
adversely 184:10
advisable 248:12
Advisory 5:4; 16:17; 35:5
advocate 109:5; 130:4; 138:20
AE's 183:7
Affairs 16:21
affect 28:22; 183:18; 184:10; 230:7
affected 37:8; 77:6
affecting 198:7
affects 263:13
affinity 106:1
afraid 226:16
afternoon 127:6; 132:20; 133:20; 138:11; 141:10, 18; 142:2, 19; 143:2, 18; 227:13, 17; 246:10; 254:22; 264:2
afternoon's 123:10; 127:3
AFTERNOONSESSION 124:1
again 31:8, 11; 44:25; 48:18; 53:14; 55:5; 66:12; 68:19; 71:21, 24; 77:18; 80:21, 25; 84:9; 98:10; 99:1, 5, 25; 109:17; 113:6; 114:18; 116:20, 24; 119:8; 124:8; 138:1; 157:22; 158:4, 14; 162:12; 166:18; 171:4; 179:24; 180:19; 187:16, 25; 192:17; 212:4; 241:9; 244:9; 249:13; 261:8; 263:3, 5, 10, 15, 16; 267:8
against 108:1; 127:25; 265:22
Agarwala 142:6; 180:19; 192:6; 206:23; 207:1, 24
age 22:7; 23:24; 27:20; 49:5, 8; 59:3; 83:23; 84:4; 94:23, 23; 100:5, 7, 8, 8, 9, 10; 109:18, 18; 128:4; 144:11; 169:15; 172:11; 251:6; 252:3
Agency 7:6; 46:25, 25; 68:3; 70:17; 126:2; 255:13
Agency's 7:15; 126:13; 255:22
agenda 7:5, 18; 11:24; 126:1, 16; 143:2
agent 26:15, 16, 22; 31:4; 32:17; 43:14; 74:17; 107:6, 7; 113:7; 121:15; 154:2
agents 15:17; 22:17; 23:4, 5, 6, 19, 20, 24:25; 27:12; 28:15, 16, 25; 29:2; 31:20; 33:25; 34:14, 15, 19, 21; 36:16; 40:10; 45:7; 60:24; 73:4, 14; 107:20; 110:24; 116:4; 121:10, 10; 122:6; 135:21; 136:17; 149:3
aggregate 209:18

aggressive 146:18
ago 13:17; 128:2; 130:16; 151:6; 232:16
agonist 121:14, 16
agonists 23:18
agony 128:15
agree 75:7; 100:22; 102:15; 111:9; 113:24; 118:1, 21; 165:19; 193:21; 219:4; 266:24
agreeable 118:12
agreed 18:13; 46:24; 68:4
agreement 18:11
agrees 92:1
ahead 69:5; 72:18; 102:21; 195:1
Ajay 19:16; 35:1, 6
AJCC 144:16; 147:21
al 238:19, 24
Alabama 125:15; 238:19
alarming 256:10, 17; 258:8
ALBAIN 6:11, 11; 15:13, 14, 23; 63:6, 7, 17; 65:6; 81:22, 23; 83:5, 20; 84:7, 19; 85:3; 102:12, 20; 109:9, 10, 14; 118:4, 5; 119:7, 8; 121:24, 25; 125:12, 12; 201:15, 16; 202:10, 21; 203:8; 221:12, 13, 19; 222:1, 4; 264:12, 14
albeit 112:24
albumin 169:15; 173:5; 200:14; 253:6; 269:2
Alexander 142:9
alive 145:5; 151:2; 171:5; 220:6, 12; 232:17; 236:21
allocated 248:3
allocation 250:19
allow 49:23; 65:9; 202:8; 204:15; 212:21; 215:3; 218:9; 227:5
allowed 68:24; 74:22; 133:7; 161:19; 164:24; 168:17, 20, 25; 191:7; 205:14; 222:19, 22; 225:24
allowing 255:3
allows 174:11
alluded 151:9; 163:4
almost 11:21; 40:11; 133:7; 144:16; 238:15
alone 9:18; 51:1; 128:12; 129:2; 152:12, 18; 153:18; 154:7, 12; 158:11; 161:10; 162:19; 164:13; 170:23; 171:6; 191:10; 199:9; 201:22; 206:3; 212:25; 213:6; 229:24; 230:12; 233:19; 238:16; 239:2; 256:3; 257:1, 3; 260:21; 268:6
along 21:16; 26:14; 86:12; 204:5; 207:8

alpha 25:4; 156:19; 162:18; 166:7; 248:1, 2, 3; 250:19
alpha-interferon 154:6; 160:2, 24; 198:25; 230:12
alphabetically 109:11
alter 71:13
alternate 72:1
alternating 168:5
alternative 151:24
although 39:23; 52:24; 76:10; 87:11; 89:2; 92:3, 7; 109:22; 122:16; 140:12; 187:15; 202:17; 229:7; 235:8; 253:1
always 8:21; 36:4; 53:11; 55:3; 108:24; 132:6, 8; 163:2; 168:9; 217:23; 263:6
ambiguous 208:12
amenable 45:13; 50:19
amended 49:23; 252:1
amendments 226:25; 227:1
America 104:11
aminoglutethimide 13:21; 29:5; 37:24; 73:8, 12, 13, 17, 25; 74:2; 89:2
AML 162:16
among 53:15; 55:6
amount 36:11; 205:25
amounts 39:15, 23; 41:17; 112:2
ample 143:12
analyses 46:16; 47:20, 21, 23; 48:3, 25; 64:23, 24; 77:7; 82:21; 104:7, 12; 165:14; 166:3; 176:13; 177:5; 195:15; 202:11, 18; 209:7; 220:14; 229:1, 13; 231:14; 232:13; 233:10; 234:2, 10; 236:15, 22; 240:12; 246:23; 248:16; 249:14; 254:15; 257:3; 260:13; 265:24
analysis 46:10, 15, 16, 22; 48:10, 19, 21; 53:5, 9, 15, 18, 21; 54:5, 21; 55:1, 6, 9, 12, 19; 56:17; 58:20, 22; 64:25; 65:1, 10; 68:13; 80:2; 81:16; 82:15, 24, 25; 84:1, 9, 12, 13; 90:14; 95:10, 11, 12; 97:16; 104:10; 116:14; 144:23; 148:8; 166:6, 8, 10; 167:6, 10; 169:6; 171:23; 173:2; 174:9, 16, 17, 18; 175:25; 187:24; 193:12, 13; 197:7; 202:23; 203:2, 9; 205:4; 209:1, 13, 22, 23, 24, 24; 211:21; 215:23; 216:6; 218:24; 219:15, 20; 220:11, 11; 221:22; 222:9; 226:3; 231:7, 19; 232:1, 5, 6; 234:15; 237:6; 239:21; 241:15, 23; 247:4, 7, 13, 18, 20, 23; 248:3, 9, 13,

14, 21, 22; 250:3, 10; 251:15; 253:11, 13; 254:3; 259:1, 19; 260:6, 10; 261:1, 3, 3; 266:25; 267:5, 10, 23; 268:10, 13, 18; 269:8, 11, 12
analytical 63:12
analyze 12:16; 85:6; 115:7; 210:2
analyzed 80:3; 162:24; 209:4, 17; 232:4
analyzing 209:16
anaphylactic 180:22
anaplasia 21:17
anastrozole 29:8, 24; 30:20; 31:2, 6, 14, 21; 32:9, 16, 23, 24; 33:3, 7, 13; 36:14; 37:17; 38:4; 40:1, 7, 12, 18; 41:3, 5, 6, 13, 14, 16, 17; 42:1, 5, 10, 24; 43:2, 6, 8, 12, 13, 14; 62:13; 73:2, 9, 20; 89:20; 110:3; 114:15, 16; 116:5
anchored 138:24
and/or 45:15; 57:14; 59:5; 75:21; 80:4; 146:19
Anderson 5:22; 124:21; 147:1; 238:23
androgenic 28:2
androgens 28:9, 9, 13; 34:16
androstenedione 28:3; 29:20; 39:1
anemia 151:13
anergized 199:4
Angela 39:5; 42:18
angina 98:21
angiogenic 180:6
animal 43:15; 159:11, 12
animals 37:9; 42:23, 25; 43:1; 159:20
announcement 7:1; 125:22
answered 85:10; 167:18
antacids 205:15
antagonists 23:21
antagonize 36:7
anti 180:5
anti-cancer 172:12; 252:4, 20
anti-estrogen 17:11, 17
Anti-seizure 106:16
antiaromatase 28:24
antibiotic 151:18
anticancer 169:20
anticell 156:3
anticipate 264:18
antiestrogen 27:5; 30:12; 43:15; 90:21
antiestrogens 23:18, 20; 24:3; 25:1; 26:7, 12; 35:13; 36:9, 17; 42:16
antihistamines 203:25; 205:12

antitumor 30:6; 43:14; 73:15
Antonio 75:11
anxiously 129:12
apologize 212:23
apoptose 25:15
apoptosis 157:15
apoptosis--and 158:17
apoptotic 157:16; 158:19, 21
apparatus 21:12
apparent 146:16; 240:18; 241:7, 25
apparently 88:15
appear 146:18; 206:13
appearance 7:3; 125:25
appeared 99:10; 101:8; 220:16; 226:1; 260:9
appears 152:10; 210:14; 247:24; 269:8
applicable 257:9
applicant 228:7; 229:15; 230:10; 232:24; 236:19, 25; 237:3, 20; 242:24; 243:21; 244:14; 258:19
applicant's 236:11; 243:10
applicants 236:7; 255:6, 8
application 8:8; 78:21; 101:3, 12; 227:20; 252:14; 254:24; 260:1
applied 34:3; 165:2
applies 107:2
apply 258:2
Applying 256:8
appreciate 87:23; 123:8; 196:3
approach 68:23; 107:8, 11; 116:13
approached 97:3
approaches 266:21
appropriate 66:10; 175:17; 203:15; 226:1; 236:7; 251:14; 259:17; 262:9
appropriately 197:18; 266:6
approvability 260:17
approvable 122:25
approval 8:18, 23, 25; 9:6, 11, 12, 13, 17, 1^o, 21; 10:7, 13, 15, 16, 18, 20, 23; 11:10, 17; 14:20; 17:1; 30:21; 43:22; 61:11; 62:7; 78:22; 90:20; 101:13; 117:10, 11, 14, 24; 118:1, 22; 150:6; 177:12; 186:24; 228:7; 237:20; 245:6
approve 118:6; 133:11; 137:25; 266:7
approved 11:15, 16, 23; 12:7, 22; 13:7, 10, 11, 12, 17; 15:24; 17:10, 13; 26:11; 30:17, 20; 31:7;

32:8, 16, 17; 37:20; 41:2, 3; 102:1; 110:3; 135:20, 21; 136:16; 148:16, 17, 18; 19:12; 263:4; 267:2, 8; 270:17, 23; 271:4
approving 113:10, 12; 266:10; 267:14, 16
approximately 49:15; 50:13; 54:9; 58:13; 60:19, 20; 65:19, 20; 68:19; 72:14; 78:8, 10; 79:9; 93:24; 94:10, 12, 24; 95:5; 138:14; 152:20; 247:12; 258:13
approximations 23:9
April 166:1; 229:15
ARBC-3 73:15
arbitrarily 40:6; 41:12
arbitrary 247:6
area 29:15; 38:14; 104:3, 7, 10; 110:4; 134:8, 13; 184:19; 258:17
areas 246:17
argument 85:14; 86:7, 8; 199:16; 214:22
arguments 115:10
Arimidex 13:7, 12, 16, 17, 22, 24; 14:5, 7, 12, 14; 37:21; 80:2, 4
arisen 12:11
arm 12:19; 45:4, 5; 47:18; 113:63; 81:18; 86:2; 115:19; 91:5, 5; 104:17; 136:24, 24; 161:19; 175:6, 6; 187:11; 191:12; 196:9, 22; 201:12; 202:3; 210:15, 15; 213:3, 4, 6, 7; 230:15, 19; 232:21; 233:11, 12, 13, 16, 18, 19; 234:21, 22, 23; 235:1, 2, 3, 13, 14, 14; 236:5, 6; 238:8, 12, 14, 16; 239:15, 15; 240:24; 241:1, 1, 4, 12, 21; 242:15; 243:22; 244:3, 5, 12; 245:2, 14; 246:6; 250:15; 251:1, 2, 4, 9, 11; 258:24; 260:12; 267:12; 269:4
armed 137:13
arms 14:11; 45:9; 94:3, 19, 24; 98:23; 99:2, 12; 117:8; 183:8; 187:1; 191:3, 25; 193:23; 194:3, 13; 196:24; 202:1; 204:2; 216:21; 217:4; 220:23; 230:6; 232:10; 233:6, 24; 237:8; 238:11, 14; 241:17, 23; 242:20; 247:9; 267:11; 268:24
Aromasin 37:22; 38:5
aromatase 17:8; 23:18; 24:3; 28:5, 15; 29:11, 18; 10:17, 22; 31:15; 32:5; 7:17; 34:11, 12; 35:11, 15, 16; 36:13, 21; 37:3, 4, 13, 16, 19; 38:5, 6, 7, 17, 22, 23, 23; 39:6, 6, 8, 10, 16, 18, 18, 19, 23; 40:1, 9, 20; 42:9, 13, 14, 16, 22;

43:11, 13; 62:11; 72:20, 22; 73:10; 74:6, 13; 88:23; 89:16; 110:5; 111:15; 114:1, 2, 14; 115:19; 122:3
aromatization 28:9, 20; 41:10, 18, 20, 21, 25, 42:2, 4, 9; 73:3, 11, 23
around 5:9; 83:9; 129:11; 133:1, 2; 155:24; 159:8; 233:17
arrest 211:8
arrive 27:11; 137:13
arthralgia 60:20
article 258:21
artifact 222:15
ASCO 152:16
ASH 198:2
ask-I 209:19
aspect 246:16; 262:5
assess 241:4; 246:5; 254:18
assessed 50:1; 59:14; 197:2; 214:17; 243:1, 7
assessment 67:13; 76:21, 21, 21, 23; 80:10; 195:12, 13; 196:1; 236:5, 10; 245:16; 264:16, 17
assessments 47:6; 196:20
assigned 44:17; 57:2
assignment 77:10, 15; 78:24; 107:5
assist 36:3
Assistant 134:6
associated 147:18; 153:23
assume 85:22; 202:18; 215:5; 257:14
assumed 58:6; 210:5; 221:2
assuming 216:21
assumption 47:10; 58:2
assurance 114:24
assure 103:2
assured 69:10, 13
asterisks 252:17
astonished 136:23
astoundingly 225:4
at-home 204:21
atherosclerotic 98:22
Atkins 142:8; 143:4, 15, 16, 18; 155:1, 2; 162:2; 163:4; 179:18; 181:17; 189:24; 201:17, 25; 202:16; 258:18
attack 132:1
attacked 217:21
attempt 69:14; 76:23; 86:20
attendant 33:15
attending 20:2, 15
attention 22:5; 26:2; 62:19; 113:10; 116:25; 167:24, 25; 248:13

attributable 151:17; 152:12
attribue 86:16
attributed 71:24; 243:20
audience 8:7
audio 5:11
August 58:15
available 10:4; 20:3; 23:5, 16; 29:18; 33:20; 37:25; 38:3; 45:6; 46:13; 66:9; 83:18; 89:3, 22; 113:17; 131:2, 13; 142:3; 167:9, 18; 241:14; 243:4; 265:20
average 74:3; 191:24, 24
avoid 71:7; 137:24
await 110:15; 122:8
awaiting 129:12
aware 7:20; 107:4; 126:18; 202:11; 207:24
awareness 127:11
away 107:9; 132:16, 16, 17; 133:3; 140:4
awful 74:2
axis 53:23; 54:4; 55:14, 19; 248:5

B

B 156:15
B16 159:14
back 34:1; 38:2; 42:12; 60:20; 80:24; 88:2; 104:19; 123:9; 132:14; 143:4; 200:21; 203:15; 216:4; 227:13; 257:20; 258:1; 264:1, 24
background 8:17; 64:3; 133:25; 143:3, 20; 256:14
bad 74:25; 144:10; 154:18
badly 10:19
balanced 49:12, 18; 50:4, 16, 23; 59:2; 109:2; 170:12; 230:6
Balch 144:21; 145:13; 238:19
bald 133:2
bar 251:3, 8; 253:12
bars 251:1, 2, 3; 260:2
base 73:25; 248:21
Based 7:5; 26:9, 11; 40:24; 66:18; 75:2; 76:22; 80:17; 101:13, 25; 103:6; 126:1; 152:5, 6; 166:3; 178:22; 180:24; 207:3; 215:23; 230:24; 237:1, 3, 23; 239:23; 243:10, 23; 247:20; 266:7
Basel 35:7
baseline 44:21; 47:6, 25; 48:4; 49:4; 50:3, 16; 53:7, 19; 54:3, 23; 55:2, 10, 18; 59:2; 92:16; 165:5; 171:1; 172:16; 179:14; 196:17,

19, 21; 236:12; 239:11; 252:9; 253:6; 256:7; 259:18; 262:11; 264:24; 269:9
basic 265:15
Basically 108:5; 111:5; 128:6; 214:2
basing 197:6
basis 11:17; 13:9; 18:2; 61:11; 113:16; 122:5; 127:20; 140:16; 166:18; 167:7; 196:14; 208:21; 214:11
baths 131:18
bay 137:22
Baylor 6:5; 125:5
BCNU 149:5
bear 5:6; 203:11
bearing 26:6
beast 137:21
beat 15:21; 16:5; 129:18
beating 15:2
beautifully 30:8
became 10:20; 33:7; 45:6; 132:18; 133:6; 139:11
become 23:5; 27:22; 30:7; 132:21; 135:14; 269:5
becomes 38:21; 215:24; 262:24; 263:5
becoming 32:1; 38:13
began 29:4; 128:18
begin 5:12; 8:11
beginning 30:9; 33:18, 23; 204:9; 262:16
behalf 16:22; 141:6; 254:25
behind 202:5; 252:11
Beijing 93:23
belly 132:19
belong 38:4
below 106:3
benefit 11:5; 15:16, 17, 18, 21; 16:1, 3, 6; 18:23; 46:6, 8; 47:22; 52:18, 23; 53:3; 56:16; 61:19; 67:1, 2, 4, 5; 73:22; 78:17; 84:22; 91:20, 20; 110:1, 9, 22, 24; 121:16; 135:5, 20; 137:2, 5; 138:2; 148:19; 149:10; 153:4, 10, 13; 161:17; 163:21; 175:23; 177:9, 12; 179:21; 180:10; 183:13; 188:1; 189:4; 190:3, 9; 202:24, 25; 218:7; 225:14; 230:17; 249:3, 9, 12; 258:23, 25; 259:4; 260:9; 267:5, 7, 10, 12
benefit-risk 19:4
benefits 56:14; 62:6
benefitted 150:16
besides 103:19
best 23:6; 87:5; 106:8; 127:24; 147:14; 204:23

beta 25:4
better 21:13; 27:13; 30:13, 13; 31:15; 33:4; 43:3, 4, 6; 66:20, 22, 24; 73:17; 79:19; 89:9; 136:11; 140:22; 147:12; 167:16; 205:21; 207:8; 217:24; 251:5
beyond 83:24; 132:5; 135:7; 144:6; 191:20, 23; 232:19
Bhatnagar 19:16, 17; 35:1, 4, 6; 72:19, 25; 74:8; 89:14
bias 107:5, 17; 222:21; 259:18
biases 255:25
BID 168:9
big 132:19; 226:22; 265:1
biggest 139:19; 262:12
Bill 35:21; 38:14
billion 178:8, 9
Billy 127:9; 128:4; 129:12
bimolecular 57:25
bind 25:1, 12
binding 24:14; 25:5; 36:4, 7
binds 35:23
bioavailability 71:5
biochemotherapy 152:4, 11, 17, 19; 153:17; 154:13; 259:3
bioequivalence 69:13, 19; 70:14, 17; 91:14
bioequivalent 70:18; 91:15
biologic 21:8; 197:4, 8, 16; 198:15; 207:19; 215:18, 24; 267:1
biological 40:21; 41:22; 256:2
biologics 110:25; 180:6
biology 25:17; 29:15; 167:24; 216:18; 218:23
biopsies 198:9
biostatisticians 64:6
biostatistics 20:13, 17
biosynthesis 17:9; 28:21; 36:12; 37:5
Birmingham 125:15
birth 129:8
bis 84:10; 85:4
bis-phosphonate 84:8
bis-phosphonates 84:14, 17, 20, 23
bit 5:7; 24:1; 32:24; 64:3; 88:25; 91:4; 93:2; 96:16; 111:20; 132:3; 133:25; 173:9; 179:20, 23; 200:2; 207:17; 218:13
black 187:10
blastic 49:24
BLAYNEY 6:13, 13; 7:12; 13:6, 7; 66:16, 17; 67:6; 68:12; 69:3, 6, 23; 71:16;

72:1, 7, 16; 86:13; 102:23, 24; 103:5, 8, 10, 13, 16, 22; 113:23, 24; 115:11, 24; 126:10
bleed 211:8
bleeding 33:6
blind 76:24; 107:7, 19
blinded 46:21; 66:11, 15; 75:16; 77:10, 25
blindedly 77:14
block 36:17; 83:12, 15; 156:2, 3, 4
blockade 27:6
blocked 201:5
blocker 158:10; 181:11, 12
blockers 205:10, 15, 16
blocking 17:8; 114:2
blocks 196:6, 13
blood 27:25; 41:9; 121:1; 153:1; 181:7
blue 176:19; 248:4; 251:2
blush 131:20, 22
Board 167:4; 189:12; 208:17, 24; 209:3; 217:17
body 41:9
bone 49:24, 24; 50:8, 9; 55:24; 60:19; 72:2, 4; 82:5; 84:16, 25; 86:15; 95:4; 99:22, 23; 110:18; 200:16; 252:6, 23
bone-only 92:10
book 78:6
borderline 152:21; 153:4
both 9:2; 13:17, 19; 14:5, 8, 11; 28:17; 31:19; 33:17; 35:24; 37:13; 38:3, 25; 43:14; 45:15; 46:16; 49:13, 15; 51:14; 52:2; 57:24; 59:6; 60:7, 10, 12, 16; 66:7; 69:19; 94:19, 24; 98:23; 99:2, 3; 101:5; 104:6; 138:24; 145:7; 158:3; 160:3; 161:8, 10, 11; 191:25; 204:2; 206:18; 217:3; 240:6; 241:5; 243:13; 256:21
bottles 203:21
bottom 129:17; 138:1
box 224:1; 268:3
brain 145:21; 146:3; 147:15; 168:20, 23; 213:14; 215:4
Branch 134:4; 153:11
brave 142:13
break 88:8; 224:24; 227:12
breakdown 94:9, 15
breast 8:20; 9:7, 22; 10:9, 25; 11:7, 16; 13:18, 25; 14:21; 16:12, 25; 17:5, 11, 16, 25; 18:3, 16, 19; 19:2, 6, 10, 13, 22; 20:21; 21:3, 5, 6, 10, 18; 22:2, 6, 8, 10; 23:10; 25:19; 26:7, 16; 30:2, 3; 32:6; 33:25; 34:3,

19; 35:22; 36:6; 38:16; 39:12, 17; 41:1; 42:20; 43:23; 44:2; 45:14; 48:22; 56:9; 57:5, 13, 14, 22; 58:23; 60:2; 61:12; 62:5, 9, 11, 18; 72:9, 10; 79:8; 87:2; 90:18; 91:2; 96:14; 101:19; 102:4; 109:19; 111:15; 112:5; 114:10; 117:12; 118:3; 119:6; 156:23
breast-conserving 59:19; 60:3
breath 130:2
brief 12:5; 21:1; 70:2
briefing 70:13; 71:17; 78:6; 83:1, 21; 102:24; 114:4; 166:1; 203:2
briefly 56:19; 177:15; 240:2; 255:1; 260:16; 267:21
bring 128:10; 258:12
brings 110:4
brink 128:10
broad 246:17
broadened 225:23
Brodie 39:5; 42:18
broken 148:5; 193:25
brought 13:8; 258:18
Bruce 6:9; 125:10
Building 7:16; 126:14
built 81:25; 183:15
bulk 93:7, 8, 13
bump 258:10
burden 146:20; 159:22
burdening 138:18
busy 136:14
buzz 24:5

C

C 160:5; 198:23
calculations 77:21
California 6:14
Californians 69:17
Call 5:2; 25:1; 29:4; 119:21; 124:3; 160:22; 173:21, 24; 196:7; 227:12
called 23:21; 36:9, 13; 38:4; 131:20; 177:19
came 88:24; 94:3; 116:12; 162:23; 207:4; 215:2, 13; 223:15; 255:10
can 8:22; 12:1; 22:10, 20; 23:2; 25:3; 26:22; 27:21, 24; 32:24; 36:7, 10; 54:8; 60:11; 62:25; 64:3; 66:2; 67:22, 25; 73:21; 74:1; 75:15; 80:14, 19, 25; 81:9; 82:18, 20; 87:23; 93:8; 94:9; 97:2, 24; 98:13; 101:2; 102:21; 105:5, 9; 108:14, 18; 115:22; 116:16; 120:21; 127:15, 18; 128:24; 129:2, 6;

135:23; 137:14; 139:7; 143:10; 145:3, 19, 25; 148:6; 149:15; 150:9; 152:1; 155:11, 19, 24; 156:16, 17, 19, 19; 157:14, 24, 24; 158:2, 20, 23; 159:7, 21, 21; 161:1; 162:10, 17; 164:6; 170:1, 18; 171:10, 14; 172:16; 174:14; 176:1, 17, 24; 178:25; 180:19, 23; 181:8; 184:19, 20, 21; 185:13; 186:25; 187:6, 14; 193:16; 194:4; 195:7; 200:21; 205:6, 21, 22; 210:19; 212:12; 215:1; 216:8; 217:19; 218:8; 222:8, 20; 223:3; 226:4; 233:16; 246:16; 250:2; 256:15; 257:2; 258:10; 259:15; 260:19, 21; 264:18; 266:16, 17; 267:20; 268:20
Cancer 5:19, 22; 6:10; 8:20; 9:7, 22; 10:9, 25; 11:7, 16; 13:18, 25; 14:21; 16:12, 25; 17:5, 11, 16, 25; 18:3, 16, 19; 19:1, 2, 6, 10, 13, 22; 20:21; 21:3, 5, 6, 10, 18; 22:2, 6, 8, 10, 15, 16; 23:10; 25:19; 26:8, 17, 20; 30:2, 3; 32:6; 33:25; 34:3, 19; 36:6; 38:16; 39:14, 17; 41:1; 42:20; 43:23; 44:2; 45:14; 48:22; 56:9; 57:13; 58:23; 60:2; 61:12; 62:5, 9, 11, 18; 79:8; 87:2; 90:19; 91:2; 94:5; 96:14; 101:19; 102:4; 109:19; 111:15; 112:5; 114:10; 117:12; 118:3; 119:6; 124:16, 21; 125:11; 127:25; 131:5; 132:22; 133:5; 134:7; 135:2, 13; 138:13; 144:1; 145:18; 156:23, 24; 197:25; 265:16
cancer-related 81:11
cancers 35:22; 135:3; 143:25; 155:13; 173:6
candidates 23:11; 30:25; 140:7
capable 33:17
capillary 151:13
captured 196:19
carbamazepine 106:18
carbazine 154:3
carcinoma 26:20; 63:4; 99:13; 160:4
cardiac 213:16
cardiopulmonary 211:8
cardiovascular 60:25; 98:20, 24; 101:7; 181:23
Care 5:15; 19:5; 31:3; 62:17; 111:15; 116:2; 121:9; 124:12; 134:23; 136:4; 139:16; 140:3, 4, 10; 189:24; 204:16, 17; 243:5; 262:14

careful 122:7
carefully 145:3
caregiver 136:4
Carolina 20:11
CARPENTER 125:14, 14
carried 74:10; 170:8; 195:10; 231:1
carry 145:10; 207:21
cart 180:20
cascade 35:24
case 13:3; 24:12; 55:14; 71:10; 81:16; 97:1; 103:5; 107:24; 112:21; 115:8, 17; 161:9; 198:25; 215:22; 224:11, 15; 230:2; 250:2
case-by-case 122:5
cases 13:20; 99:22; 143:23; 236:21; 248:16
castrate 27:23
catalyzed 28:4; 106:12
catch 130:2
categorical 252:21; 254:12
categories 93:4; 148:5; 268:8
categorization 77:21
categorized 246:17; 252:5; 253:2
category 93:7; 98:9; 214:3, 8
Caucasian 49:10; 94:25; 100:12
cause 24:16; 99:25; 155:19; 181:8; 206:18
caused 33:5; 156:10; 157:20
causes 25:5; 100:2; 210:25; 256:25; 264:6
caution 245:12
caveat 118:17; 121:25; 178:2
CD3 197:23; 198:4, 5
Cell 6:6; 24:16; 25:1, 14; 36:11; 39:8, 14, 17, 17, 20, 21, 22; 40:14; 125:6; 156:2, 3, 5, 5, 15, 15; 158:3, 20; 160:4; 163:12, 12
cell-free 40:10
cell-mediated 156:2
cells 38:15, 16; 40:16; 42:7, 21; 155:22; 156:7, 9, 9, 15, 16, 17, 17; 157:3, 3, 5, 5, 15, 15, 21, 22; 158:3, 13, 18, 18, 18, 21, 22; 159:2, 2, 4, 4, 6, 15; 178:8; 197:19; 200:19; 205:14
cellular 39:10, 12; 40:18; 42:14
censored 81:4, 8, 12, 18; 219:21; 220:8; 236:17, 19
censoring 80:20, 25; 81:1
Center 5:14, 23; 6:8, 10, 12; 7:7; 48:24; 76:22; 77:1,

23; 103:8, 9; 104:4, 5; 124:11, 21; 125:8, 11, 13; 126:3; 134:2, 10, 11, 20; 138:13, 14; 139:7; 160:21; 196:14
centers 18:11; 48:8; 58:16, 25; 150:14; 169:4; 252:9
central 76:20; 77:3, 9; 83:17; 174:5; 196:4, 7, 15
cerebral 211:16
cerebrovascular 61:1; 98:25; 101:7
certain 21:7; 25:9; 68:14; 131:19; 155:13; 156:23; 173:6; 267:5
certainly 12:9; 22:14; 26:15; 65:11; 68:25; 111:16, 18; 112:20; 113:4, 8; 121:8, 18; 122:18; 162:24; 163:8; 198:20; 199:15; 204:10; 214:18; 265:7; 266:20
certificates 103:16
cetera 249:18; 251:7
Chair 20:16; 64:2, 8; 69:4
Chair's 211:19
chairman 20:14, 23; 34:24; 63:24
chairmanship 46:18
chairperson 5:8
challenging 140:13
chance 100:20; 104:3; 128:7; 145:5; 150:23; 203:6; 233:19; 256:3; 257:1, 3
change 15:23; 34:10; 87:17, 21; 93:12, 14; 175:13; 208:5, 6; 233:23
changed 91:4; 131:8; 227:3
changes 25:6; 29:19; 178:22; 227:6, 8; 259:19
chapter 151:23; 256:22; 257:13
characteristic 75:21; 184:2
Characteristically 21:15; 22:1
characteristics 18:12; 44:22; 50:3; 59:2; 82:3, 17; 94:22; 159:6; 169:12; 230:6; 251:10, 20; 253:9; 256:7; 259:14; 268:23
characterized 21:10; 37:1; 39:22; 213:23
Charlie 144:21
charter 209:11, 12
chastised 27:21
check 108:8; 224:1; 242:25; 248:22
checked 223:25; 224:9
checkups 131:4
chemo-resistant 228:20
chemotherapeutic 107:6

<p>chemotherapy 27:23; 45:24; 51:1, 3, 8; 79:12, 15; 85:12; 86:1, 6; 92:11, 17; 94:20; 136:9; 146:6; 148:13; 149:15; 152:6, 13; 154:2, 5; 169:20; 170:11; 172:12; 251:7, 25; 252:8; 259:3</p> <p>chest 21:23; 245:1</p> <p>chi-square 206:5</p> <p>CHIAO 125:16, 16; 227:17; 246:25</p> <p>Chicago 125:13</p> <p>Chief 141:20</p> <p>child 129:8</p> <p>children 137:20; 140:3</p> <p>Children's 5:25; 124:25</p> <p>Chills 131:17; 132:16; 151:12</p> <p>China 93:23; 103:1; 132:11, 13</p> <p>China--that 102:18</p> <p>choice 32:2</p> <p>choices 24:1</p> <p>choose 21:9; 22:19; 23:23; 24:3</p> <p>choosing 63:19</p> <p>choriocarcinoma 39:21</p> <p>chose 40:6; 132:1; 183:20</p> <p>Chosen 40:5; 75:2; 247:7</p> <p>Christian 105:7</p> <p>cimetidine 105:12</p> <p>circumstances 255:17</p> <p>cis-platinum 149:4, 4; 152:5, 16; 153:9, 11</p> <p>claim 229:25; 255:15</p> <p>claimed 237:22; 255:7</p> <p>clarification 16:7; 66:21; 104:14; 208:9; 219:12</p> <p>clarify 14:19; 120:21; 166:14; 190:25; 208:10; 219:7; 250:4; 257:11</p> <p>Clark's 130:19</p> <p>class 36:9, 13; 129:9</p> <p>classification 49:18; 95:3</p> <p>classified 214:4</p> <p>clear 9:15; 10:2, 21; 29:15; 165:20; 166:12; 208:25</p> <p>cleared 105:23</p> <p>clearly 24:13; 56:10; 59:25; 62:7; 104:4; 248:17</p> <p>clinic 29:3; 168:1; 198:13; 204:12; 209:5; 242:15</p> <p>Clinical 6:16; 13:13, 16; 20, 22; 19:12, 21, 23; 2, 20, 22; 21:7; 26:10; 27:11, 18; 31:19; 32:1, 4; 43:18, 19, 21; 46:6, 8; 47:22; 52:18, 23; 53:2; 56:16; 57:15, 20; 58:5; 59:14; 61:19; 62:6, 16;</p>	<p>64:9, 9; 72:22, 24; 73:22; 74:11; 75:2; 77:13; 81:15; 83:24; 89:17; 91:20, 20; 94:4; 105:7; 109:19; 110:9; 111:14; 113:18; 117:1; 121:2, 23; 134:10; 138:12; 139:4; 143:6; 159:13, 23, 25; 160:6; 186:9; 190:3; 206:11; 207:5; 227:23; 228:22; 229:9; 255:23; 259:7; 265:15, 16; 268:21</p> <p>clinically 51:25; 54:18; 56:13; 61:23; 66:2; 98:1; 101:21; 112:8, 17; 113:6, 19; 193:20; 207:1; 218:7; 226:10</p> <p>clinician 192:3, 18</p> <p>clinicians 21:21; 30:2; 64:7; 186:23; 192:21; 208:17; 225:12, 20</p> <p>clinics 83:13, 16</p> <p>close 73:23; 130:3</p> <p>closed 167:5; 189:14; 208:22</p> <p>closely 162:4; 226:23</p> <p>closer 182:11; 240:17</p> <p>closing 137:23</p> <p>clotting 114:13, 16</p> <p>CNS 151:13</p> <p>coactivators 25:10</p> <p>Cochran 54:21</p> <p>code 196:8, 9</p> <p>codes 196:6</p> <p>coding 69:14; 71:2</p> <p>COHEN 6:15, 15; 90:13, 14; 102:14, 24; 103:4, 6, 9, 12, 15, 19; 104:6; 105:2; 107:12; 122:14</p> <p>collaboration 39:4; 166:9</p> <p>colleague 111:10</p> <p>colleagues 20:23; 38:12; 62:20</p> <p>collect 239:7</p> <p>collected 220:21; 239:8</p> <p>College 6:5; 19:14; 124:23; 125:5</p> <p>color 131:21; 137:16</p> <p>Colorado 130:15; 131:8</p> <p>colorectal 156:23</p> <p>column 252:3, 15; 253:3; 257:20; 267:24</p> <p>combination 45:4, 5; 68:16; 88:21; 89:9; 121:10, 21; 134:21; 136:10, 20; 141:24; 143:5; 145:14; 154:5; 155:10, 14; 160:2; 162:18; 164:19; 188:22; 206:21; 228:8, 16; 229:17, 18; 231:11; 233:14; 237:21; 240:15; 241:6, 24; 242:6; 245:17</p> <p>combinations 148:14</p> <p>combine 180:7</p> <p>combined 31:6; 32:22;</p>	<p>51:1; 75:21; 91:5; 159:21; 161:23</p> <p>combining 32:12</p> <p>comfort 114:25; 115:9</p> <p>comfortable 85:23; 116:16</p> <p>coming 85:7; 95:17; 108:2, 3; 124:5; 141:7; 200:21; 220:18</p> <p>commendably 83:22</p> <p>commending 109:15</p> <p>comment 8:1; 70:24; 79:5; 92:3; 104:8; 108:24; 113:11; 118:13; 126:24; 191:13; 192:6, 25; 201:20; 202:16; 203:1; 206:14, 16; 212:9; 215:17; 264:14; 265:12</p> <p>comments 68:11; 78:5; 102:14, 16, 20; 111:5; 113:23, 25; 115:3; 116:8, 11; 119:7; 120:8, 18; 215:17; 237:10; 241:19; 263:20; 265:10; 266:24; 267:1, 19</p> <p>Committee 5:5; 6:4; 8:17; 9:5, 15; 13:8; 16:17; 20:15; 35:5; 46:18; 62:23, 24; 63:11, 15, 18, 20, 24; 64:3, 8, 20; 65:3; 72:18; 101:2; 102:11; 109:8, 12; 116:23; 117:25; 118:1, 12; 123:6; 124:7; 125:4; 129:21; 130:6; 133:15, 21; 137:2, 25; 138:6; 141:3, 6; 190:24; 208:11, 14; 227:12; 261:19, 20; 262:1</p> <p>committee's 9:8; 126:10</p> <p>committees 68:17</p> <p>common 23:5; 99:25; 130:11; 184:4; 204:4; 249:19</p> <p>commonly 39:16</p> <p>communication 139:15; 227:9</p> <p>community 138:24; 214:23</p> <p>companies 12:12; 127:12</p> <p>company 104:22; 107:10; 130:14; 189:14; 194:24</p> <p>comparable 94:22; 96:19; 99:2, 5; 100:10, 16; 119:18</p> <p>comparative 12:10; 75:7</p> <p>comparator 13:19; 14:1; 15:3, 3, 4; 31:16; 91:12; 96:15</p> <p>compare 12:6; 13:4, 15; 35:12; 38:7; 56:22; 73:2; 82:20; 88:4; 181:19</p> <p>compared 13:20; 14:5; 25:19; 31:6, 9, 11; 37:17; 39:25; 40:8; 44:6, 9; 47:12, 14; 51:16; 52:9, 13, 19; 53:22; 55:13; 58:4, 8;</p>	<p>59:15, 21; 62:1; 69:24; 73:14; 137:6; 145:6, 15; 200:24; 233:19; 238:16; 239:11; 241:1; 252:11; 253:23</p> <p>comparing 18:5, 7; 32:23; 42:16; 43:8; 44:2; 72:21; 91:1; 119:3; 153:18</p> <p>comparison 73:19; 89:1, 8, 18, 20; 90:1, 4; 135:17; 136:7, 10; 252:12</p> <p>comparisons 13:1; 31:13; 54:3; 55:18; 73:5; 79:24; 89:16; 234:13; 266:9</p> <p>compassionate 225:13, 20; 226:5</p> <p>compelling 111:11; 112:10, 16; 142:24; 177:9, 12; 189:21; 229:25</p> <p>compete 24:14</p> <p>competitive 12:12; 28:23; 29:23</p> <p>compiled 151:23</p> <p>complement 43:7</p> <p>complete 41:21, 24; 42:4; 57:20; 64:14; 72:10, 12; 150:4, 8; 152:8; 200:18; 201:1; 209:18; 239:5; 243:2</p> <p>completed 46:10, 17; 48:9; 64:12; 89:21; 160:6, 8, 12; 193:5; 204:7; 205:1; 242:10; 250:18; 262:10; 266:2</p> <p>completely 80:5; 90:2; 157:4; 167:2; 207:18</p> <p>completeness 9:3; 114:2</p> <p>completes 12:1</p> <p>completing 45:22</p> <p>completion 78:9; 153:20; 223:24</p> <p>complex 24:23; 25:11; 28:5</p> <p>compliance 243:1, 1, 6; 263:7</p> <p>compliant 58:25; 203:21</p> <p>complicated 93:2</p> <p>complications 98:24, 25; 99:4, 15; 146:17</p> <p>components 36:19</p> <p>composite 91:24</p> <p>compound 29:5, 6; 35:2; 111:6</p> <p>compounds 29:8, 8, 12, 14, 19, 22; 31:21; 33:13; 34:22, 22; 36:9, 13; 38:2, 4, 8; 40:6</p> <p>Comprehensive 6:10; 125:11</p> <p>comprise 154:19</p> <p>comprised 93:7; 145:19; 208:17</p> <p>compromise 89:6</p> <p>compromised 89:7;</p>	<p>139:22</p> <p>computer 130:14</p> <p>concede 30:2</p> <p>concentration 88:17; 158:22; 200:23</p> <p>concentrations 37:6</p> <p>concept 24:5; 27:6; 42:12; 256:21; 257:4</p> <p>concepts 27:4</p> <p>concern 82:2; 89:5; 104:18; 106:25; 121:20; 195:11</p> <p>concerned 69:18; 83:7; 114:4, 7; 211:24; 214:24</p> <p>concerning 75:16; 200:17; 231:7</p> <p>concerns 70:15; 80:5; 82:11; 189:6; 195:6; 246:15, 16; 262:3</p> <p>conclude 108:6; 162:15; 177:2; 185:4</p> <p>concluded 87:16; 270:14</p> <p>concludes 246:7</p> <p>conclusion 43:10; 61:5; 79:23; 87:22; 154:18; 162:16, 23; 248:21</p> <p>conclusions 33:2; 43:19; 65:23; 103:21; 255:3; 256:1</p> <p>conclusive 69:2; 120:21</p> <p>conclusively 66:3, 3; 67:21</p> <p>concomitant 121:21; 205:7, 17</p> <p>concurrent 153:19</p> <p>condition 87:4</p> <p>conditions 120:6</p> <p>conduct 27:10; 33:4; 44:14; 45:6; 56:20; 109:16; 191:1; 208:19; 225:9; 259:17</p> <p>conducted 44:3; 53:6; 54:22; 61:15; 63:13; 91:14; 92:18; 149:13; 249:1</p> <p>conducting 257:18</p> <p>Conference 248:10</p> <p>confidence 53:21, 25; 55:12; 219:23; 225:9</p> <p>confident 82:11; 197:15</p> <p>confidential 68:8</p> <p>confidentiality 66:13; 67:16</p> <p>confirm 75:23; 187:25; 259:12</p> <p>confirmatory 153:5; 174:16; 185:14; 186:6, 7</p> <p>confirmed 46:5, 6; 52:12; 53:9; 55:1; 189:3; 236:7; 265:2</p> <p>Conflict 6:22, 23; 7:2, 9; 125:20, 21, 23; 126:5</p> <p>conformational 25:6</p> <p>confuse 177:20</p> <p>confusing 216:18</p>
---	--	--	--	---

confusion 70:4
Congress 255:8, 16
conjecture 83:10
conjunction 149:13
Connecticut 6:2; 125:2
consecutive 92:22; 97:21; 98:12
consent 264:9
consequently 265:18; 266:7
conserving 57:6, 14, 22
consider 87:6; 101:2; 111:24; 139:19; 140:9, 25; 190:11; 193:19; 215:22; 250:2; 255:17
considerable 29:3; 72:20
consideration 129:16
considerations 75:3
considered 10:16; 15:5; 49:25; 76:16; 81:17; 117:19; 193:2; 211:3, 5, 5, 8, 10, 12, 13, 15, 17; 235:6; 238:17; 246:2; 247:23; 249:22; 250:5; 251:20; 252:16, 25; 253:8; 255:22; 264:22
considering 96:9; 101:13; 254:24
consistency 101:16; 104:1; 234:16; 237:16; 246:24; 248:23
consistent 54:13; 67:3; 82:22; 119:25; 137:1; 170:6; 173:6; 188:9; 228:24; 251:19
consistently 53:16; 54:6, 9, 16; 55:7, 20; 56:1, 11; 61:16, 19; 199:11; 238:7, 12; 241:21; 269:3
constant 106:1, 3; 139:15
constituted 93:13
consultant 20:13; 205:24
consultants 20:2
consulting 62:20
consumer 125:9
contact 220:2
contain 35:22; 38:15, 16; 39:15, 24
contained 214:3
containing 140:8
contains 39:23
contemporary 27:3
content 199:15
context 12:20; 67:14; 110:2; 215:25
continually 47:7
continue 8:10; 46:20; 57:3; 66:11, 13; 102:22; 111:2; 128:23; 136:7, 14, 17; 178:19; 186:11; 211:20; 220:12; 222:19, 23; 254:20
continued 44:18; 216:10;

222:21, 25
continues 248:15
continuing 81:5
continuous 160:23; 252:3, 7, 8, 21; 253:1; 254:11
continuum 26:8, 14
contrast 153:2
contribute 87:21; 114:20
contributed 93:24; 240:8; 241:22
contributor 93:23
control 43:3; 87:8; 158:9, 11; 161:4, 19; 188:7; 201:25; 203:24; 204:2; 210:15; 225:7; 230:19; 233:13
controlled 9:9; 10:11; 56:8; 168:21; 189:9; 215:4; 254:25; 255:14; 259:25; 260:4; 267:15
controversial 115:5
convened 63:12
convenient 113:17
conventions 224:8
converse 219:1
Conversely 135:25
conversion 28:2, 3, 13
convert 157:12
convey 67:25
conveyed 67:25
convinced 100:25; 229:24
convincing 118:15; 249:3; 266:21
convincingly 61:14; 66:24
cooperative 226:8
coordinating 139:5
coordinator 139:4
Copenhagen 20:7
copy 7:13; 126:12
core 44:20; 45:8; 46:12; 64:12; 78:9; 81:10
corepressors 25:10
corner 129:11; 257:25
coronary 98:22
Corporation 8:13; 16:22
correct--three 191:25
correctly 22:19; 84:8; 112:11
correlate 206:19; 214:13
correlated 154:16; 179:19
correlating 214:15
correlation 217:12
correlative 57:23
corresponding 179:22; 253:23
cortisol 37:7
Cosmetic 255:6
cost 11:3; 127:13; 141:8; 183:13; 190:5

count 93:6; 236:23
counted 203:20; 236:24
counterpart 21:14
countries 17:12; 37:25; 48:8; 58:16; 64:10; 83:11; 93:20
country 108:2; 116:13, 17
couple 76:19; 116:11; 160:18; 163:5; 195:7
course 15:2; 16:4; 22:3; 33:3; 63:12; 89:5; 115:5, 10; 116:7; 141:22; 143:7, 12; 157:16; 161:20; 164:13; 165:6, 7; 168:19; 172:10; 173:2; 178:2; 180:17; 181:10, 12; 191:20; 192:9, 12; 196:15, 18, 25; 205:9; 213:5; 217:25; 221:22; 222:8; 227:4; 228:22; 229:9; 268:21
courses 116:3; 149:23
Covance 205:23
covariate 48:4; 53:10, 13, 19; 54:4; 55:3, 4, 18; 173:21, 24; 248:9; 249:24; 251:15, 18, 18; 254:10, 11
covariates 47:25, 25; 53:7; 54:23; 55:10; 171:23; 172:9, 23; 173:4, 12; 174:11; 177:6; 186:3; 240:2; 252:2, 16, 17; 253:11, 14, 15
Cox 47:15; 53:18; 82:10, 23; 171:24; 174:2; 175:20; 177:5; 189:17
CP-12 85:15
CP-40 71:17
CR 46:6, 6; 179:25; 180:7; 236:5
CR's 93:11; 96:3, 4; 161:10; 162:11; 236:6
crafts 136:18
crash 180:20
create 42:23
created 42:17
credibility 266:12
credit 109:20
criteria 45:11, 20, 25; 57:12; 75:5; 92:6, 22; 97:19; 101:12; 118:1; 168:14; 177:9; 212:2, 19; 213:8, 17; 215:12; 217:2; 221:1; 224:20; 225:25; 226:12, 21; 227:2, 5; 267:18
criteria 225:23
critical 139:1; 140:16; 221:15
CRO 166:25; 167:9; 189:15; 196:4; 208:13, 19
crops 136:13
cross 83:15; 115:19
cross-study 31:12
crossed 41:4, 5, 6, 19;

42:1; 85:16
crosses 53:25; 115:13
crossing 115:14, 17
crossover 18:5; 41:8, 13, 13, 15, 23; 44:25; 46:13; 48:18; 78:2, 3, 6, 7, 13, 14, 18; 79:3, 10, 17; 85:10, 11, 21, 23; 88:1, 4; 91:7, 9; 114:5; 115:12; 164:24
crossovers 41:12
CT 196:25; 213:13
CTC 60:18
cumulative 19:1
cure 26:16; 30:4, 5; 129:11; 133:4
curious 83:5
current 7:24; 14:20; 17:7, 24; 19:12; 20:20, 22; 21:2; 24:5; 65:23; 118:21; 126:22; 167:25
currently 23:16; 134:9, 20, 24; 135:4
curve 26:6; 144:15; 151:5; 170:17; 187:17, 20; 234:1, 7; 263:23
curves 51:14; 68:4, 9; 80:19, 24; 100:21; 149:16; 176:17; 184:19; 185:20; 187:25; 234:4, 10; 235:17, 20, 23
cutoff 48:9, 15; 167:3; 169:6; 220:6; 232:13, 15, 19, 20, 25; 233:21; 234:2, 5; 236:21; 237:14; 247:4, 6, 25; 251:16
CVD 152:18; 153:18, 19
cycle 132:6; 149:22; 168:11; 178:20; 184:1; 192:17; 207:14; 239:13, 24; 264:3
cycles 178:16; 191:24, 25; 192:10; 193:5; 194:13, 16, 16, 18; 216:20, 23; 222:16; 242:10
Cytochrome 28:4; 105:13, 19; 106:10
cytokine 156:5; 157:7; 158:7, 14; 199:9
cytokines 148:14; 156:6, 11; 157:17; 159:7; 161:14, 17; 163:18
cytotoxic 8:25; 9:3, 6, 21, 23; 10:1, 4; 11:4; 87:12; 107:7; 148:13; 178:5; 179:24
cytotoxics 117:10; 119:9

D

dacarbazine 135:21; 149:3; 258:22
daily 18:21; 41:2, 3; 127:20
dam 89:12
Dartmouth 149:5, 15

data 10:16; 14:16; 18:18; 19:9, 21; 20:14; 32:12, 22; 34:7; 35:17; 42:7; 43:10, 19; 45:6; 46:18; 48:15; 54:14; 55:25; 60:6; 63:11, 14, 18, 20; 64:15; 65:24; 66:14; 67:10, 16, 21; 70:21; 72:20, 22; 73:1, 21, 24; 74:1, 6; 75:10; 76:11; 77:14; 78:6, 7, 8, 14; 79:9, 22; 80:1; 87:21, 22; 88:2; 89:17; 90:15; 91:9, 21; 92:1, 2; 95:19; 97:23, 25; 101:16; 103:19, 20; 105:2; 106:25; 107:9, 10, 13, 14, 21; 108:1, 15; 109:24; 110:6; 111:11; 112:10, 16, 18, 22, 24, 24, 24; 113:3; 114:2, 6, 20, 25; 115:7; 117:14; 120:21; 121:5, 23; 122:9, 11; 136:22; 137:1; 143:9; 145:13; 159:13; 166:25; 167:1, 2, 3, 4, 9; 169:10; 173:17, 18, 20, 25; 175:18; 177:8; 185:25; 187:7, 8, 9, 21; 189:12, 15; 193:10, 25; 194:5, 21; 198:1, 200:3, 9; 201:18; 202:1; 203:7; 205:25; 206:2, 5, 7; 207:21, 25; 208:10, 14, 16, 24; 209:2, 5, 16, 17; 210:2; 214:12; 217:5; 220:6; 223:3; 224:4, 13, 14, 22; 229:20, 22; 230:18; 232:3, 15; 234:8; 244:14; 245:24; 247:4, 11, 13, 25; 251:16; 252:14, 25; 253:17, 19; 254:6; 255:10, 18; 258:21; 265:1, 2; 269:4; 270:16; 271:3
database 74:12; 113:8; 144:16; 145:19; 146:5, 10; 147:4; 148:4; 173:4, 17, 18, 23; 201:11; 243:12
databases 202:13
dataset 236:19; 243:10
date 48:9; 68:12, 15; 143:6; 148:19; 154:21; 160:7; 167:3; 169:6; 177:16, 24; 217:13; 219:25; 220:6; 232:15, 18, 19, 20; 233:1, 4, 21; 234:2, 5; 236:18, 21; 237:2, 2, 4; 239:10; 247:4, 5, 6, 8, 11, 23, 25; 265:2
dated 231:9; 232:1
dates 232:13, 14; 233:5; 237:14; 251:17
Daudi 156:14, 17; 157:3, 5, 21
daughter 132:24
Dave 5:16; 124:13
day 9:5; 17:4, 21; 28:24; 32:16, 18; 149:21; 167:8; 168:4, 6; 207:13; 213:12; 225:15; 226:11, 22; 236:20; 239:13, 13, 19, 24; 242:16, 17, 21

days 24:6; 43:1; 139:21; 149:21, 23; 152:24; 159:19; 168:3, 6, 9; 1:15, 15; 176:20, 21; 182:22; 183:3; 184:23; 185:1; 210:13; 211:23; 221:5; 232:19, 24; 242:17, 17, 22; 243:15, 19; 244:15; 245:23; 268:14, 16
DCIS 26:20
deal 24:22; 120:19; 225:8; 226:22
dealings 12:11
dear 127:13
death 103:16; 127:16; 137:12; 151:17; 158:20; 177:17; 178:1; 184:3, 4; 210:25; 211:12; 233:11, 12, 16; 236:23; 243:23; 244:19; 264:22; 265:2; 268:14, 15
deaths 60:16; 68:20; 81:11; 143:24; 144:1; 210:13, 16, 20; 212:1; 223:5; 232:19; 236:24; 243:20; 244:16; 264:4, 5
decade 84:4
December 166:12; 271:18
decided 87:7, 19; 166:2; 209:2, 2
decimal 76:7
cision 89:4; 115:1; 136:6; 192:1, 3, 17; 212:20
decision-making 128:19
decisions 128:16; 191:16; 192:6, 21
declared 92:21
decrease 24:7; 89:6; 185:7; 198:4; 239:14, 18
deep 21:24
defense 74:24
defenses 146:19
defer 166:5; 193:24
defined 41:12; 44:20; 48:1; 50:8; 53:6; 54:23; 61:20; 82:24; 165:1, 2; 177:10, 16; 232:6; 255:9; 265:25; 266:1
defining 266:1
definitely 202:17
definition 144:5; 173:20; 175:1; 190:3
definitive 199:21
degree 21:17; 206:6
delay 10:20
delivery 218:15
demographic 44:21; 82:3; 170:12
demographics 49:4; 10:3, 6; 186:25
demonstrate 33:8; 47:11; 54:15; 55:25; 58:3; 61:15; 117:23; 249:3; 255:7
demonstrated 11:6;

37:8; 38:14, 16; 52:4; 53:16; 55:7, 23; 56:10; 59:18, 25; 62:6; 80:5; 86:2; 101:14, 23; 228:24; 230:18
demonstrating 47:12; 58:4
demonstration 117:14
Denmark 20:8
density 110:18
Department 19:24; 20:16
dependent 21:5, 10, 18; 22:8; 25:21; 237:14
depending 34:5; 192:23
depict 40:5
deprivation 37:9
derive 28:1; 267:7
derived 18:18; 73:22
describe 51:10; 56:19; 70:4; 155:18
described 22:20; 244:2, 10; 256:21
describing 89:15
description 165:19; 208:11
descriptions 211:21
deserve 114:10
design 30:22; 31:8; 32:11; 42:17, 17; 47:10; 58:2; 81:25; 82:1; 83:9; 86:24; 91:3; 137:3; 217:24; 229:16; 230:9, 21; 259:16; 262:3; 263:16
designed 48:23; 56:21; 58:24; 68:13; 73:2; 167:13
desk 196:8
Despite 136:19; 194:12
detail 70:22; 84:19; 159:12; 205:19; 212:5
detailed 19:9
details 195:9, 25; 240:2, 4; 265:7
detect 218:21; 231:4; 257:22
detected 239:22; 257:25
deteriorated 215:14
deteriorating 223:20
deterioration 81:15; 87:3; 178:18; 239:16
determination 93:9; 192:12
determinations 63:8
determine 23:3; 196:9, 17; 217:20; 236:16
determined 7:6; 87:10, 18; 126:2
determining 75:6; 93:3
devastating 127:18
develop 22:7; 28:15
developed 11:22; 13:13; 29:7; 36:5; 40:25; 99:13; 128:7; 156:8; 209:10
developing 144:2
Development 141:19;

142:20
devil 212:5
devil's 109:5
DeVita 257:13
DeVita's 256:22
diagnosed 25:23; 71:23; 128:4
diagnosis 21:20; 98:21; 173:15, 18, 19; 222:17; 223:1; 239:10, 10; 253:7
diamonds 248:5
Diana 214:2; 223:22
diaries 203:21
diarrhea 151:11
diary 243:1, 2, 2
dichotomous 172:13; 174:4
dictates 23:5
die 128:6; 129:8; 135:11; 163:24; 223:20
died 81:10; 103:17; 169:8; 182:21; 183:1, 3; 193:5; 211:2, 22; 212:3; 214:16; 219:15, 25; 220:5, 10; 222:11, 11, 14; 224:23, 23; 233:1, 3, 4; 243:15, 19; 244:15; 245:22; 264:21
diet 34:6
differ 95:11; 108:9
differed 236:11
difference 36:15; 42:5; 43:5; 53:10; 55:2; 58:5, 17; 72:9, 23; 74:13; 76:4, 12, 15; 80:17; 97:12; 115:6, 8, 9; 116:1; 119:11, 14, 15; 130:9; 153:16; 169:23; 171:11; 182:3; 186:15; 187:2; 195:2, 4; 206:4, 6; 209:6; 228:13, 15; 232:9; 233:6, 24; 234:9; 237:7, 12, 25; 240:8, 18, 23; 241:16, 22; 245:9, 11; 247:8, 9; 261:2; 265:1; 267:11; 269:11, 24
differences 33:14, 20; 42:13; 47:14; 51:24; 53:15; 54:5, 18; 55:6, 20; 58:8; 61:23; 65:18; 76:14; 77:6; 78:3; 84:17; 87:16; 90:9; 97:3, 5; 110:7; 116:15; 183:8; 218:22; 236:16; 265:4
different 9:1; 24:1; 39:6; 70:16; 82:17; 83:11; 104:2, 12; 113:1; 117:8; 127:23; 133:1; 168:24; 173:9; 178:21; 184:14; 193:20; 199:16; 200:22; 216:20, 24; 217:2, 3; 218:23; 230:11, 15; 232:23; 240:3; 247:19; 251:16, 16, 17
differential 175:2
differentiating 40:20
differentiation 21:13
differently 179:20, 23; 218:4

differs 117:11
difficult 74:9; 163:21; 167:21; 186:11; 197:20; 230:18; 262:8
difficulty 161:13
diffuse 25:1
dihydrochloride 124:6; 126:11; 134:22; 136:1, 21; 141:12, 13, 24; 142:20; 155:4; 227:21; 269:13; 270:2, 17; 271:4
dimension 178:22
dimerization 25:7
diploid 21:16
direct 36:23; 73:19; 89:8; 186:5; 217:12; 227:9
directed 201:16
direction 10:19; 263:17
directly 68:3; 200:4; 225:12
Director 5:14; 6:18; 124:11; 134:9
disappear 207:18
disappointing 88:20
disclose 126:9
disclosed 46:23
discomfort 99:14
discontinuation 81:1; 99:22; 223:25
discontinuations 60:15; 99:19
discontinue 99:16
discontinued 44:23; 45:5; 48:16; 81:14; 221:4, 23, 24
discoverer 33:19
discrepancies 77:15, 19, 19
discrepancy 214:16
discretion 57:8
discriminate 108:1
discuss 19:16; 91:20, 23; 143:6; 216:1; 229:16; 265:5
discussants 109:9, 13
discussed 46:24; 111:21; 264:7
discussing 124:5; 165:24
discussion 30:16; 35:14; 70:3; 109:8, 12, 16; 111:3; 117:9; 118:4; 123:10; 127:3; 142:3; 143:12; 261:24; 262:1; 265:10; 268:20; 270:5, 20
discussions 7:17; 68:3; 126:11, 15; 163:20
disease 17:16; 19:4; 21:8, 22, 24; 25:20, 22, 23; 26:16, 19, 22; 30:23; 31:25; 32:15; 34:7, 11; 44:8, 11, 18, 22; 45:1, 18, 23, 24; 46:7; 48:2; 49:18, 20, 20, 21, 22, 24; 50:1, 3, 4, 7, 9, 10, 12, 16, 18, 19;

51:8; 53:8; 54:12, 25; 55:25; 57:16, 16; 59:7, 8, 11, 11; 61:22; 72:3; 81:14; 82:4; 92:9, 10, 12; 93:4, 4, 5, 7, 8, 11, 12, 13, 14; 94:19; 95:4, 4, 16, 18; 97:2, 4, 5; 98:22, 22; 99:10, 23; 101:9; 116:3; 120:5; 127:19; 129:18; 137:9, 12, 17; 144:10; 145:21; 146:3, 19; 147:23; 153:25; 154:19; 162:9, 9, 12, 12; 163:16; 167:21; 169:22; 172:19, 21; 173:16; 174:1, 19; 176:8, 18, 19; 177:15, 17, 21, 25; 178:12, 17, 20, 21; 179:3, 10; 180:1, 4, 7, 12, 14; 182:14; 188:25; 192:13, 16; 194:8, 9; 196:18; 197:1, 9; 198:21; 203:11; 204:5; 212:7; 213:7; 216:7, 10, 13, 14, 15; 217:18; 218:1, 6, 7; 220:23, 24; 221:2, 4, 25; 222:2, 10, 18, 20, 22; 223:1, 9, 19; 224:1, 9, 24; 228:20, 21, 24; 229:3; 235:5, 7, 12, 24; 238:15; 240:20, 24; 241:5; 242:1, 11; 252:5, 7, 23; 256:6; 262:13; 263:12, 13; 264:4, 10, 23; 265:3; 266:5; 267:2, 3, 14, 17
disease-free 21:19; 50:20; 173:11, 14; 253:6; 269:2
diseased 163:9
diseases 13:3; 155:14
disinterested 208:16, 24
dismissed 195:19
displayed 165:16
disrupt 159:2
disrupters 34:14
dissertation 166:1
distant 107:1; 144:7; 147:13, 24; 148:2; 238:20
distinctively 69:11
distinguishing 69:15
distributed 59:8; 191:8, 11; 194:3; 223:2
distribution 84:3; 170:17; 185:20; 187:25; 193:23; 250:15
divide 25:15; 166:7
divided 233:12
Division 6:18; 67:10; 166:11; 229:15, 20; 230:1, 4, 13, 15
dizziness 181:13
DNA 25:12
doctor 127:16
document 43:7; 44:3; 70:14; 71:18; 83:2, 21; 102:25; 114:4, 5; 166:2; 204:15; 217:16
documentation 224:5;

10
documented 84:24;
 90:8; 216:6, 9, 14, 15;
 236:24; 259:22; 263:8
documenting 42:8;
 237:2
documents 203:2
domestic 132:15
dominant 48:2; 50:5, 7,
 9, 11; 53:8; 54:12, 24;
 55:25; 61:22; 95:3; 96:23;
 97:2
donations 127:10
done 26:10; 36:8, 12;
 63:15; 73:3; 77:3, 13;
 81:15, 16; 82:9; 84:15;
 103:8, 9; 105:24; 109:20;
 115:7; 117:4; 150:2;
 158:9; 159:11; 162:17;
 166:25; 168:9; 172:15;
 175:20; 181:16; 187:22;
 189:10; 190:17; 191:17;
 196:1, 2, 14, 14; 200:1, 4,
 22, 25; 202:11; 203:20;
 208:2, 13; 209:1, 8; 215:7;
 218:9; 222:4; 247:4;
 250:14; 264:19; 265:8, 17;
 266:17; 267:9
done--none 196:11
Donna 6:5; 125:5, 17;
 228:1; 254:22
dose 17:3, 21; 32:16, 17;
 41:2, 3; 89:4; 132:7, 8, 9,
 9; 135:22; 139:13; 140:21;
 154:9, 12; 159:20, 20;
 161:14, 16; 167:16, 19;
 181:18, 19; 186:8; 191:16,
 16; 192:1, 19, 20, 23;
 201:18, 21, 25; 202:2, 9;
 211:23; 214:22; 215:8;
 229:17; 243:11, 12, 16, 20;
 244:16; 245:23; 249:17
dose-response 88:18,
 23
doses 37:6; 85:2; 191:17;
 242:14
dosing 206:19; 243:3
dossier 37:11
double 70:25
double-blind 18:5, 7;
 32:10; 43:25; 44:17, 25;
 48:14, 18; 54:15; 56:7, 22;
 57:2; 59:23; 61:9; 69:21;
 71:21, 25; 78:22; 90:24;
 118:15, 18
double-blinded 107:3,
 17
double-dummy 32:10;
 69:8, 22, 23; 71:9; 90:25
double-placebo 70:5
doubling 152:18, 19
doubt 74:1; 83:8; 248:12
Doug's 106:23
Douglas 6:13
Douset 73:7
down 89:11; 93:15;
 110:23; 134:4; 148:5, 9;

164:6; 193:25; 218:10;
 224:17; 257:24; 258:12;
 267:16
downregulating 159:4
downregulators 34:15
downstream 24:15
DR 5:3, 6, 12, 13, 13, 16,
 18, 20, 22, 24; 6:1, 3, 5, 7,
 9, 11, 13, 15, 16, 18, 23;
 8:3, 10, 11, 15; 12:4, 5, 8,
 15, 21, 23, 24, 24, 25;
 13:6, 6, 7, 11; 14:18, 18,
 19, 25; 15:13, 13, 14, 14,
 20, 23; 16:2, 7, 8, 13, 16,
 16, 16, 16; 19:11, 13, 16,
 17, 20, 22; 20:5, 6, 9, 12,
 15, 15, 19, 23, 24, 24, 24;
 30:9; 32:7; 35:1, 4, 4; 36:8;
 38:11; 39:4, 5; 42:17;
 43:17, 20; 46:18; 62:22,
 25; 63:3, 6, 6, 7, 16, 17, 23,
 23; 64:1, 5; 65:6, 11;
 66:16, 16, 17, 17, 21; 67:6,
 8, 68:12, 16; 69:3, 5, 6, 20,
 23, 25; 70:2, 6, 8, 10, 24,
 24, 25; 71:10, 11, 13, 16,
 19; 72:1, 6, 7, 12, 16, 17,
 19, 19, 25; 73:1; 74:1, 8,
 12, 16, 20; 75:9, 9, 14;
 76:18, 18, 19; 77:2, 18, 20,
 23, 25; 78:1, 5, 12, 13, 14,
 21; 79:4, 6; 80:7, 11, 16,
 19, 20; 81:21, 22, 22, 23;
 82:14; 83:5, 9, 20; 84:3, 7,
 12, 19, 23; 85:3, 6, 8, 8, 9;
 86:10, 11, 11, 12, 13, 22,
 24; 87:1, 23; 88:7, 11, 13,
 22; 89:7, 14, 14, 19, 24,
 25; 90:4, 6, 7, 10, 11, 13;
 91:6; 96:9; 102:6, 12, 14,
 20, 21, 22, 23, 24, 24;
 103:4, 5, 6, 8, 9, 10, 12, 13,
 15, 16, 19, 22, 23, 23, 25;
 104:6, 8, 14, 15, 16; 105:2,
 5, 7; 106:5, 7, 13, 15, 16,
 18, 22, 22, 23; 107:12, 16,
 23; 108:4, 5, 7, 18, 20, 21;
 109:6, 9, 9, 10, 14, 22;
 111:7, 8, 9; 112:22;
 113:22, 23, 24; 115:3, 3, 4,
 11, 24; 116:7, 8, 8, 10, 11,
 19, 21; 118:4, 5, 7, 13, 14,
 17, 25; 119:7, 8, 12, 13,
 14, 16, 23; 120:4, 8, 10,
 15, 19, 23, 23, 24; 121:6,
 6, 7, 20, 24, 24, 25;
 122:10, 14, 15, 23, 25;
 123:4, 6; 124:4, 10, 10, 13,
 15, 17, 20, 22, 24; 125:1,
 3, 5, 7, 10, 12, 14, 16, 17,
 19, 19, 22; 126:9; 127:2;
 129:21, 24; 133:16, 18, 19,
 20, 23; 134:4; 138:6, 9;
 140:5; 141:3, 5, 17, 18, 22;
 142:5, 5, 7, 7, 8, 11; 143:3,
 14, 16, 18; 154:24; 155:1,
 2, 2; 160:20; 162:2; 163:4;
 179:18; 180:19; 181:17;
 189:23; 190:20, 20, 23, 25;
 191:5, 13, 19; 192:6, 8, 9,
 25; 193:3, 7, 11, 16, 24;

194:4, 6, 9, 10, 10, 10, 11,
 15, 19, 20, 20, 21; 196:3;
 197:3, 17; 198:12, 18;
 199:13, 21, 25; 200:3, 6, 8;
 201:10, 10, 15, 15, 16, 17,
 25; 202:10, 16, 21; 203:5,
 8, 13, 18, 19; 204:8; 205:7,
 8, 23; 206:9, 9, 10, 10, 22,
 23; 207:1, 20, 24; 208:2, 8,
 8, 9, 15, 25; 209:3, 9, 17,
 22; 210:1, 10, 10, 11, 18,
 25; 211:1, 19; 212:12;
 213:25; 214:9, 13; 215:15,
 15, 16, 17; 216:3, 3, 4, 8,
 14, 15, 16, 25; 217:1, 8;
 218:12, 14; 219:1, 4, 5, 5,
 7, 9, 11, 11, 12; 220:3, 15,
 15, 16, 25; 221:7, 7, 8, 10,
 12, 12, 13, 17, 19, 21;
 222:1, 3, 4, 6; 223:7, 10,
 11, 13, 15, 18; 224:4, 13,
 16; 225:1, 2, 2, 3, 11;
 226:4, 9, 18, 18, 19, 24;
 227:11, 17, 17, 24; 228:1;
 238:19; 240:1; 246:7, 10,
 25; 254:20, 22; 256:21, 23,
 25; 257:11, 12; 258:18;
 261:20, 23, 25; 262:2;
 263:18, 18, 18, 21, 25;
 264:1, 3, 12, 12, 14, 18;
 265:9, 12, 14; 266:23, 23,
 24; 267:19; 269:18, 21, 23;
 270:7, 11, 13, 22, 25;
 271:2, 9, 11, 14
dramatic 156:14; 198:4;
 199:1
dramatically 156:19;
 159:22; 171:2; 176:21;
 198:10; 253:22
draw 22:4; 255:3
drawn 87:22
driven 68:15; 91:21
drop 181:7; 205:2
dropped 91:6; 216:5;
 242:11
drove 93:8
Drs 7:12; 126:8
Drug 7:8; 9:2; 11:8, 12,
 24; 12:13, 22; 13:20; 15:6,
 11, 15, 22; 16:6, 21; 17:24;
 26:13, 24; 27:2; 30:20;
 31:7, 10; 33:11, 20; 69:19;
 71:15; 72:21, 21; 74:2;
 78:17; 106:20; 110:2;
 111:18; 113:9; 117:21;
 121:7, 14; 126:4; 128:21,
 24; 129:13; 133:11; 137:6,
 18; 138:1, 1; 140:19;
 178:5; 179:25; 182:22;
 186:24; 197:16; 199:7;
 203:22; 204:10; 206:12;
 207:11; 211:3, 6, 9; 212:8;
 215:10, 23; 227:20; 246:2;
 255:5; 256:15; 257:15;
 262:15; 263:7, 12, 16;
 267:8
drug--and 266:25
drug--the 220:22
drug-drug 104:16;

120:20; 121:17
drug-related 246:5
Drugs 5:4; 8:25; 9:1, 3, 3,
 6, 21, 23; 10:1, 5, 5, 8, 15,
 24; 11:1, 4, 6, 9, 14, 22, 23;
 13:11; 15:24, 25; 16:3;
 28:21; 31:23; 35:5; 71:1, 2,
 13; 74:5; 76:12; 104:21,
 25; 105:15; 106:16;
 110:10, 21; 111:22;
 113:20; 117:11, 17, 23;
 118:2, 6; 121:4; 128:10;
 182:16, 19; 183:4; 203:24;
 204:12, 18; 205:7; 206:15;
 208:5; 211:11, 13, 15, 17;
 215:19; 256:9; 257:8, 18;
 266:7; 267:17
DSMB 209:10
DTIC 135:21; 148:16, 22;
 149:10, 15; 152:17;
 153:11; 154:7; 230:12;
 231:15, 16; 245:25
due 60:15; 87:18; 177:17;
 178:1; 182:14; 183:2, 3, 9;
 210:13; 216:13; 224:1, 23;
 256:4; 259:18; 264:4, 6,
 21, 22
Dugan 19:20, 22; 43:17,
 20; 63:3, 16, 23; 64:5;
 69:20, 25; 71:11, 19; 72:6,
 12; 77:2, 20, 25; 78:5, 13,
 21; 80:11, 19; 84:3, 12, 23;
 85:6; 86:10, 22; 89:19, 25;
 90:6, 10
Duke 20:10; 88:22
dummy 71:1
durable 153:3; 154:9
duration 30:6; 46:7, 8;
 51:5; 52:22, 22; 95:14;
 96:19; 110:12, 14, 17, 19;
 122:9; 144:24; 148:23;
 150:7; 161:12, 25; 162:21;
 164:11; 177:11
durations 100:16; 117:4;
 122:1
during 46:12, 13; 47:1;
 79:14; 83:9; 84:25; 98:5;
 133:21; 142:3; 215:5, 6,
 10; 227:4; 242:17, 18;
 243:3
DUTCHER 124:22, 22;
 190:23, 25; 191:13; 192:8,
 25; 193:16; 194:4, 6;
 223:7, 11, 15; 263:18, 21;
 265:12
Dutcher's 201:11
dying 146:16; 183:2;
 224:18; 233:19; 266:19
dysfunction 151:15
dyspepsia 181:10
dyspnea 151:14

102:15, 16; 109:17; 114:9;
 116:2; 162:15; 185:22;
 187:20; 189:23; 198:19;
 217:9; 225:24; 228:19;
 241:2; 253:12; 264:1
earliest 23:6
early 34:21; 37:9, 15;
 45:6; 64:16; 69:1; 81:1, 3;
 99:19, 21; 100:23; 132:5;
 160:19; 178:10; 183:17;
 227:8
easy 131:15; 132:23
ECOG 95:2; 146:10;
 147:4; 148:4; 149:8, 13;
 228:25; 229:1, 11
Edinburgh 38:12; 39:4
education 127:11;
 140:14, 14; 263:1
effect 9:10, 11, 13, 16, 18;
 10:12, 13, 14; 11:2, 9, 17,
 19; 15:1, 2, 9; 36:19, 23;
 78:15, 19; 85:5; 88:15;
 101:1; 117:23; 154:14;
 158:11; 164:6; 167:23;
 172:2, 24; 175:8, 10, 16;
 177:6; 186:1; 189:18;
 197:10; 201:22, 23;
 205:13; 207:22, 22;
 240:14; 241:6, 24; 245:15;
 249:23; 250:8; 253:16, 18,
 20; 254:18; 256:5; 257:22,
 23; 258:1; 260:14; 269:8
effective 15:3, 5, 7, 12;
 18:21; 24:11; 26:15; 27:7,
 12; 28:17; 33:3; 34:12, 22;
 43:12, 14; 62:12; 76:9;
 79:25; 119:4; 120:12;
 135:8; 144:13; 164:4;
 190:5; 255:7; 256:15;
 257:8, 15; 258:11
effectively 42:10; 200:21
effectiveness 101:14,
 17, 23; 122:11; 154:12;
 255:9, 15, 23; 259:7;
 266:21
effects 10:3; 66:6; 86:13,
 17, 18; 87:11; 88:4; 104:5;
 108:25; 109:21; 110:3;
 129:2; 133:6, 13; 135:25;
 157:20; 180:25; 183:9, 24;
 206:19; 248:18; 263:8
efficacious 37:13
efficacy 11:12; 15:11;
 18:25; 19:20; 37:8; 43:21;
 44:4; 46:4, 11; 51:11;
 56:12, 23; 61:14, 17; 62:1;
 69:7; 76:15; 80:6; 87:18,
 22; 89:6, 8, 9; 91:25; 95:9;
 100:14, 23, 24; 103:20;
 117:20; 120:16; 143:10;
 155:4; 167:2, 5, 7; 176:2;
 185:9; 188:16; 189:14;
 201:18, 208:22; 209:12;
 229:22, 25; 231:11, 21;
 233:13; 237:11, 22; 238:2;
 241:19; 245:6, 16; 246:16,
 22; 247:3; 249:19; 255:3;
 261:4, 12; 267:23; 269:13,
 16; 270:1, 8, 14, 16; 271:3

E

ear 129:15
earlier 26:3, 3, 3; 29:14;
 44:10; 90:19; 93:17;

efforts 66:12
EGF 75:19
EGR 76:4, 13; 113:2
 germont 142:9
eight 14:11; 131:9
Either 10:11; 14:16; 15:1;
24:3; 25:10, 15; 27:23;
28:22; 31:1, 15; 36:7;
38:19; 41:1, 42:23; 44:17;
49:14; 50:5, 13; 57:2, 5;
60:24; 62:13; 63:1; 66:18;
67:3; 80:4; 83:13; 96:25;
98:21; 117:2; 122:14;
136:3; 145:14; 147:9;
148:1; 159:20; 162:19;
167:9; 173:23; 196:22, 23;
199:22; 201:12, 13; 203:1;
219:15, 17; 220:14, 21;
224:10; 250:8, 8, 254:14;
259:10
elderly 136:15; 140:5
electronic 103:19
elegant 35:21
element 25:12; 139:1
elements 37:2
elevated 146:22; 147:18;
148:2; 154:1
elevation 238:11
eligibility 92:6; 213:2;
225:3; 227:5
eligible 44:16; 57:1, 5;
 92:10; 186:17; 221:5
 minates 158:10
Ellis 20:9; 75:9, 14; 88:22,
22; 112:22
eloquently 116:2
else 13:14; 32:17; 70:22;
161:6; 193:17; 206:25
emaciated 135:14
embargoed 167:2
emboli 99:5
embolism 60:25
emerged 26:13
emotional 135:1
emphasized 230:4
emphasizes 238:24;
247:19
employed 69:8
encase 71:1
end 34:1; 35:17; 41:9;
67:4; 92:3; 128:21;
130:11; 154:25; 167:8;
256:16; 258:5, 13; 261:15
ended 210:8
ending 128:20
endocrine 17:25; 18:25;
19:12; 20:21; 21:2; 23:12;
30:1, 25; 32:5; 34:8; 37:14;
79:12; 44:24; 45:22;
 10; 66:6; 75:15; 79:2, 8,
 11
endocrine-sensitive
46:1
endogenous 163:12
endometrial 22:15; 63:4;

99:13
endothelial 163:14
endpoint 11:11; 12:18;
18:14, 25; 32:20; 46:3;
51:12; 56:17; 57:19;
64:12; 78:23; 79:7; 91:17,
24, 25; 100:23; 104:13;
111:4; 117:5, 20; 118:9,
11, 19, 22; 164:23; 165:2;
178:15; 189:10; 216:17;
217:15, 25; 218:1; 231:2;
260:6
endpoints 14:22, 24;
15:1; 46:4; 56:12; 57:21;
61:17; 63:8; 91:18, 19;
165:8; 177:14; 231:21;
257:3
energy 131:18
engineer 130:15
England 258:20
enjoy 136:17
enjoyed 102:24
enough 67:23; 69:1;
85:22; 88:13; 104:4; 266:2
enroll 83:13; 109:19;
212:18
enrolled 46:1; 48:7;
58:16; 72:14; 83:16, 23;
90:2; 93:19; 169:4, 7;
182:12; 186:22; 210:3, 6
enrollment 48:10, 23;
58:23; 89:21; 90:3; 225:5;
250:18
ensure 224:8; 230:6
entail 129:2
entails 139:10
entered 92:8; 134:8;
221:3
enters 225:8
entire 203:14; 261:1;
263:13; 268:10
entrant 69:12
entrants 102:25
entry 50:18; 57:12, 17;
58:10; 166:17; 168:14;
212:11; 213:11; 220:19;
221:1, 2; 226:21; 229:12;
230:25; 231:23; 234:20,
25; 237:24; 238:5; 239:9;
244:17
environment 39:9;
106:14; 163:7, 8, 18; 201:3
enzymatic 38:18
enzyme 28:4, 22, 22;
29:10, 14, 21, 23; 38:17,
18, 19; 39:19; 114:3; 159:2
enzymes 38:25; 40:22;
105:25
EORTC 153:8, 14
epidermal 112:23
equal 15:22; 45:17; 46:7;
49:9; 53:12; 60:10; 97:18;
98:11; 100:5, 6, 9; 147:17;
153:24
equality 66:23, 24
equally 191:8, 11; 194:2;

223:2
equals 55:24, 25; 234:23
equipotent 40:11
equity 134:15
equivalence 15:10; 33:8
equivalent 15:4, 6; 16:5;
31:15; 69:23; 96:25;
111:12
ER 45:15; 49:13; 57:14;
59:5; 97:12; 113:19
ER/PR 102:13
era 151:18
Eric 133:19, 23
ERPR-positive 122:12
error 250:23
especially 12:17; 28:11;
73:2; 154:20; 190:18;
214:21; 218:8; 262:6;
266:24
essence 67:10, 12; 68:8,
10
essentially 64:16, 20;
68:23; 75:23; 77:5; 83:3;
169:22; 222:23
establish 65:9; 142:22,
23; 159:19
established 32:2; 62:11;
65:13; 70:20; 148:19;
154:21; 189:24
establishing 65:25; 67:4;
255:23; 259:6
esteem 108:2, 3
esteemed 111:10
estimate 17:19; 240:14
estimated 47:17; 58:12;
78:9; 144:1
estimates 104:9; 175:10,
19; 229:22
estimation 179:1
estradiol 24:25
estrogen 17:9; 21:11;
24:13, 13, 22, 23; 25:2, 3,
3, 4, 13; 27:6, 10, 16, 25;
28:1, 21; 34:14, 15; 35:23,
23, 24; 36:4, 8, 11, 12, 17,
18, 20; 37:5, 8; 38:15;
39:24; 74:19; 113:13, 16;
114:8
estrogens 28:4, 13
et 238:19, 23; 249:18;
251:7
Ethan 238:23
ethically 66:10; 259:11
ethnicity 100:11
Europe 38:1, 104:10;
108:9; 119:19
evaluable 45:18; 49:20;
80:9, 12, 15; 92:9; 93:5;
186:19, 20; 193:2, 8, 14;
216:12, 13; 219:13; 221:9;
239:9
evaluables 223:8
evaluate 57:24, 25;
100:24; 164:18; 169:8;
178:14; 180:5; 231:10;

249:23; 250:7; 251:14;
256:11
evaluated 50:5; 78:8;
117:2; 136:6; 192:11;
196:17; 204:12; 208:20;
223:11
evaluating 78:15
Evaluation 7:8; 76:22;
80:17; 92:17; 96:17;
126:4; 188:16; 189:14;
192:12; 193:6, 15, 18;
208:22, 22; 209:12;
215:14; 219:14; 222:5, 8,
14, 16, 18; 223:14, 21;
262:4; 263:24; 264:19, 20
evaluations 47:4; 92:16,
18, 22, 23, 25
even 7:3; 27:13, 21;
76:12; 82:4, 7, 19; 83:25;
109:25; 116:14; 125:25;
128:17; 131:19; 132:17;
135:4; 136:14; 145:8;
150:21; 160:5; 171:3;
176:25; 185:23; 193:14;
197:6, 25; 202:8; 215:21;
216:2; 222:4; 239:1;
247:4, 13, 13, 15, 21;
255:6; 265:17, 23; 266:8,
20; 267:12
evening 132:3
evenly 59:8
event 7:17; 78:11, 12;
126:15; 221:25
events 17:22; 24:16;
33:6; 35:24; 47:7; 60:9, 12,
13, 15, 18, 18, 23, 25;
61:1, 1, 6; 68:14, 18, 23;
81:17; 89:23; 98:20, 20;
99:15; 100:7, 10, 11, 24;
101:6, 8; 114:13, 17;
180:24; 181:2, 16, 22, 23,
23, 24; 182:2, 2, 2, 8;
183:6; 210:4, 5, 8, 12, 14;
233:2, 3; 243:11; 244:14
eventually 35:25; 67:4;
110:23
everybody 84:13; 88:8;
115:13
Everyone 5:5, 10; 90:13;
113:19; 124:4; 174:6
evidence 48:22; 57:16;
58:22; 65:5; 66:9; 67:2, 2;
81:2, 14; 101:14, 17, 23;
103:17; 119:18; 133:2;
199:18, 22; 230:2; 236:1;
237:17; 238:1; 241:9;
242:2; 245:18; 246:22;
247:2; 249:3, 22; 255:9,
10, 19; 259:15; 260:19, 20,
22, 23; 261:4, 9, 11;
266:21; 269:12, 16; 270:1,
8
evidenced 114:18
evident 176:7; 222:7
evolution 29:4
evolved 166:8
evolving 64:17, 21
exact 29:10; 187:9

exactly 12:19; 65:12;
70:3; 183:24; 207:8;
210:9; 212:7
exam 224:11
examination 76:17
examined 258:21
examining 249:16; 259:2
example 21:24; 23:20;
24:12; 25:3; 31:16; 33:16;
83:12; 110:12, 19; 115:18;
159:14; 200:14, 25; 239:6;
251:5; 252:19; 254:4;
257:11
examples 24:16
exceeded 161:11
excellence 134:11
excellent 67:9; 109:15;
197:17; 208:15; 220:3
excellently 267:15
except 13:15; 60:19;
92:9; 168:18; 169:23;
238:11; 239:10; 242:14;
245:1
exception 13:5; 146:3;
212:18; 214:6, 7, 10;
225:16, 25
exceptions 7:10; 8:21;
85:1; 126:6; 168:17;
214:5; 219:10; 225:6;
227:7
excess 225:5
excessive 244:4
excitingly 26:21
exclude 7:20; 126:18;
243:22
excluded 126:10; 173:7;
193:9; 239:3; 265:6
exclusion 7:21; 45:20;
126:19; 213:1; 254:10
exclusions 212:13
Executive 6:3; 125:3
executives 136:13
exemestane 29:9; 31:11,
14; 73:9
exist 22:14; 195:24
existed 63:21; 128:17
existing 12:6; 31:23
exists 26:24
exited 85:20, 21; 86:3
expanding 198:10
expect 87:14, 15; 92:23;
106:4; 122:14; 169:14, 18;
176:11; 179:22; 181:5;
262:14
expectancy 128:12
expected 96:9; 162:22;
175:9; 180:24; 183:9
expense 127:13; 135:24;
141:8
expensive 150:12
experience 19:1; 32:4;
108:13; 111:14; 136:8;
139:2, 13; 143:6; 155:11
experienced 150:13;
151:9, 12; 152:2; 162:21;

243:14
experiences 141:8
experiment 105:24;
157:2, 21
experimental 42:17;
136:24; 137:3; 159:22
experiments 201:6, 8
expert 20:10; 35:7
experts 20:2, 3; 62:20;
64:9
explain 33:19; 180:9
explanation 72:2; 76:9,
14; 121:1; 202:22; 218:18
exploratory 76:16;
97:16, 22; 248:17; 253:4
explore 170:14; 248:18
explored 162:24
exposed 36:11
exposure 56:3
expressed 76:3, 13
exquisite 29:9
extend 133:12
extension 46:14; 191:22
extensive 77:5; 136:7;
161:5, 7, 8
extensively 35:2; 138:23
extent 87:11; 107:14;
196:18
extra 69:14
extracted 39:7
extraordinarily 226:7
extreme 195:2; 198:21;
265:23
extremely 136:1

F

face 30:24; 202:15
faced 30:3
fact 22:7, 10, 13, 19; 24:5,
9, 23; 26:10; 28:20; 29:2;
30:12; 31:5; 32:1, 7, 11;
33:18; 39:22; 76:2; 83:15;
89:3; 101:15; 106:11, 20;
110:1; 112:5; 119:24;
128:24; 137:4; 142:22, 24;
143:1; 155:12, 17; 161:16;
162:17; 167:1, 8; 169:13,
25; 173:14; 175:2, 15, 18,
176:24; 177:8; 178:7;
181:3; 184:3, 15; 188:20;
189:8, 17, 20; 192:5;
197:9; 198:3, 7, 10, 23, 24;
199:7; 204:18; 208:23;
222:6, 9, 24; 224:19;
226:25; 227:9; 251:14
factories 40:11, 17; 76:11;
112:23; 113:2; 146:24;
166:22; 173:5, 15; 174:7;
180:6; 239:7; 257:2
factoring 256:14
factors 25:11; 40:20;
75:20; 144:20, 23; 146:22;
147:19; 150:19; 170:12;
172:11; 195:18; 202:7, 14;

228:25; 229:3, 6; 230:5,
23; 238:7; 239:6; 241:20;
245:13; 251:23; 253:1, 1,
3, 4, 6, 18, 25; 260:11;
268:21, 23
facts 101:21
fadrozole 37:24
failed 27:5; 112:6;
161:21; 225:18; 231:13
fails 116:5, 5
failure 18:23; 46:5; 52:3,
5, 8; 56:15; 61:18; 78:25;
91:24; 177:22, 24; 179:5,
14; 189:1; 211:2, 5, 15
fair 66:21; 67:8; 171:10;
193:18; 217:9; 225:11
fairly 24:19; 32:8; 72:7;
111:11; 193:1; 225:4
fairness 7:24; 126:22
fall 54:19
falling 137:25; 214:8
false 256:14, 19; 257:1;
258:3, 6, 7, 14; 265:19;
266:10
familiar 105:2; 108:7, 11;
139:11
families 127:22; 128:15
family 27:11; 75:18, 24;
76:4, 13; 129:4, 6; 131:9;
132:24; 133:5; 135:18;
136:18; 140:15; 262:13,
14, 17; 263:14
far 22:6; 106:3, 107:9;
135:22; 193:25; 202:23;
209:16; 266:2
fared 145:8
farmers 136:12
fashion 22:16; 44:25;
48:18
fast 131:25
fat 28:11
father 130:13
favor 120:13; 122:21;
123:2; 238:8; 241:21;
245:13; 269:3, 15; 271:7
favorable 9:10, 11, 17;
10:12, 13, 14; 11:2, 9, 17,
19; 15:1, 2, 9; 19:4; 21:22;
67:23; 111:5; 117:23;
122:5; 159:5; 163:7, 8;
189:3; 238:18; 239:1;
269:5
favored 53:11; 55:3;
100:17; 170:9; 251:11;
260:12
favoring 51:25; 54:6;
55:21; 81:20; 84:6;
234:22; 235:2, 14; 240:23;
250:14; 258:24
favours 53:24, 24; 55:15,
16; 222:24; 238:12; 251:9
FDA 6:4, 15, 17, 19; 7:19;
9:9; 10:16, 17, 19; 11:8,
14, 23; 14:20; 16:17, 17,
25; 18:4, 11; 20:25; 30:18;
32:7, 8; 43:22; 90:12, 14;

92:1; 95:10, 11; 100:25;
101:12; 102:9; 103:23;
105:3; 108:21; 111:2;
113:11; 114:4, 18; 117:3,
22; 118:20; 119:8; 120:19;
122:10; 125:4, 16, 18;
126:17; 130:6; 141:22;
150:5; 151:6; 163:20;
165:24; 166:9; 173:2;
174:9; 177:9; 193:18;
194:23; 202:23; 203:1, 6,
14; 212:6; 217:6; 227:16,
19, 20, 24; 228:4, 11, 11;
232:8, 25; 236:5, 10, 14,
17, 23; 237:1, 6; 240:1, 3,
12; 241:15, 23; 245:4;
251:19; 253:4; 255:1, 17;
261:21; 264:16, 19;
265:13; 268:7, 9; 269:7;
271:11
FDA's 8:18; 118:1;
211:21; 259:6; 260:12;
267:22; 268:13
FDA--well 97:16
feasibility 186:7
feature 22:9; 91:7
features 21:8; 22:4, 20;
153:23
February 68:22
Federal 255:5
feel 116:16; 120:17;
135:16, 18; 197:15
feeling 120:2; 207:17;
269:7
feels 135:17
fell 263:23
fellow 134:4
felt 40:19; 79:1; 85:25;
86:4, 5; 212:17; 229:20
female 251:6; 259:1
Femara 8:8, 12, 18; 9:1;
10:10; 11:24; 13:17, 24;
14:4, 5; 16:10, 24; 17:1, 3,
7, 8, 10, 13, 15, 20, 22, 24;
18:5, 7, 15, 20, 20; 19:3, 5,
9, 18, 21, 23; 20:14; 31:8;
35:7, 18; 37:11, 21; 41:2,
4, 6, 13, 14, 19, 24; 42:5;
43:18, 21, 22; 44:2, 4, 17;
45:5; 47:11; 51:6, 14, 16,
19, 20, 25; 52:6, 9, 11, 13,
14, 17, 19, 20, 25; 53:2,
12, 22, 24; 54:7, 15; 55:4,
13, 15, 22; 56:1, 4, 10, 23;
57:2; 58:3, 18; 59:13, 20;
60:2; 61:5, 11, 16, 19;
62:1, 1, 4, 12, 15, 17;
65:25; 66:2; 72:13; 79:20,
25; 81:8, 18, 20; 84:6, 10,
18, 18; 85:17, 21; 89:20;
117:2; 119:3, 3; 120:17;
122:20, 25
Femara's 17:14
fevers 131:16; 132:16
few 17:22; 26:2; 82:21;
85:1; 92:8; 100:24; 142:2;
144:13; 153:3; 182:15;
183:3; 190:25; 245:4;

257:8
fewer 33:5; 182:17;
204:5, 5
fibroblasts 39:13
field 257:9
fifth 132:12
Fifty-five 59:10
Fifty-four 243:14
Fifty-two 59:6
fight 127:25; 128:23;
163:16
fill 204:18; 223:23
filling 205:2
final 46:16; 64:25; 80:7;
166:10; 167:10; 208:9;
209:1, 22, 24; 232:1;
247:4, 7, 20, 23; 248:3
Finally 10:1; 20:13;
66:12; 142:25; 153:4;
154:20; 158:7; 166:11;
174:2; 175:5; 182:6;
183:15; 228:1; 261:15
financial 7:19, 25;
126:17, 23; 134:14
find 93:7; 112:10, 16;
118:14; 136:25; 194:5;
221:8, 10, 23; 234:16;
236:2; 241:10; 250:5;
266:12, 17, 20
finding 197:4, 16;
207:10; 216:2; 228:14, 16;
232:11; 246:18, 19, 22;
249:6, 8; 254:17
findings 116:12
fine 265:7
finished 232:3
finishing 133:25
Finland 91:13
firm 7:25; 126:23
firms 7:7, 18; 126:3, 16
first 5:7; 9:23; 11:1;
13:16, 22, 25; 14:21;
15:18; 16:11; 17:4; 18:3, 6,
16; 19:2, 6, 9, 11, 21;
21:11, 20; 24:10; 26:23;
29:4, 5; 30:20; 31:5; 32:8;
33:7; 34:10, 10; 35:10;
37:23; 44:13; 45:25;
61:15; 63:7, 10; 64:11;
69:8; 77:2, 3; 79:6; 81:24;
83:22; 89:24; 90:17;
93:10, 18; 96:9; 105:11;
109:14; 117:25; 120:25;
129:8; 130:10; 131:15;
132:13; 136:22; 137:18;
138:1; 139:8; 142:13;
144:20; 152:24; 155:8, 11;
160:19, 22; 161:7; 173:16;
174:18; 177:17, 20;
180:19, 20; 193:6, 15, 21;
201:23, 24; 207:13; 211:1;
215:8, 13; 216:6; 221:15,
17, 19; 222:5, 7, 14, 16,
18; 223:1, 13, 21; 232:9,
24; 239:9, 13, 19; 242:14;
247:3; 260:25; 263:22;
264:19; 266:20; 267:24;

269:10
first-line 12:8; 31:20;
32:5; 43:22; 44:7; 56:8;
61:11; 62:4, 16; 78:24;
79:21; 80:2; 96:13; 102:1;
112:4; 231:13
Fisher 20:12; 70:6, 10,
10; 71:10; 82:14; 83:9;
104:8
fit 132:11
fits 116:18
five 11:22; 13:12; 39:5,
25; 42:1; 57:10; 64:9;
132:9; 138:15; 139:21;
144:11; 147:9; 164:4;
176:4; 186:21; 232:3;
242:17, 21; 260:17
five-year 110:12
flame 129:3
flashes 69:16, 18; 71:16;
86:14; 99:14
flawed 255:25
flawless 259:17
Fleming 20:15, 16; 46:19;
63:24; 64:1, 1; 65:11;
66:17, 21; 67:8; 68:16;
109:23; 142:7
flush 181:6
flushes 71:24
flushing 207:5, 16
focus 111:20; 228:12;
232:8; 266:3, 4
focused 72:4; 215:18
focusing 246:15, 24
follow 35:14; 64:21;
116:10; 151:2; 185:11;
199:13; 215:16
follow-up 46:20; 81:24;
106:23; 134:20; 170:18;
186:21; 219:16; 220:1, 8,
14; 221:14; 232:18; 233:4,
24; 234:8; 236:12; 241:14;
252:14; 253:17, 19
followed 45:2; 57:9;
149:22; 193:8; 220:4, 7,
12, 13
following 7:1, 9; 17:1, 11,
17; 18:20; 22:5; 57:7;
90:21; 91:6; 112:13;
116:20; 125:22; 126:5;
134:6; 227:24; 228:13;
231:6; 237:10
follows 17:7; 58:20
fondly 127:8
Food 255:5
foot 137:24
foreign 108:2
forest 53:20; 54:8; 55:11
forethought 225:22
form 18:2; 24:11; 34:19;
39:7; 64:7; 127:25;
172:13; 174:4; 224:10, 12,
15
formal 87:8; 208:10
formestane 37:24; 73:8

forming 25:11
forms 26:19; 61:11;
 '03:5; 205:1, 3
rth 63:20; 83:19; 93:15
Forty 232:17
Forty-three 78:25
forward 75:8; 90:1;
 111:19; 113:11; 122:8
found 38:19; 75:22;
 91:15; 104:17; 112:22;
 128:3; 130:23; 139:12;
 147:9; 186:8; 193:18;
 225:19; 239:13; 248:18;
 249:24; 258:23; 267:5
Foundation 127:5, 8, 9,
 21; 129:12; 254:24; 260:1
founder 127:7; 134:9
four 39:10; 56:3; 57:3;
 58:22; 132:9, 14; 141:7;
 159:16; 164:4; 196:6;
 232:19; 233:4; 242:22
fourth 11:24; 22:25; 76:7
fractures 61:1; 99:9, 10,
 10; 101:8
framework 166:16
frankly 128:19
free 39:9; 163:12; 197:18;
 202:7
Freedom 7:15; 126:13
frequently 60:17; 68:17
ends 133:6; 135:18
ull 7:11; 126:7; 133:7, 7
fully 33:16
function 24:22; 157:19;
 158:23; 159:9; 197:24;
 200:13; 213:16
functional 21:11
functioning 27:24
functions 24:23; 155:25
fundamental 36:15
further 16:9; 19:2; 30:25;
 43:7; 44:24; 45:1; 47:20;
 76:17; 79:2; 109:7;
 116:21; 121:16; 170:14;
 177:6; 198:9; 204:4;
 207:21; 248:15; 250:6, 10;
 251:14; 254:21; 267:19;
 271:11
Furthermore 250:16;
 254:1
furthest 142:10
future 11:9; 15:16, 16, 25;
 16:3; 23:7; 74:21; 88:5;
 110:21; 114:19; 117:22;
 118:6

G

ain 11:10; 117:24;
 151:14
gained 66:5; 79:21
gamma 168:21
gather 115:7
gathered 64:5

gave 67:9; 131:19;
 132:18; 133:5; 168:3, 5,
 10; 211:21; 216:20; 219:8;
 255:17; 257:12, 12
GCP 48:24; 58:24
GEHLSON 141:17, 19;
 155:2; 190:20; 191:5, 19;
 192:9; 193:3, 11, 24;
 194:9, 15; 196:3; 197:17;
 198:18; 199:21; 201:10;
 204:8; 205:8; 206:22;
 208:2, 15; 209:9; 210:1,
 18; 211:1; 212:12; 216:8,
 15, 25; 217:8; 219:9;
 220:3, 25; 221:10, 17, 21;
 222:3, 6; 223:10, 13, 18;
 225:11; 226:9, 24; 264:3,
 18
gender 169:15; 172:12
Gene 6:6; 25:13; 39:18;
 42:22; 125:6
general 8:23; 12:25;
 21:12; 22:5; 23:10; 42:9;
 102:20; 106:24; 107:18,
 22; 108:1; 111:16; 119:9;
 134:1; 147:11; 182:7;
 191:15; 207:7; 214:3
generalizable 101:18
generally 10:4; 11:1;
 12:10; 104:18; 135:8;
 255:21
generated 100:21;
 121:23
generation 29:5, 7; 37:23
generic 37:2; 91:13
gentleman 136:13
gentlemen 20:25; 35:5;
 127:20; 227:18
geographic 104:3, 7, 10
George 5:20; 124:17
gets 197:3
GI 151:10; 181:23; 211:7;
 252:6
given 66:17; 69:9; 70:3;
 74:2; 82:2, 11; 127:16;
 128:2, 5; 129:4; 130:8;
 168:8; 195:16, 24; 196:8;
 203:22; 210:4; 242:15;
 254:18; 266:18
giving 139:2; 200:13;
 201:2, 7; 253:16
glad 129:19
gland 28:8; 39:1
Glaspie 142:5; 218:12,
 14, 14; 219:4
glass 65:14
glasses 97:18; 100:6
goal 30:5; 157:9; 160:22;
 161:18
goals 30:8
goes 21:16; 43:7; 69:7;
 88:5; 122:7; 262:21
gold 27:13; 32:25; 33:9;
 36:10
Good 8:15; 16:18; 27:2;
 30:19; 35:6; 43:20; 49:8;

65:11; 90:13; 94:4; 97:23;
 103:25; 123:7, 9; 127:6;
 133:20; 134:17; 138:11;
 140:6; 143:18; 150:17;
 165:19; 166:24; 174:9;
 175:25; 179:18; 191:5, 19;
 193:11; 205:8; 209:9;
 210:1; 220:25; 227:17;
 235:6; 246:10; 254:22
Grade 60:18; 181:16, 22;
 182:8, 12, 13, 15, 17, 18;
 210:12; 243:15; 244:1, 3,
 4, 7, 8, 22, 24, 25; 245:22,
 25; 268:16, 17
graduate 129:9
Graham 127:4, 4, 6, 7, 8;
 129:22
grand 74:14
grandchildren 137:20
granted 7:12; 126:8;
 212:14; 213:1, 1; 214:5, 6,
 11; 219:10; 225:6, 25;
 227:7, 7
granting 225:16
graph 247:18; 251:1, 3, 8,
 11; 253:12
graphically 51:13;
 145:24
grave 166:23
great 24:22; 116:3; 121:8;
 159:12; 205:19; 225:8
greater 34:22; 45:17;
 46:7; 49:9; 53:24; 55:15;
 60:9; 74:5; 95:1; 97:18;
 98:11; 100:6, 9; 108:3;
 115:15; 147:17; 150:22;
 153:24; 162:8; 169:21;
 172:11, 20, 20; 176:13;
 177:10; 213:11
green 176:22; 248:2
GRIEBEL 125:17, 17;
 228:1; 254:20, 22, 23
Groebner 130:1, 2
groin 130:24, 25
group 19:22; 52:24;
 56:24; 59:5; 60:14; 64:6,
 21; 65:4; 74:18; 76:10;
 81:13; 84:9; 97:13;
 100:10; 109:18, 23; 110:9;
 112:9, 9, 10; 122:15;
 144:20; 145:16, 22; 148:7,
 8, 9, 10; 154:19; 161:2, 4,
 8; 164:18; 170:6, 9, 19, 22,
 23; 171:6, 6; 175:22;
 176:9, 18, 19; 182:23, 24;
 187:8, 17; 191:9, 10;
 194:16, 17; 205:4; 206:1,
 3, 12; 210:20; 211:1, 4, 7,
 11, 14; 212:25; 213:9, 10,
 13, 15, 18, 19, 20, 21;
 218:20; 222:23, 24; 223:2;
 226:8; 239:1; 240:19;
 241:19, 25; 256:13;
 258:20; 264:5; 268:10;
 271:12
grouped 252:9
groups 49:5, 13, 19;
 50:4, 17, 24; 59:3; 60:16;

61:3; 75:7; 82:20; 99:6;
 144:19; 169:14, 16, 23;
 170:13; 171:11; 182:4;
 191:8; 195:3, 17, 19;
 202:13; 206:7; 210:7;
 223:3
grow 24:16; 25:15;
 132:22
growth 36:1, 3, 18, 20,
 22, 23; 43:1; 112:23;
 113:1; 201:8
gruesome 137:8
guard 265:22
guess 76:24; 89:13;
 118:3; 194:22; 212:5;
 216:16; 225:7
guests 16:18; 142:2
guidance 255:22; 259:6,
 14; 260:2
guide 210:5
guideline 65:4, 17;
 249:14
guidelines 15:25; 64:22;
 174:13; 248:11
guides 68:17

H

H-2 159:1
H1 205:12
H2 158:10, 12; 181:12;
 201:4; 205:9, 10, 14, 15
half 9:5; 68:19; 114:16;
 145:5, 22
half-empty 65:14
half-full 65:14
halfway 90:3
hamster 39:11
hand 36:21; 67:15, 18;
 123:2; 269:16, 19; 270:23
handout 117:7
hands 118:20, 24;
 120:10, 14; 122:20, 22;
 123:3; 269:20; 270:12;
 271:1, 10
hang 128:7
hanging 129:5
happen 110:18, 18;
 257:2; 258:16
happened 26:1; 85:11;
 106:6; 107:25; 171:8;
 181:5; 220:9; 221:14
happening 226:20
happens 24:15; 156:6;
 262:18; 263:9
happy 111:18; 128:20;
 136:25; 138:4, 15; 261:17
hard 12:16; 107:7, 19;
 115:5; 266:12; 267:11
harm 67:2
harmful 67:7
Harmonization 248:10
Harold 19:11; 20:20;
 74:16

Hartford 6:2; 125:2
Harvard 142:8
Harvey 19:11, 13; 20:20,
 23; 36:8; 74:16, 20; 116:19
Harvey's 96:9
hat 133:3
hazard 51:22; 52:7;
 53:20, 22, 23, 25; 76:6;
 95:24; 171:24; 175:20;
 233:9, 10, 15, 16, 22;
 240:6, 11, 13
head 133:2; 213:14
headache 131:20;
 181:10; 207:5
headaches 132:17, 18;
 244:4
health 62:9; 184:5;
 204:16, 17; 263:1, 6
hear 114:6; 127:21;
 195:8, 25; 203:14
heard 21:1; 30:16; 31:7;
 32:21; 37:21; 90:19; 91:3;
 92:6; 93:17; 94:11, 23;
 95:6; 102:14; 108:25;
 116:2; 135:25; 138:20, 21,
 21; 141:10; 151:9; 155:9;
 189:23; 191:21; 209:3;
 217:9; 228:19
Hearing 8:4, 5; 13:23;
 33:11; 127:1, 3; 138:22
heart 98:22, 22; 129:17;
 131:25; 181:8
heartbreaking 127:21
heaven 22:16
heavy 87:12
held 107:23
help 21:8, 9; 42:8; 127:15;
 197:15; 205:24; 223:7;
 226:15
helpful 155:3; 197:8;
 200:2; 249:16
helps 101:16; 207:18
hematological 182:6
hemiparesis 99:1
hemoglobin 213:20
hemorrhagic 99:1
Henning 20:5
hepatic 146:17; 182:2
hepatitic 160:5
hepatitis 198:23
HER-2 75:11; 112:22;
 113:2
HER-B 75:18, 24
HER-B1 75:19, 21
HER-B2 75:20, 21
heretofore 114:13
Hershey 19:14; 134:2, 2
heterogeneous 163:22;
 219:3
Hi 64:1
hidden 69:11, 13
hide 69:14
high 29:10; 106:2; 128:9;
 132:7, 9; 135:22, 24;

139:13; 154:9; 161:14;
167:16, 19; 181:18, 19;
199:15; 202:9; 214:22;
225:4; 226:7; 246:1;
265:19
high-dose 139:2, 5;
140:7; 148:17; 149:18, 22;
150:17, 23; 151:8; 153:2,
12
higher 52:12, 14, 18, 20,
24; 55:22; 59:14, 17, 20;
86:4; 152:11; 199:18;
243:17; 244:19; 245:2;
251:4
highlighted 23:10;
163:20; 177:22
highlighting 35:17
highlights 210:24
highly 37:12; 79:18;
81:19; 82:3; 84:5; 95:24;
96:6; 98:6; 150:11; 152:25
hindsight 166:23
histamine 124:5; 126:11;
130:8; 131:13, 20, 24;
132:8, 19; 134:22; 136:1,
21; 139:8; 140:12; 141:12,
13, 24; 142:14, 16, 20;
155:4, 10, 13; 156:7;
157:9, 24; 158:5, 11, 14,
23; 159:1, 20; 160:1, 8, 10,
16, 24; 161:2, 8; 162:17;
163:17; 164:7, 10, 15, 22;
167:14, 15, 22; 168:8;
170:19, 22; 171:5, 16;
172:4, 6, 24; 176:1, 9, 18,
22; 177:3, 7; 180:23, 25,
181:21; 182:3, 9, 24;
183:10, 17, 24; 184:9;
185:4; 186:8; 187:7, 17;
188:5, 23; 189:19; 190:2,
8, 12; 192:21; 197:4, 10;
198:5, 16; 200:21, 24;
201:2, 5, 7, 22; 202:6;
204:1; 206:1, 18; 207:2,
22; 208:4, 7; 210:15, 20,
211:11, 14; 213:3, 4, 10,
15, 19, 21; 217:7; 227:21;
230:17; 239:15; 242:20,
21; 243:13; 244:3; 249:4;
250:15; 251:1, 4, 9, 11;
261:5; 264:5; 269:13;
270:1, 17; 271:3
histamine-related 181:2
histamine/IL-2 191:9;
211:4; 223:2; 228:8, 16;
229:17, 18; 230:12;
231:11; 232:20; 233:12,
14, 16, 18; 234:22, 23;
235:2, 14; 236:13; 237:21;
238:8, 12, 14; 240:15, 23;
241:1, 4, 6, 12, 21, 24;
242:6, 13; 243:22; 244:5,
13; 245:13, 17; 260:12;
264:6; 267:25; 268:4, 6,
15, 19; 269:4
histologic 21:13
historical 73:4, 21;
202:12
history 25:22, 24; 50:16;

258:19
hobbies 136:18
hoc 82:23; 259:19
hold 108:2; 203:6
holding 68:25; 129:10
holds 200:18
home 128:6, 25; 130:3;
131:3; 132:4; 136:3, 4;
139:16, 16; 140:2; 203:20;
204:16, 17, 23; 214:21;
243:5; 262:21; 263:1, 6, 8
homogeneous 164:3;
218:20; 219:2
homogenizes 164:5
honest 130:3
honestly 130:7
honor 141:17
honored 141:21
hope 27:11; 43:10; 128:6,
11; 129:3, 3, 5, 7, 8, 10;
134:16; 137:19, 19, 19, 20;
185:14; 204:21; 209:19;
266:15, 16
hormonal 9:1, 2, 3; 10:8,
15, 24; 11:1, 6, 8, 9, 14, 21;
14:20; 15:17; 17:4; 22:11;
23:23; 24:10; 31:4; 33:25;
34:2; 62:4; 74:17; 85:24;
102:2; 110:24; 112:7;
117:11, 21, 23; 118:2, 22;
119:4, 10; 121:10, 10, 21;
122:16; 267:1
hormone 12:6, 7; 21:5,
10, 14, 18; 22:7; 23:1;
25:7, 21; 45:15; 48:1, 60:1;
61:21; 86:6; 102:3;
117:17; 119:5, 5
hormone-dependent
36:6
hormone-sensitive
32:15
hormones 23:3; 37:7;
75:6; 86:1; 116:19
horrible 135:2, 15
Hospital 5:25; 20:7;
124:25; 128:25; 152:24
hospitalize 136:2
host 146:19
hot 69:16, 17; 71:16, 24;
86:14; 99:14
hours 149:21
huge 74:14; 190:8
Hukkelhoven 16:13, 16,
20
human 37:9; 38:20; 39:8,
12, 16, 21; 40:15; 43:13;
128:11; 155:25; 156:15,
16
humans 208:2
hundreds 108:10, 10
Huntingdon 124:18
husband 130:12
hyperbilirubinemia
151:11
hypercalcemia 85:1

hypotension 151:10
hypotheses 155:18;
165:6; 166:19; 171:3;
185:23; 249:16; 254:2, 4
hypothesis 106:21;
161:15; 166:15; 183:17;
201:5; 231:25; 250:16, 20,
24; 259:21
hypothetical 199:24;
256:16

I

I/II 229:19
lan 256:23
ICH 174:13; 249:13
ICU 129:2
idea 103:25; 219:18, 24
ideal 75:5; 163:17; 199:6
ideally 65:12; 226:19
identical 14:10; 32:11;
38:18; 40:11; 49:1; 71:3, 4,
12; 90:20; 182:25; 222:23
identifiable 251:21
identified 173:3, 5;
196:7; 220:7; 227:3;
248:17; 253:9
identifies 183:23
identify 21:8; 105:6;
214:1; 225:13; 226:15;
265:5
identity 69:12; 76:24;
77:1, 24
II 11:18; 92:8; 134:21, 25;
143:9; 149:2; 152:5;
160:9; 168:9; 185:12;
186:11, 13; 187:7; 188:17;
197:22
IIA/II B 59:10
III 18:2, 5; 56:7, 21; 59:24;
90:25; 130:19; 134:19;
136:23; 143:6, 11; 149:2,
8; 150:2; 152:15; 153:7;
160:9; 164:9; 185:10;
186:15; 187:1, 8, 10, 21;
188:1, 7; 230:11
IIIB 45:12; 50:19; 59:11;
92:7; 94:11
IL 164:12; 217:6
IL-2 149:18, 19, 22;
150:17, 23; 151:8, 20, 24,
25; 152:1, 2, 6, 17; 153:2,
9, 12, 15; 154:9, 12;
158:11; 167:15, 16, 19;
168:1; 170:19, 22, 23;
171:5, 6; 172:24; 176:19,
23; 181:18, 19, 21; 182:23;
183:10; 185:5; 187:8;
188:23; 189:20; 190:2, 8;
191:10; 201:19, 25; 202:2,
9; 206:1, 3, 21; 207:23;
211:1, 7; 212:4, 25; 213:5,
6, 9, 18, 20; 214:22;
216:23; 222:24, 25;
230:17; 233:19; 234:21;
235:1, 2, 13, 14; 236:6, 13;

238:16; 239:15; 241:1;
242:14, 15, 22; 243:13;
244:2, 10; 245:6; 249:4;
250:15; 251:2; 261:5, 12;
264:4, 5, 6; 267:12, 24;
268:1, 5, 14, 19; 269:14;
270:2, 18; 271:4
IL-2/histamine 216:23
IL-2/interferon 153:19
ill 86:1, 4
illustrated 253:12
illustrates 247:18; 251:8
illustration 156:13;
248:6
imagine 155:8; 180:19;
221:24
imaging 236:7, 18; 237:2,
4
imbalance 170:4, 5;
174:21, 21; 195:16, 24;
238:13; 269:9
imbalances 169:16;
171:22; 195:18, 20, 21, 23,
23; 238:7, 10, 12; 239:22;
240:6, 8; 241:20, 21;
245:13, 15; 249:9; 250:14;
251:9, 13, 21; 253:4, 9, 12,
15, 19, 21; 254:19; 257:2;
259:18; 260:11, 13;
266:13, 18; 268:22; 269:1,
3, 5
immediate 178:6
immune 163:9; 199:23;
202:6, 8; 217:21
immunosuppression
155:19; 156:8
immunosuppressive
155:17
immunotherapeutic
179:24
immunotherapeutics
155:14
immunotherapy 136:9;
148:13; 152:6, 12; 178:3,
4, 180:5
impact 26:14; 115:16
impacts 92:19; 262:13
impair 87:13
impaired 146:19
imperfections 259:9
implement 65:15
implementation 86:23;
262:4
implemented 243:3
importance 33:24;
35:15; 38:13; 67:18;
121:18; 247:19; 265:15
important 22:12; 25:6;
27:2; 28:13, 14; 37:7;
38:21; 51:25; 54:18;
56:13; 61:23; 62:9; 66:5, 8;
67:13; 87:24; 88:5;
121:11, 12; 137:4; 140:8;
146:7, 11; 147:2, 6, 19;
179:25; 184:2; 203:12, 14;
214:19; 215:25; 224:16,

20; 227:25; 246:8; 255:2;
262:24; 263:2
importantly 56:2;
163:19; 254:13; 255:12
impossible 241:4;
259:11
impractical 150:12;
259:11
impression 85:14
impressive 9:14
improve 135:22; 164:11;
171:15; 176:1; 215:21
improved 25:16; 26:16;
98:15; 100:18; 153:10, 13;
154:15, 16; 164:13;
170:19; 171:17; 176:14,
20, 25; 177:4; 180:8, 13;
184:16, 23, 25; 185:18;
188:23, 25; 189:1, 2;
190:4; 217:10
improvement 97:17, 19,
19, 24; 98:1, 4; 161:1;
171:2; 179:1, 6, 10, 13;
180:14; 185:22; 217:11,
12; 218:5
improves 11:8; 142:17;
185:5
improving 184:16
inaccurate 137:17
inactivators 28:22
inactive 217:3
Inc 141:14
inception 139:7
incidence 60:14; 61:6;
69:16; 86:14; 181:15, 22;
244:8, 18, 19, 24; 245:25;
246:5
include 56:14; 148:13;
153:8, 24; 168:15; 172:11;
225:20; 253:24; 255:24;
257:1; 269:1
included 45:4, 11, 20;
46:4, 15; 47:5, 20; 48:21;
57:12, 21, 25; 58:22;
98:20, 25; 99:4, 14;
146:22; 160:16; 193:9, 13;
204:14; 209:13; 219:14,
20, 21; 221:22; 222:9, 10,
12; 223:8; 226:3; 236:14;
240:3, 4; 245:24; 251:21;
253:3, 5, 13, 15; 265:6
includes 46:11; 48:20;
58:20; 119:24; 162:16;
184:3, 3
including 61:21; 73:18;
151:25; 219:22; 239:15,
18
Inclusion 45:11; 215:12;
225:23; 254:9
inconclusive 65:25
inconsistent 140:4
incorporated 147:5
incorporating 148:8
increase 9:23; 117:18,
22; 158:22; 177:10;
181:21; 182:7; 201:1;
231:4; 233:3

increased 146:20; 253:22
increases 154:13
 creasing 26:2; 38:13
increments 68:19
IND 165:12
indeed 21:6; 31:22; 82:20; 103:3, 17; 114:22, 25; 201:23; 202:14; 224:12
Independent 20:14; 21:14; 46:17; 54:12; 56:21; 64:6, 17; 91:22; 144:25; 202:14, 19; 208:10, 14, 16; 209:2; 212:16
independently 208:20; 209:5
Indian 6:7; 125:8
Indiana 5:20; 124:17
indicate 11:12; 106:9
indicated 14:21; 17:4, 15; 32:7; 62:4; 67:20; 95:25; 210:12; 219:12, 25; 233:15
indicates 19:3; 29:17
indicating 79:24; 233:22; 240:7
indication 13:9; 16:11; 17:1, 14; 32:9; 62:7; 90:17; 95:18; 112:5; 113:10; 17:10, 11, 20; 142:21; 145:23
indicator 146:18, 20
indirect 79:23
individual 57:8; 60:12; 74:4, 5, 10; 107:4; 209:8
individually 104:12; 172:22; 173:10; 250:1
individuals 141:7
indolent 22:3; 25:20
induce 157:15
induced 156:9
inducer 106:5, 10; 121:1
inducers 106:14, 19; 121:3
induction 25:8
industry 255:23
ineffective 137:17; 157:23; 158:3; 256:9; 257:18; 265:21
ineligibility 226:12
ineligible 167:19; 212:9; 219:8; 226:7; 266:18
inert 200:12
inevaluable 266:19
inevitable 137:11
infarction 98:21; 211:17
 ection 151:17
 erior 97:1; 146:2
inferiority 11:11; 67:14
infers 260:23
infiltration 217:19
inflammation 198:24

influence 82:4; 83:6; 150:19
influenced 167:10; 228:25; 229:3; 260:13; 268:21
influencing 17:9
influenza 211:2
information 7:5, 15; 10:18; 46:12; 64:13, 18, 21; 65:2; 67:13, 18, 19, 24; 68:2, 5, 8, 20; 91:22; 105:4; 116:6; 120:18; 126:1, 14; 137:15; 143:20; 147:21; 160:14; 204:23; 216:18; 219:16; 220:21; 239:5, 8, 8; 243:4, 9; 249:17; 259:9; 262:22; 263:22
infrequently 101:8
infusion 149:21; 160:23
inherent 256:2
inhibit 27:9; 29:21; 36:21; 38:22, 23; 40:22; 42:14
inhibited 201:4; 202:7
inhibiting 29:14; 33:17; 36:12
inhibition 36:23; 37:3, 4, 5; 39:20; 40:1; 41:20, 21, 24, 25; 42:4; 72:21, 22; 74:6, 14; 106:1, 3; 156:9
inhibitor 17:8; 31:11, 15; 33:8; 37:13; 38:6; 43:11; 89:16; 105:13; 115:19; 122:3
inhibitors 23:19; 24:3; 28:23; 29:18, 23; 30:10, 17, 22; 32:5; 33:21; 34:12, 12; 35:11, 16; 36:13, 21; 37:17, 20, 23; 38:5, 8, 22; 40:21; 42:14, 16; 43:13; 62:11; 88:24; 110:5; 111:15; 114:1, 14
inhibits 42:9; 104:25
initial 8:19; 9:7, 22; 10:8, 24; 11:6, 15; 22:20; 44:23; 46:11; 48:14, 16; 78:17, 22; 82:1; 98:10, 14; 115:20; 117:12; 118:2; 119:4; 134:18; 155:11; 173:22, 25; 253:7
initially 63:11; 91:4; 194:23
initiated 13:14; 36:4; 160:20
initiates 35:24
initiation 18:10
inject 155:9; 159:14
injected 142:13; 180:20
injection 124:6; 140:12; 141:12, 13; 155:5; 159:18; 181:9; 204:10, 14, 18, 24; 207:3; 242:21
injections 201:2; 242:16, 22
inoculated 42:22
Inpatient 139:3, 14, 21; 150:12; 152:23

insert 17:14
inside 241:5
insight 200:2
insights 66:5
insignificant 40:13; 226:10
instance 31:13, 14; 87:12; 121:12, 13
instances 26:17
instead 205:15; 252:21
Institute 5:19; 124:16; 138:13; 145:18
institution 77:9, 11; 94:4; 138:25
institutions 93:22, 23
instructed 25:14
instrument 86:23; 183:16, 23; 184:2
instrumental 86:24
insure 45:25
intact 21:11
integrals 84:4
integrity 66:15; 67:17
intended 249:14; 250:7
intensive 152:23
intent 32:11; 90:8; 165:20, 21; 166:14
intent-to 53:14; 55:5; 174:19; 179:6; 184:8
intent-to-treat 48:19; 54:2, 14; 58:20; 94:6; 165:3, 4; 166:18; 170:7, 17; 172:2, 3; 179:2; 182:23; 184:11; 185:16; 187:11; 193:12; 201:13; 210:21; 216:22; 218:24; 226:3; 228:14; 231:20; 232:10; 237:11; 245:9; 260:6; 261:1, 3; 267:10
interact 104:21
interaction 45:7; 75:12; 88:14; 91:6; 104:16; 105:12, 19; 106:21; 120:20; 121:8; 174:12, 15, 24; 175:1, 14; 208:5; 248:16; 249:23, 24; 250:5
interactions 105:14, 14; 121:17
interacts 207:23
Interest 6:22, 24; 7:2, 7, 9, 19, 24; 68:25; 125:20, 21, 23; 126:3, 5, 17, 22; 134:15
interested 114:12
interesting 33:14; 75:10; 88:1; 100:4; 104:24; 112:23; 156:20; 174:25; 233:20
interfere 204:1
interferon 149:4, 9, 10; 152:17; 153:9, 12; 156:18; 162:19
interferon-gamma 158:8
intergroup 153:18

interim 46:16, 22; 64:23, 24; 65:1, 23; 167:6; 185:9, 13; 187:24; 188:16; 189:3, 13; 208:21; 209:12, 23
interims 46:16
interleukin 132:8; 139:3, 8; 140:8, 21
interleukin-2 131:13; 132:19; 134:22; 135:22; 136:1, 21; 139:5; 140:7; 141:25; 142:17; 148:17; 155:5; 156:11, 18; 157:6, 17, 23; 158:3; 159:7, 21; 160:2, 24; 162:18; 164:11, 22; 167:13, 14; 168:2, 18; 170:9; 176:1, 2; 177:3; 186:8, 16; 187:3; 190:12; 192:20; 194:16; 198:1; 208:4, 6
intermediate 147:14
internal 101:16; 104:1; 237:16; 246:24; 248:23
internally 77:13; 119:25
international 64:6; 168:6; 230:10; 248:10
Internet 137:14
interpret 230:19
interpretable 250:1
interpreted 245:12
interrupted 88:15
interval 21:19; 50:20; 53:25; 84:21; 173:11, 14; 269:2
intervals 47:5; 53:21; 55:12; 149:24
intervened 25:25
intervention 26:3; 267:7
into 12:19; 23:1, 7; 25:17; 26:20; 28:3, 13; 42:22; 54:19; 64:4; 70:17; 74:21; 77:8; 80:22; 82:1; 83:7; 85:5; 86:19; 108:2; 110:4; 115:9; 116:18; 120:2; 121:19; 131:11; 132:11; 136:15; 147:21, 24; 148:8; 158:19; 159:12, 15, 23; 180:21; 183:15; 184:4; 191:22; 196:10, 22, 23; 202:20; 207:4; 213:2; 215:2, 3, 13; 225:24; 240:1; 246:17; 252:9; 253:14; 258:7; 262:21
intolerant 167:19
intracellular 36:2
intratumoral 28:18; 35:15
intrigued 114:1
intriguing 110:6
introduce 5:10; 35:1; 70:8; 124:8; 142:2; 255:1
introduced 113:20; 232:1
introduces 40:14
Introduction 8:14; 16:15; 17:19, 22; 123:8; 258:22
Introductions 5:2; 124:3

Introductory 141:16
intuitively 157:1
invasive 26:20, 20
investigate 27:9
investigation 34:6
investigations 255:11, 12
investigator 20:6, 8; 57:8; 79:5; 196:6, 7; 209:21; 212:21; 222:21; 226:2, 15
investigators 64:9; 77:16; 97:24; 107:4, 8, 19; 134:18; 168:2; 178:14; 196:12; 206:24; 209:8; 212:17; 214:15; 227:3; 228:25
investigators--that 198:2
invite 63:23
involve 7:17; 126:15
involved 50:6, 14; 64:20; 95:6; 129:1; 139:6, 17; 140:10; 189:13; 202:5; 208:18; 239:1
involvement 7:21, 25; 58:10; 126:19, 23; 144:5, 7; 194:24; 195:3, 12, 15; 196:2; 235:9; 238:24
involves 149:19
involving 77:21; 144:16
irrelevant 137:17
irreversibly 29:20
ischemic 99:1
issue 7:1; 13:15; 62:9; 63:25; 69:6; 79:3; 86:25; 88:23; 107:5, 18; 120:20; 121:8, 12; 125:23; 215:24; 216:2, 4; 224:16; 237:25; 242:5; 262:6, 25
issues 87:25; 128:13; 129:14; 203:4; 227:25; 228:13; 232:9; 246:9; 247:17; 249:10; 263:11; 265:13
it--cytotoxic 267:1
it--you 78:1
Italian 258:20
items 214:3
ITT 55:17; 237:12; 246:18; 248:3, 9, 20, 23; 249:4; 254:5; 267:24; 269:12
IV 92:7; 128:4, 14; 138:2; 143:21; 144:4, 17, 20; 147:22; 151:21; 160:23; 173:19; 174:1; 229:2

J

Janice 124:22
January 48:9; 93:19
Japan 132:12, 13
jaundiced 135:14
JCO 256:23

JEG-3 39:22
job 132:11; 254:25
jobs 131:8
Jody 6:7; 125:7
Joe 130:1
Joel 191:21
John 6:16; 67:9; 125:14; 142:5; 145:18; 218:13, 14; 219:1
John's 106:16
JOHNSON 6:16, 16; 8:11, 15; 12:5, 8, 23; 13:11; 14:25; 15:14, 20; 16:2, 8; 20:24; 30:9; 32:7; 119:13, 14
join 261:18
Journal 258:21
Jude's 5:24; 124:24
judgment 262:22
Judy 125:16
July 18:3; 169:5; 231:9
June 18:10; 231:19

K

Kansas 5:14; 124:11
Kaplan-Meier 51:13; 68:4, 9; 170:16; 175:10, 19; 176:17; 178:25; 234:1, 10
Karen 6:3; 125:3; 127:4, 6
Karnofsky 97:20; 178:18
Kathy 6:11; 64:1; 102:9; 125:12; 203:5
kay 55:18
keep 68:7; 132:12; 164:20; 186:23; 192:7, 13, 15; 203:21; 255:2
keeping 137:21
KELSEN 5:16, 16; 85:8, 9; 106:22, 23; 107:16; 108:4, 18; 124:13, 13
Ken 124:18
kept 69:21; 77:12; 191:14; 254:13
key 47:25; 53:6, 19; 54:3, 23; 55:10; 65:21; 189:6; 230:5
key-if 158:17
kidney 213:16
kidneys 252:6
kids 134:16
kill 156:17; 157:5; 178:10
killer 156:2, 3, 5, 16, 17; 157:3, 5, 22
killing 156:20; 157:23, 25
kind 21:8; 22:2, 5, 10; 76:20; 129:16; 155:10; 167:21; 262:22
kinds 22:17; 83:18; 108:10, 14; 192:23; 209:7
knew 77:1; 88:18; 217:16
knife 168:21

know--l 104:19
knowledge 24:18; 77:15; 106:8; 120:24
known 60:23; 83:6; 105:1, 12; 106:7; 110:20; 121:4; 127:9; 128:13; 155:16; 202:15; 228:21; 236:20; 245:7; 253:25; 268:22
knows 22:16; 131:25
KPS 45:17; 49:9
Kupffer 163:12
Kurt 141:19; 143:18

L

lab 37:15; 226:12
label 254:19
label-how 104:20
labeled 121:4
labeling 120:21; 121:3; 122:7
labelling 249:17
laboratories 73:7
laboratory 29:3; 47:6; 147:5; 174:5
lack 180:3, 12, 14; 201:18; 229:20, 22; 237:16
ladies 20:25; 35:5; 127:20; 227:18
Lady 124:23
languages 83:18
large 12:14; 18:14; 23:12; 26:9; 31:5; 43:25; 54:14; 59:23; 61:9; 73:15; 74:11, 22; 82:16; 83:22; 88:16; 100:11; 101:15; 116:25; 119:17, 22; 146:17; 155:22; 189:8; 193:1; 202:13; 215:20; 240:13, 22; 259:16; 265:17; 266:19
largely 101:9
larger 14:9; 101:19; 113:8; 178:11; 201:8
largest 18:19; 56:6; 61:15; 62:15; 93:22; 107:24, 25
laser 137:16
Last 9:5; 11:22; 13:12; 26:2; 37:19; 48:11; 72:8; 75:10; 79:16; 93:19; 102:12; 129:6; 138:10; 155:21; 158:25; 160:1; 169:6; 177:23, 25; 188:12; 197:19; 210:3, 6; 211:23; 219:12; 227:13; 231:18; 232:18, 25; 233:4; 236:18; 20; 243:16, 19; 244:16; 245:23; 253:3; 256:24; 260:17; 271:2
lasted 97:20; 181:3
lasting 149:23
late 25:24; 26:1; 35:21

lately 114:20
later 12:2; 25:16; 29:8; 64:24; 130:21, 22; 240:2, 5
latter 63:10
Laura 138:10, 11
LDH 146:23; 147:1, 5, 18, 25; 148:1, 2, 2, 8; 154:1; 169:16; 170:8; 172:13, 13; 174:3, 7; 238:11; 252:7, 20
lead 99:16; 255:25
Leader 6:16; 19:23; 125:17; 228:1; 254:23
leading 58:18; 64:4; 93:21; 209:24; 211:12
leads 35:25
leaks 151:14
learn 34:20; 131:23; 140:11, 17, 19
learned 157:11; 158:25
least 33:8; 40:17; 49:19; 60:9; 67:10, 14, 22; 80:22; 105:24; 106:7; 111:12; 116:16; 131:12; 135:5; 193:5; 195:7, 24; 202:23; 214:16; 216:19; 217:13
least--l 102:17
leave 143:12
leaves 259:8; 264:8
leaving 81:18; 97:4
led 30:21; 144:21
leeway 255:17
left 57:8; 218:3; 257:24
lefthand 257:24
leg 130:16; 132:20
legs 132:19
length 215:6
lengthening 133:10
lengths 72:20
lesions 49:24; 93:7
less 33:6; 49:7; 51:23; 52:7; 53:12, 23; 55:4, 15; 59:16; 86:8, 17; 100:5, 8; 108:2, 11; 139:13; 144:12; 145:5, 21; 148:25; 150:23; 202:8; 207:17; 233:18; 241:6; 249:20; 251:6; 269:5
lesser 11:3; 21:16; 74:6
lethal 127:25
letrozole 8:12; 17:3, 21; 19:17; 29:9, 13, 23; 31:8, 8, 14, 21; 33:12, 13, 15, 16, 19; 35:2, 3; 36:14; 37:1, 11; 38:3; 40:1, 8, 12, 17; 42:8, 24; 43:2, 4, 5, 8, 11; 73:3, 9, 12, 13, 16, 20, 24; 76:1, 5, 9; 88:17, 19; 89:6; 90:17, 19, 24; 91:1; 94:3, 6, 13, 17; 95:15, 19, 22; 96:2, 20, 24; 97:9; 98:3, 13, 15; 99:8, 20; 100:14, 17; 101:1; 102:1; 105:22, 25; 106:20; 110:7; 111:12, 16; 112:21; 113:4, 25; 114:7; 116:5; 121:15
letrozole/tamoxifen

91:5
letting 141:9
leukemia 160:4
level 42:6; 47:16; 58:11; 65:18, 20; 117:3, 6; 121:2; 130:19; 175:1; 186:2; 195:5; 210:6; 247:14; 248:1, 2
levels 27:25; 28:1; 89:6; 105:20; 106:2, 20; 201:1
LHRH 23:18, 21; 121:14, 15
life 30:6, 13; 79:15; 86:19, 20, 23, 25; 87:5, 7, 9, 13, 17, 20, 24; 128:8, 12, 13; 129:14; 133:8, 10, 12; 135:24; 139:20, 22; 140:22, 23; 164:14; 183:15, 18; 185:7; 190:5; 204:3, 7, 25; 205:4; 262:7, 17
life-threatening 13:3
lifetime 144:1
ligand 25:7
ligands 25:5
light 128:21; 131:21
likelihood 30:4; 137:10
likely 22:7; 67:1; 97:14
limit 172:15; 174:6
limitations 255:2
limited 150:13; 151:20; 154:12; 189:25; 228:20; 259:10
limits 63:20
line 13:18, 22, 25; 14:21; 16:11; 17:4; 18:3, 6, 16; 19:2, 6, 9, 22; 22:24, 25, 25; 34:10, 13, 15; 35:18; 39:17, 21, 22; 61:16; 62:12; 73:16; 89:24; 90:18; 93:10; 96:10; 138:1; 156:15; 176:18, 19, 22, 23; 248:1, 2
lines 39:14
lipids 110:18
LIPPMAN 5:22, 22; 7:12; 116:9, 10; 124:20, 20; 126:8; 197:3; 198:12; 199:13; 206:10; 215:15, 16
list 73:13; 117:7
listed 91:18; 94:16; 96:24; 100:1; 172:21; 173:4, 8, 9; 190:17; 193:4; 205:17; 219:10; 234:18; 236:17; 238:10; 241:20; 243:9; 244:1; 245:4; 252:2; 255:22; 256:25
listening 129:15; 135:16; 202:4
listing 225:6; 253:13
listings 77:14
lists 228:4; 229:6; 253:3
literally 128:10; 131:17
literature 79:24; 87:9; 106:8; 156:22; 173:13;

188:9; 229:8; 235:9
little 5:7; 14:2; 24:1; 64:3; 84:19; 85:13; 88:20; 91:4, 21; 93:2; 96:16; 111:1, 20; 114:12; 128:11, 14; 129:5, 10; 130:3; 132:3; 133:25; 162:4; 173:9; 179:20, 23; 182:11; 200:2; 207:17; 208:12; 218:13; 259:8
live 128:5; 131:1; 133:7; 164:1, 3
lived 217:6
liver 21:24; 50:12; 95:5; 97:4; 128:5; 135:9, 10, 13; 142:18; 145:10, 13, 19, 25; 146:1, 6, 11, 14, 17; 147:14; 153:25; 154:19; 160:11; 161:3, 5, 6, 7, 9, 10, 11, 22, 24; 162:10, 11, 11, 20, 24; 163:3, 6, 9, 10; 164:2; 165:4, 15, 17, 18, 22; 166:2, 4, 17, 21; 169:25; 170:3; 171:1, 9, 12, 17; 172:2, 7; 174:19, 24; 175:3, 4, 7, 8, 11, 15; 176:5, 8; 177:4, 7; 179:9, 14; 180:11; 182:25; 184:14, 25; 185:6, 21; 186:1; 187:14, 23; 188:11, 13, 14, 24; 189:7, 20; 190:6, 14; 191:4, 11; 194:24; 195:3, 12, 15, 15; 196:1, 16, 18, 20; 197:5, 9; 198:15, 17, 19, 20, 24; 199:10, 19, 22; 200:10, 15, 18, 22, 24; 201:1, 6, 9, 14; 202:12, 15, 19; 210:21; 211:5, 15; 213:16; 216:22; 218:17, 19; 228:9, 15; 229:7, 11; 230:24; 231:1, 7, 15, 15, 22, 25; 232:5; 234:19, 24; 235:17, 21; 237:22, 23; 238:5, 6; 239:17; 240:9, 17, 20, 24; 241:5, 15, 17, 19, 25; 243:17; 244:17; 245:12; 246:18; 249:6, 7; 250:9, 14, 16, 19, 23; 251:13, 24; 252:6; 254:5, 16; 260:10; 261:10, 13; 266:5; 268:1, 11, 19, 24; 269:25; 270:3, 4; 271:6
lives 136:17
living 130:15
Lloyd 20:12; 70:10
load 199:1
local 72:3; 76:22; 135:7
locally 31:24; 44:7; 45:12; 50:18
located 224:14
locoregional 45:13
log 174:3
log-rank 53:5; 233:9, 20
logical 93:2
logistic 47:22; 55:9
logs 204:10, 15, 18, 24
long 21:19, 19; 30:6; 82:17; 87:2, 4; 116:3;

191:14; 192:2; 197:20; 219:21
anger 27:7, 7, 24; 30:11, 66:7; 84:21; 88:20; 110:19; 122:9; 129:5, 10; 162:21; 217:6; 233:24
Longmont 130:15
Lonnig 73:7
look 23:24; 25:22; 26:6; 38:21; 63:9; 65:22; 71:3, 18; 72:8; 73:6; 76:2, 8; 81:7; 82:18; 84:19; 86:12, 20; 87:24; 88:2; 89:9; 93:10; 96:7; 100:11, 20; 104:3, 4, 19; 112:18; 121:19, 22; 133:2; 156:22; 158:7, 17, 18; 161:23; 162:4, 5, 10; 165:21; 169:12, 20; 170:3, 5, 21, 25; 174:11, 19, 24; 176:7, 13, 17, 22; 178:11, 11; 179:23; 180:3, 11, 12, 17; 181:15; 182:6, 11, 12, 17, 21; 184:7, 13, 22, 24; 185:16, 20; 188:5, 13, 15; 198:13; 200:3; 202:18, 23; 217:17, 25; 218:1; 234:15; 235:4; 240:17; 247:2; 262:5, 17, 20; 263:3, 6
looked 70:17; 71:12; 75:19, 20; 78:7; 84:1, 3; 98:9; 100:7; 106:8; 109:17; 144:19, 21; 149:3; 165:7; 172:19, 21; 178:16; 179:17; 210:4; 214:13; 234:18; 236:1; 241:9
looking 12:17; 32:22; 65:13, 17, 19; 66:22; 68:18; 74:5; 80:13; 89:20; 90:1; 97:17; 98:11, 19; 105:19; 107:8; 118:10; 134:21; 140:9; 145:3, 18; 146:15; 148:4, 5, 22; 151:24; 152:5, 16; 153:11, 14; 172:1; 181:18; 197:14, 23; 208:3; 216:16; 221:10; 256:12, 12
looks 23:9; 63:14; 71:14; 74:25; 80:16; 194:23
looseness 226:13
lose 79:20
losing 269:5
Loss 131:18
lost 219:21; 220:2, 8, 13; 221:14; 262:5
lot 71:18; 82:16; 83:13; 109:22; 111:21; 114:23; 118:15; 130:9; 151:8; 166:24; 197:6, 13; 198:22, 24; 199:14; 200:1; 204:6, 10, 19; 206:15; 215:7, 19; 222:2; 262:11, 14; 265:5, 21
Louis 133:24; 134:8, 8, 10; 137:24
loved 127:15, 22; 129:4
low 21:15; 39:15; 60:12,

16; 61:5; 69:16; 72:7; 80:12; 86:14; 96:8, 16; 106:1; 132:8, 9; 136:2, 20; 137:10; 140:20; 154:12; 201:18, 21, 25; 202:2; 236:4; 257:4
low-dose 151:20, 25; 152:2
lower 67:21; 71:18, 23; 92:24; 140:21; 161:16; 200:23; 233:15, 15
lowered 121:1
Loyola 6:11; 125:12
lung 21:25; 147:14, 25; 159:17; 197:14; 199:15, 16, 20, 22; 200:17; 235:9; 239:2; 252:6
lungs 21:23; 131:11
luxury 22:14
lymph 58:10; 130:25; 147:13; 252:5
lymphocyte 155:25; 197:24, 25; 198:10; 217:19
lymphocytes 163:15; 178:10; 198:3, 7; 199:3, 7; 200:20
lymphogenic 21:25
lymphoma 156:15
lysis 156:3

M

M.D 5:22; 124:21; 147:1; 238:23
M01 246:15
M1a 147:24; 148:7, 9
M1b 147:25
M1c 148:1, 7, 9
MA-O103 230:16; 244:12
macrophages 155:23, 24; 156:1, 10; 157:12, 20; 163:11; 200:17
Madam 20:23; 34:24; 69:4
magnitude 240:14
main 18:12; 248:6
mainly 105:23
mainstay 34:6
maintain 66:13; 87:4; 140:1, 23; 159:9; 161:17; 186:2
maintained 67:17
major 29:19; 32:20; 34:8; 46:4; 51:10; 80:17; 87:1, 15, 15; 95:17; 99:21; 106:11; 121:20; 212:10; 227:25; 228:12; 229:6; 238:10; 244:13; 246:9, 14, 16; 249:7
majority 50:17; 79:12; 100:12; 180:24; 182:13; 183:2; 200:15, 19; 210:12; 221:24; 222:13, 17;

226:11; 227:1; 242:9
makes 72:23; 112:21; 163:12
making 115:1; 241:4; 262:21; 265:20
malaise 151:12
male 169:15; 172:12
malignancies 63:1
malignant 130:19, 23; 190:1; 253:25
mammography 57:22; 59:18
mammoplasties 39:13
manage 136:12
managed 134:23
Management 20:14; 143:21; 191:14
manager 130:14
manifest 151:14
manner 23:3; 68:24; 75:17
Mantel-Haenszel 58:9
Mantel-Haenzel 54:21
manufactured 91:13
many 26:10; 33:12; 35:22; 36:2; 38:16; 83:5, 11; 85:10; 102:25; 109:17, 18; 122:2; 127:20, 23; 130:11; 135:3; 140:6; 155:16; 168:1, 15; 186:10; 191:4; 194:2; 204:16; 215:2; 216:6, 12; 219:15; 225:18; 227:8; 238:7, 15; 241:1; 257:7; 262:25; 266:13; 268:22
March 48:10; 58:15; 167:3; 169:5, 7; 231:18; 232:25; 234:2; 247:7, 11, 22; 252:14; 253:17
Margaret 19:20; 43:17
mark 69:15; 210:8
marked 69:11
marker 197:24
markers 57:25; 75:16, 25, 25; 197:23; 198:6
market 12:13; 17:19
marketing 11:10; 117:24; 228:7; 237:20; 245:6
marking 70:15
marks 80:20, 25; 81:2
marrow 200:16; 213:16
Martin 6:15; 90:14
Marty 104:16; 119:23
Maryland 39:5
mastectomy 57:5
material 80:8; 83:1
materials 63:22; 103:2, 13
mathematical 218:18
Mathias 16:20
matter 12:25; 54:19; 108:12; 163:24; 176:3; 271:15
Matthew 20:9; 88:22

mature 10:17; 14:17; 247:12
Maxamine 213:7
Maxim 130:8; 134:15; 141:14, 20; 205:24
Maxim's 137:18
maximal 37:5
may 7:14; 8:1; 9:12; 54:19; 62:21; 64:7, 18, 24; 65:18; 68:18; 69:3; 85:4; 87:13; 92:11, 12; 98:3; 106:19; 110:7, 7; 113:4, 16; 114:7, 10; 118:20; 120:10; 121:22; 126:12, 24; 128:21; 139:16; 147:18; 163:5; 175:23; 178:4; 179:25; 180:9; 197:11; 198:20; 200:1; 212:6, 18; 214:24; 215:7; 218:9, 23; 225:14; 226:22; 227:7; 249:15; 255:24; 256:3, 4, 5; 264:23
maybe 40:19; 64:3; 70:2, 4; 80:7; 83:19; 85:2; 86:17; 104:22; 105:3; 119:17; 131:25; 133:3; 142:11; 179:23; 191:1; 195:6; 262:11; 267:20
McDONOUGH 124:18, 18
MCF-7 39:17; 42:20
McGuire 35:21; 38:14
mean 15:11; 74:1; 78:12; 89:12; 90:7; 106:13; 108:11; 110:13; 115:13; 118:5; 120:25; 184:7; 209:19; 215:18; 219:19; 221:17; 223:8; 225:5, 11; 226:6, 21; 246:4; 265:16
meaning 12:19; 121:2; 254:2
meaningful 66:2; 98:1; 218:7
meaningfully 67:23; 68:1
means 15:6; 79:13, 20; 85:22; 132:7, 12; 158:19; 173:20; 202:18
meant 37:5; 78:18
measurable 45:17; 49:20; 57:16; 92:9; 93:4, 11; 194:9; 213:7
measurable/evaluable 93:13
measure 27:25; 97:24; 114:24; 197:18; 200:10, 10, 12; 233:13
measured 41:10; 82:18; 218:2
measurement 75:4
measurements 47:5; 103:7, 14
measures 200:12
measuring 207:19
mechanism 35:11, 12; 36:16
mechanisms 36:2

median 32:22; 49:5; 50:20; 51:5, 15, 18; 52:8; 59:3; 94:23; 95:6, 14, 15, 22; 96:20, 21; 117:4; 131:1; 144:10, 11; 145:15, 20; 147:15; 148:6, 23, 23; 150:7, 8; 151:1; 152:9, 20; 154:16; 161:25; 162:13; 171:14, 15; 176:8, 10; 177:11; 184:7, 20, 22, 25; 186:21; 188:6, 8, 9, 14, 15, 17; 191:15; 194:12, 15, 17; 216:19; 231:4; 232:23; 233:6; 234:21; 235:1, 6, 8, 13; 238:19; 240:23; 247:10; 267:25; 268:2, 4, 6
Medical 5:14, 15, 17, 21, 23; 6:1, 8, 12, 12, 13, 15; 20:10; 47:1; 62:20; 124:11, 12, 13, 20, 22, 23; 125:1, 8, 10, 13, 13, 15, 16, 17; 133:25; 134:2; 142:8; 166:25; 189:16; 212:15, 16, 20, 20; 225:19; 226:1, 2, 6, 14, 19; 227:2, 10; 228:1; 254:23
medication 49:2; 118:23; 211:23; 214:21; 243:7, 16, 20, 21; 244:16; 268:15, 16
medications 111:17; 121:21; 205:18; 245:23; 263:4
Medicine 6:6; 19:13, 14; 26:25; 99:16; 125:6
meet 10:10; 68:18; 92:21; 94:4; 213:7, 15
meeting 5:4, 7, 9; 6:25; 7:2, 4, 9; 8:6; 20:3; 65:3, 24; 68:15, 19, 24; 69:1; 125:24, 25; 126:5; 155:11; 189:2; 232:16
meetings 136:14
megestrol 13:19; 31:4, 6, 9, 11, 16; 89:1
Melanoma 127:5, 8; 128:4, 14, 22; 130:12, 19; 131:8, 10; 134:10, 12, 13; 135:2, 6, 7, 10; 136:9; 137:5, 8, 21; 138:3, 13, 14; 141:1; 142:14; 143:3, 17, 21, 24; 144:2, 4, 5, 10, 17, 20; 151:21; 152:7; 153:22; 154:18; 155:6; 156:24; 159:14; 160:4, 9, 25; 163:22; 164:12, 19; 168:15, 25; 169:1; 173:7, 19; 177:18; 178:1; 182:15, 18; 183:2, 11; 186:9; 188:10, 13; 189:9; 190:1, 3; 191:3, 4, 7, 10; 199:2, 3; 224:17; 228:9, 19; 229:2, 3; 231:12; 237:21; 249:2; 253:25; 258:18; 261:6, 13; 262:6; 264:22, 22; 268:20; 269:14; 270:3, 19; 271:5
member 75:18
Members 16:17; 20:24, 25; 35:4; 36:14; 75:24;

76:4, 13; 141:22, 23;
227:18, 19; 228:4; 262:13,
14
membrane 40:15
Memorial 149:14; 229:10
memory 13:9; 65:6;
129:6
Memphis 5:25; 124:25
mention 92:19; 209:3
mentioned 15:19; 18:24;
91:7; 99:12; 105:17;
153:3; 168:10; 176:20;
197:11; 201:18; 221:13,
23; 241:2; 257:4; 258:9
Mercy 124:23
mere 257:1, 2
message 251:2; 254:8
met 46:19; 64:11; 89:22;
148:2; 169:25; 174:24;
177:8; 182:25; 187:14;
210:21; 212:19; 215:12;
225:25; 229:15; 250:9, 9;
260:2; 267:18
meta-analyses 152:10
metabolism 104:25;
105:23
metabolite 106:11
metabolites 157:13, 14;
159:3
metabolized 105:22
metastases 50:12; 82:5;
84:16, 25; 95:5; 135:9;
142:18; 144:8, 25; 145:4,
6, 7, 10, 13, 20, 21, 25;
146:1, 3, 6, 11, 15, 18;
147:10, 13, 14, 25, 25;
153:25; 154:1, 19; 160:11;
161:5, 7, 9, 22, 24; 162:20,
24; 163:3; 164:2; 165:5,
17, 18, 22; 166:17, 21;
168:20, 23; 169:1; 170:4;
171:1, 9, 12, 17; 172:2;
175:3, 4, 7, 11, 15; 177:4,
7; 179:9, 15; 180:11;
184:14, 25; 185:6, 21;
186:2; 187:23; 188:11, 13,
14, 24; 189:7, 20; 190:6;
191:11; 196:16, 18, 21;
198:19; 201:14; 202:12,
15, 19; 215:4; 216:22;
218:19; 229:7, 11; 230:24;
231:23; 234:19, 24;
235:18, 21; 237:24; 238:5;
239:2, 8; 240:19; 243:17;
244:17; 245:12; 260:10;
261:10; 269:25
metastasis 21:20, 21;
72:5; 128:5; 172:7;
173:22, 25; 238:13, 17, 20;
241:2; 246:19; 249:6, 7;
250:16, 20, 23; 251:24;
253:7, 8; 254:5, 17; 268:1,
5, 11, 11, 19, 25; 270:4
metastasized 131:10;
190:14; 228:9; 237:22;
261:13; 270:3; 271:6
metastases 176:4
metastatic 8:20; 9:7, 22;

10:9, 25; 11:7, 16; 12:9;
13:18, 25; 14:21; 30:3;
31:25; 34:11; 44:8; 45:14,
23; 50:17; 57:16; 112:5;
117:12; 118:2; 119:6;
122:1, 6, 8; 141:1; 143:17;
144:4, 10, 24; 146:8;
147:10, 11; 152:6; 153:22;
154:18; 155:6; 160:3, 25;
162:5, 7, 8; 164:12, 19;
173:9, 16; 176:4, 14;
191:4; 224:17; 228:19;
231:12; 249:2; 252:4, 7,
23; 258:18; 261:6; 262:6;
268:20; 269:3, 14; 270:18
meter 168:4, 6
method 93:3; 155:21
methodologically 120:1
methods 236:16
mets 148:1; 165:15;
166:3, 4; 175:8; 231:15
mg 17:3, 21; 18:21; 31:9;
32:16, 17; 41:2, 3; 44:2, 3;
88:25; 89:1, 11; 168:8
mg/ml 141:13
mice 42:22; 159:15
Michael 142:8; 143:3, 15
Michigan 6:10; 125:11
microdialysis 200:4, 22
microphone 213:25
microsomes 39:8
middle 243:3
Midwest 252:10
might 30:18; 65:21;
68:13; 78:19; 89:9; 92:23;
95:10, 17; 96:8; 99:15;
101:18; 104:18; 105:4;
108:9; 119:24; 121:12, 16;
127:13; 161:16; 179:22;
202:6; 203:25, 25; 213:24;
222:22; 230:2, 7
mike 192:8; 201:17
mild 101:6; 108:25;
181:1; 183:7
mildly 114:12
Miller 38:11; 39:4
milli 168:5
milli-International 168:4
Milton 134:2
mind 26:6; 28:16; 33:24;
112:21; 254:13; 255:2;
266:12
Minimal 103:6, 20; 180:1;
190:7; 259:17
minimum 151:2; 192:10
minister 130:13
minor 87:11; 133:6, 12
minus 153:9, 12, 15;
160:24
minutes 131:24; 132:1;
160:18; 181:3
miracle 26:24
mirrored 181:17
miss 257:22
missed 78:1; 80:8; 191:2;

197:11; 226:11
missing 205:25; 206:2, 5,
7
Missouri 133:24
Mitch 73:7
mix 156:14
MM1 160:22; 188:4
MM2 161:18; 188:4
MO1 185:10; 187:19, 25;
188:7, 14; 249:1
MOA-2 72:25
modalities 36:7
model 43:15; 159:14, 23;
171:24; 173:7; 174:15;
175:20; 239:23; 240:4;
250:4, 7; 251:19, 21, 23;
252:13, 24, 24; 253:4, 5,
14, 20, 24; 254:9
modeling 82:10
models 62:13; 82:23;
174:2; 189:17; 240:3;
251:16, 16
moderate 101:7; 108:25;
181:1; 183:7
modern 28:24
Modernization 255:16
modest 10:3; 11:1
modification 114:10;
147:22
modify 207:3
modulator 114:9
mole 130:16, 18, 22
molecular 29:19
moment 211:20
monitor 103:11; 192:16;
212:15, 16, 20, 21; 226:1,
2, 14, 20; 227:2, 10
monitored 47:8; 103:10;
167:5; 205:19; 224:7
Monitoring 46:18; 63:11,
14, 18, 20; 64:2, 7, 17, 19;
65:4; 68:17; 114:23;
166:25; 167:4; 189:12, 13,
15, 16, 16; 208:10, 12, 14,
17, 24; 209:3; 224:8
monitors 224:8; 225:19;
226:6
monocytes 155:22, 23;
156:1, 10, 24; 157:2, 4, 11,
20, 22; 158:4, 20; 163:11
monotherapy 45:9
month 92:17, 25; 96:16;
152:20; 167:2; 221:20;
232:2; 233:7; 256:24;
268:2
monthly 92:25; 167:7;
208:20
months 14:11, 13, 13;
45:21; 47:7; 48:10; 51:16,
16; 52:8, 9; 57:3; 64:24;
68:21; 78:9; 80:9, 18, 22;
92:18, 23; 95:15, 16, 23,
23; 96:20, 20; 100:18, 18;
128:5; 130:6, 21, 22;
131:1, 3, 6, 9, 15, 15;
132:23; 135:11; 144:11;

145:20; 147:16; 148:7, 7,
9, 9, 23, 24; 150:7; 151:1;
152:9; 161:25; 164:4;
169:6; 170:18; 176:9, 10,
15, 15; 185:11, 17, 21;
186:2, 21; 187:9, 19, 20;
188:6, 8, 11, 15, 18;
191:20; 210:3, 5; 219:16;
221:15, 17, 19; 231:5, 5;
232:3; 234:21, 22; 235:1,
2, 7, 10, 13, 13; 238:21,
21, 22; 247:10; 263:23;
266:20; 267:25, 25
morbidity 184:4
more 17:20; 18:21; 22:6,
7; 24:21, 22; 26:21; 29:13;
36:23; 37:16; 38:8; 40:17,
17; 42:9; 43:11, 12, 14;
45:23; 50:14; 51:24; 56:2,
4; 62:12; 69:3, 17; 70:22;
72:3; 76:9; 84:19; 86:7;
88:11, 25; 92:13; 97:20;
100:4; 102:20; 104:18;
106:24; 107:18; 108:7;
111:1, 25; 112:1; 113:22;
115:18; 118:15; 136:19;
137:20; 139:11, 11; 145:3;
146:18; 156:24; 161:2, 9;
162:4; 170:22; 171:5;
176:11, 23, 24; 180:22;
193:16; 194:6; 198:16, 18;
200:2; 205:3; 206:25;
210:14; 215:25; 216:1;
218:15, 20; 222:25;
225:22; 227:11; 232:19;
233:4; 240:2; 241:3;
242:10; 244:3; 253:5;
254:13; 255:13; 256:16,
17; 258:8, 25; 263:22;
265:23
morning 8:15, 18; 11:25;
13:24; 14:4; 16:18, 23;
19:8; 20:1; 35:6; 43:20;
90:13; 99:12; 102:15, 16;
124:9; 131:16; 132:2, 2, 20
morning's 5:4; 8:6
mortality 184:3
most 10:1; 22:9; 24:10;
39:15, 16; 60:17; 80:25;
81:2, 3; 89:15; 97:13;
99:25; 101:6; 112:16;
116:17; 135:10; 137:3, 7,
16; 140:1, 11, 11, 17;
143:7; 144:12; 146:6, 11;
147:1, 6; 148:24; 160:14;
163:19; 167:18; 175:5;
183:7; 194:22; 202:22;
223:16, 17; 227:1, 6;
234:7; 239:1; 240:18;
241:25; 242:10; 245:25;
248:15; 265:16
mostly 61:2; 154:10;
183:2, 8
motivated 204:22
Mouridsen 20:5, 6; 79:4,
6; 86:24; 87:1
mouse 159:14
move 8:5
moved 131:8, 10

moving 31:19; 249:6
MP-US-MO1 228:12;
229:18, 24; 230:3, 14, 21;
232:8; 238:4; 243:9;
244:13, 20, 23; 245:1;
246:9; 267:22
MRI 168:22; 213:14
Mrs 129:22
much 8:2; 34:24; 62:19,
22; 69:17; 84:9; 89:9;
102:6; 104:19, 20, 25;
107:2; 123:6; 129:24;
130:11; 133:18; 136:10;
138:4; 139:12; 141:9, 17;
154:22; 155:2; 190:19;
191:17; 196:3; 203:22;
215:25; 218:19, 21;
225:16; 234:9; 256:18
multicenter 90:25;
101:15; 119:17, 25; 137:1;
164:17; 259:16; 260:5
multinational 44:1; 56:8,
22; 59:25; 61:10; 117:1
multiple 56:12; 61:17;
147:12; 153:25; 165:6;
166:19; 171:3; 185:23;
215:1; 234:13; 238:25;
246:23; 254:2, 3, 15, 15;
257:3, 3; 266:9; 267:4
multiplicity 247:17;
249:9; 254:2, 14
multivariate 47:23;
144:23; 202:11, 17;
229:13
muscle 28:11
must 10:10; 86:5; 223:25;
240:25; 242:20
myelogenous 160:4
myocardial 98:21;
211:16
myself 131:23

N

n 170:4
N-2 57:15
nadir 247:24
NADPH 157:12; 159:2
name 16:20; 20:9; 35:6;
90:13; 127:6; 133:23;
138:11; 141:18; 200:6;
254:22
namely 174:21; 246:17;
252:3
Naredi 142:11; 160:20;
199:25; 200:3, 8, 8
narratives 210:19;
243:24
National 5:18; 124:15
natural 25:22, 24; 156:2,
3, 4, 16, 17; 157:3, 5, 22
nature 39:12; 67:13
nausea 151:11
nays 123:4
NCI 134:5; 153:11

NDA 8:12; 18:2; 35:18;
123:1; 124:6; 141:13;
160:14; 186:18, 19;
199:25; 227:23; 228:3;
245:5; 247:8; 250:22;
252:13
nearing 153:19
nearly 48:25; 90:2; 99:22;
127:18; 180:23
necessarily 15:11;
108:16; 146:16; 214:7
necessary 108:16;
226:21
need 7:20; 12:6; 15:17;
108:8; 110:23; 111:2;
122:7; 126:18; 140:10;
157:8; 159:8, 13; 170:13;
180:17; 218:15; 223:21;
242:15; 263:11; 270:15
needed 62:10; 210:7;
227:3
needs 121:23; 128:22;
139:23; 260:23
negates 70:15; 224:19
negative 66:4; 78:19;
146:23; 257:19; 258:1;
265:17
negatively 183:18
negotiate 121:5
neither 9:24; 65:25; 66:3;
202:24
neoadjuvantly 26:18
neoplasms 25:20
NERENSTONE 5:3, 6;
6:1, 1; 8:3, 10; 12:4, 21,
24; 13:6; 14:18; 15:13;
16:7, 16; 35:4; 62:22; 63:6;
66:16; 69:5; 70:2, 8, 24;
72:17; 76:18; 81:22; 85:8;
86:11; 88:7, 11; 102:6, 21,
22; 103:23; 104:14; 105:5;
106:22; 108:21; 109:6;
111:7; 113:22; 115:3;
116:8, 21; 118:7, 17, 25;
119:12, 16; 120:8, 10, 15,
23; 121:6, 24; 122:10, 15,
23, 25; 123:4, 6; 124:4;
125:1, 1, 19; 127:2;
129:21, 24; 133:16, 18;
138:6, 9; 141:3, 5; 154:24;
190:20; 193:7; 194:10, 20;
200:6; 201:15; 203:5, 13;
206:9; 208:8; 210:10;
211:19; 213:25; 214:9, 13;
215:15; 216:3; 219:5, 11;
220:15; 221:7, 12; 225:2;
226:18; 227:11, 17;
261:20, 23; 263:18, 25;
264:12; 265:9; 266:23;
267:19; 269:18, 21, 23;
270:7, 11, 13, 22, 25;
271:2, 9, 11, 14
neurological 181:23
neutralizing 104:2
New 5:17; 9:6; 10:8, 15,
24; 11:7; 12:6; 13:4; 15:6,
11, 25; 16:6, 24; 19:5;
23:5; 24:17; 27:4; 30:1;

34:7, 18; 62:17; 71:2;
110:15, 24, 24; 117:10, 21,
22; 124:14, 23, 23; 128:21;
173:3; 220:11; 227:20;
257:5; 258:20
newer 23:19, 21; 34:14;
62:10
newly 71:22
next 27:8; 33:18; 64:25;
105:17; 110:4; 117:7;
130:1; 133:19; 169:8;
245:4; 268:3; 269:23
nice 123:7; 176:14;
201:17
nicely 116:20; 187:10
night 131:17
nightmare 128:18
Nine 48:20; 64:24; 68:21;
131:7; 258:6
NK 156:9; 157:15; 158:3,
18, 21; 159:4
no's 122:23
nodal 57:15; 144:7;
147:24
node 58:10; 147:13;
235:7
node/lung 235:5, 12, 24
nodes 130:25
nodule 82:6
Nolvadex 11:16; 91:15
nominate 248:12
non 11:10; 58:24; 93:12
non-compliant 48:24
non-controversial
123:7
non-double-blind
118:16
non-endocrine 40:16
non-evaluable 49:21,
22, 25; 193:4
non-exploratory 231:22
non-IL-2 246:6
non-inferiority 117:15,
19
non-liver 250:9; 268:5,
11
non-measurable 93:4
non-measurable/evaluable
93:12
non-measurable/non-evaluable 93:5
non-randomized 11:18
non-supportive 249:15;
259:9
non-tumor 35:25; 37:14
non-visceral 145:6, 7;
173:8; 252:5
nonclinically 90:8
none 8:10; 37:6; 63:22;
169:17; 232:14
nonfunctional 199:4
nonsteroidal 17:8;
29:22; 38:5, 7

nontumor-related
210:16
nor 9:25; 46:14; 66:1, 3,
24; 87:15; 208:6
normal 131:22; 133:8;
140:2; 147:25; 148:1, 2;
158:23; 172:15; 174:6
normalcy 140:23
normalize 172:14; 174:6
normally 67:24
North 20:10; 104:11;
124:18; 142:12; 252:10
notable 168:16, 24;
170:8; 175:5; 186:15
notably 160:14; 173:5
note 86:12; 233:20;
240:25; 247:11; 248:4;
253:22
noted 7:21; 45:3; 77:16;
80:25; 109:1; 126:19;
148:18; 162:20; 177:19;
251:10; 253:24
notice 156:22; 253:5
noticed 161:4; 209:5
noticing 119:10; 122:2
notion 27:10
notions 27:4
Novartis 8:13; 16:21, 22;
17:23; 18:11; 19:19, 24;
35:7; 100:22; 103:11;
105:5, 8; 117:3
November 46:22; 48:8;
63:15; 64:25; 65:2, 19, 22,
23, 24; 68:10, 12, 22, 24;
69:1; 93:18; 100:21;
166:11; 232:2; 247:6;
252:2, 25
now-only 252:15
nowadays 137:15
nubbin 69:6
nude 42:22
null 166:14; 231:25
number 14:2, 6; 50:5;
60:11; 68:14; 72:10, 12;
81:7; 82:10; 83:16, 23;
89:22; 93:6; 95:6; 99:2;
111:25; 119:15; 144:19,
24; 146:8; 147:9; 149:2;
152:5; 155:17; 159:17;
160:3; 162:5; 164:1;
169:21; 170:14, 21;
171:21; 172:19; 179:19;
182:7, 21; 187:15; 190:16;
191:24; 193:1, 18; 194:13,
16, 17; 195:2; 198:6;
200:17; 203:19, 24; 204:3,
25; 210:4; 211:25; 212:9;
216:19, 23; 217:10; 218:6,
21; 223:4, 5; 238:13;
247:20; 252:4, 7, 20;
264:9; 266:10; 269:2
numbers 23:12; 60:24;
77:22; 83:16; 94:16; 99:5,
6, 11, 20; 100:1; 104:4;
112:11; 155:22; 169:13;
182:25; 195:16, 24; 219:7;
243:16; 266:19

numeric 58:17
nurse 125:7; 136:4;
138:12, 17, 22; 192:4;
204:13, 17
nurses 131:20; 138:24;
139:16, 17; 140:18; 263:2
nursing 138:25; 140:15

O

O'Brian-Fleming 65:4,
17
o'clock 132:2
O24 75:11
objective 46:5, 8, 20;
47:21; 52:12; 53:1; 54:22;
87:1; 142:19; 164:9;
175:25; 231:10
observation 113:7;
137:6; 177:17
observations 97:21
observe 167:22; 183:6;
220:19
observed 33:4; 92:19;
99:19; 177:25; 240:8;
241:22; 244:23; 250:16;
251:9; 260:13; 269:24
obtained 7:14; 39:13;
126:12; 239:12
obvious 70:18; 89:16;
121:18; 171:8
obviously 110:16;
121:22; 139:22; 197:6;
216:1; 262:23
occur 21:21; 24:16;
64:23; 68:24; 132:1
occurred 65:1; 68:14;
81:1; 99:11; 101:8;
232:19; 233:2; 241:11;
244:22; 247:15; 256:5;
258:17
occurrence 247:12
occurs 25:8, 14; 27:17
Ocular 99:11; 169:1;
188:12; 191:2, 4, 7, 9
ODAC 20:24; 26:11; 32:7;
102:8; 109:9, 13; 141:23;
190:22; 227:18; 261:20,
25
odds 52:14, 20; 55:11,
13, 14, 22; 56:4
off 95:17; 99:17; 130:18;
132:7; 163:16; 192:8;
205:2; 207:2; 221:20;
223:15; 226:13, 22;
263:23
offer 30:10; 34:21; 135:5;
159:5; 263:14, 15
offered 29:6
offering 30:13; 262:20;
263:15
offers 135:20
Office 7:15; 126:14;
127:21; 136:5; 137:13;
263:9

Officer 6:15; 141:20
official 103:18
offshore 114:19, 23
often 135:14; 137:13;
248:12; 263:7
old 13:4; 27:13; 33:8;
130:12, 13; 132:25; 187:7
older 22:6; 23:19, 25;
24:2; 27:19, 20, 21; 28:7;
31:23; 49:7; 84:5
onboard 84:11
once 18:21; 25:8, 14;
27:4; 41:2, 3; 60:9; 135:7,
10; 136:5; 137:21; 176:4;
196:6, 21; 215:9, 13
Oncologic 35:5
Oncologist 5:15, 17, 21;
6:2, 12, 14; 20:10; 124:12,
13, 22; 125:10; 133:24;
258:20
Oncology 5:4, 23; 22:14;
24:5, 11; 124:20; 125:2, 7,
13, 15; 131:19; 135:3;
139:3; 256:22; 257:10;
258:17
one 12:5; 13:20; 14:4;
15:1; 21:17; 23:24; 25:3;
36:6, 10, 15, 19; 39:11;
40:4, 7, 14, 16, 19; 42:3;
45:23; 48:5, 24; 49:19;
50:13; 62:25; 63:3; 65:18,
19; 67:15; 73:14, 21;
75:14; 76:3, 19; 80:7; 82:5,
5; 84:13; 85:2; 88:11, 14;
90:2, 3; 92:11, 13, 17, 23;
93:3, 6; 95:2, 17; 96:12;
98:9; 99:13; 104:4, 8, 21;
105:3, 12, 13; 107:12;
113:11, 15; 114:13; 115:4,
11, 15, 17, 22; 119:10,
19, 19, 21, 24; 120:2;
127:15; 129:4, 6; 132:7,
13, 20; 134:18, 20; 136:15;
139:19, 23; 147:11; 159:6,
20, 20; 161:9; 162:7;
163:7; 166:23; 167:5, 17;
169:14; 170:13; 172:21;
173:7, 23, 24; 176:3, 8, 11,
13, 18, 19, 23, 24; 185:13;
189:13; 191:21; 193:16;
194:6; 195:7; 196:23, 23;
198:2, 12; 199:13; 201:24;
203:20; 206:24; 207:4;
208:9, 18, 21; 211:4, 11,
14, 16; 212:24; 214:25;
215:17; 217:20; 218:15;
219:12, 19; 220:14;
225:15; 226:12, 23;
229:10, 11; 232:9, 25;
233:7; 236:5; 238:15, 17,
20; 240:13, 19; 245:5;
246:18; 248:13; 249:1;
250:2; 254:5, 5, 19;
255:14; 256:10; 257:12;
262:4, 12; 265:8; 266:8;
270:15
one-half 164:22
one-third 49:15, 50:13;
94:12; 216:5; 256:18;

- 262:25; 263:22; 264:1, 8, 9, 20; 265:6; 266:5, 18, 19, 19; 268:24; 269:14, 24; 270:3, 18; 271:5
- pay** 138:17
- paying** 167:23, 25
- PAZDUR** 6:18, 18; 12:15; 16:17; 20:24; 107:23; 108:5; 119:23; 121:20; 141:22
- PELUSI** 6:7, 7; 86:11, 12; 87:23; 125:7, 7; 261:25; 262:2
- penalized** 225:21
- Penn** 19:14; 134:3
- Pennsylvania** 19:15; 134:1
- people** 76:23; 82:17; 83:14; 124:8; 130:11; 131:21; 133:12; 135:11, 16; 190:16, 17; 193:19; 204:4, 7; 205:20; 209:16; 218:21; 225:13; 263:5; 270:7
- per** 17:3, 21; 46:21; 47:18; 58:13; 168:4, 6; 208:21; 216:20; 247:22; 248:3
- percent** 22:21, 22; 41:20, 25; 47:12, 13, 16; 48:13, 15, 17; 49:6, 7, 8, 9, 13, 14, 17, 20, 21; 50:11, 12, 18, 22, 52:6, 13, 13, 14, 18, 19, 20, 25, 25; 53:2, 2, 21; 54:10; 55:12; 58:4, 5, 7, 11; 59:5, 6, 10, 11, 15, 15, 20, 21; 60:10, 19, 21; 72:14, 22, 22, 23; 73:11, 12; 74:13; 76:5, 6; 78:10, 25; 79:2, 9, 14, 16; 81:8, 8, 9, 9, 13; 85:15, 16, 18, 20, 25; 86:3; 88:16; 93:24; 94:10, 12, 13, 17, 17, 19, 24; 95:1, 3, 4, 4, 5, 96:3, 3, 4, 4, 5, 5, 8, 10; 97:10, 11, 19, 24; 98:3, 5; 100:16, 16, 19, 19; 111:23; 112:1, 12, 14; 134:12; 143:25; 144:1, 12; 145:24; 148:23, 25; 150:3, 4, 24; 151:1, 9, 12; 152:8, 9, 25; 154:3; 158:21, 21; 171:18; 172:4; 177:10; 187:2; 200:15, 16; 202:3; 204:6; 206:2, 4; 225:5; 231:3, 4; 233:1, 3, 18; 234:20, 25; 235:11; 236:4; 241:12, 15; 243:10, 14, 15; 244:7, 18, 22; 245:21, 22; 246:1; 247:12, 15; 257:14, 17, 21, 23; 258:2, 11, 12, 14; 268:8, 15, 16, 17
- percentage** 51:7; 52:25; 60:18; 71:23; 74:22; 80:8, 11; 86:4; 98:23; 113:14; 122:17; 154:10; 158:18; 251:4
- percentages** 99:3
- perfect** 137:3; 183:21
- perform** 166:3
- performance** 47:5; 49:8; 88:3; 95:1, 2; 97:17, 20, 25; 98:2, 4, 10, 11, 14, 16; 100:18; 146:7; 147:17; 150:17, 21; 153:24; 154:11; 169:15; 172:16; 178:18, 23; 193:19, 20; 194:1; 201:12; 212:1; 214:9, 11, 14, 17; 215:11; 224:18, 19; 239:11, 14, 16, 18, 22, 23, 24; 251:6; 252:9; 269:1
- performed** 46:22; 47:4; 48:5; 53:20; 55:11; 92:16, 25; 102:19; 105:11; 234:15; 238:6; 239:21; 250:10
- Perhaps** 22:9; 26:23; 27:13; 33:15; 34:5, 13, 15; 71:23, 24; 72:3; 74:14; 75:9; 86:16; 115:25; 119:22; 121:8; 129:7; 136:19; 144:20; 203:10; 263:19
- period** 30:14; 41:7; 81:3; 149:22; 166:9; 193:15; 215:6, 11; 264:21
- periods** 205:13
- peripheral** 28:10, 10, 18; 38:23; 99:3
- peripherally** 38:19
- person** 70:7; 142:10, 14; 263:6
- personally** 70:21; 128:3; 266:11
- perspective** 65:12, 14; 135:19; 255:1
- persuasive** 101:22, 22; 120:1; 228:14, 15; 232:11; 238:1; 259:23
- pertains** 63:8
- perturbed** 74:21
- Peter** 142:11; 160:20; 161:3; 199:25; 200:8; 207:24
- Peter--I** 199:25
- PFISTER** 105:7, 7; 106:7, 15, 18
- PgR** 45:15; 49:14; 57:14; 59:5
- ph** 73:7, 8; 121:14
- phagocytic** 155:22; 205:14
- Pharma** 35:7
- pharmaceutical** 12:12; 127:12
- Pharmaceuticals** 8:13; 16:21; 134:15; 141:14, 20
- pharmacokinetic** 45:7; 88:14; 91:6; 105:14; 160:12; 208:3, 6, 7
- pharmacokinetics** 200:25
- pharmacologic** 33:14; 37:1
- pharmacologists** 105:4
- pharmacology** 19:17; 27:18; 35:3, 16; 38:8; 105:8
- Phase** 11:18; 18:2, 5; 21:15; 44:20; 45:8; 46:12, 14; 56:7, 21; 59:24; 63:12; 64:12; 90:25; 134:19, 21, 25; 136:23; 143:6, 9, 11; 149:2, 2, 8; 150:2; 152:5, 15; 153:7; 160:9; 164:9; 168:9; 185:10, 12; 186:11, 13, 15; 187:1, 7, 8, 10, 21; 188:1, 7, 16; 197:21; 229:19; 230:10
- phenomena** 158:12
- phenomenon** 205:11
- phenytoin** 106:19
- Phoenix** 6:7; 125:8
- phone-in** 83:17
- phosphonate** 85:5
- phosphonates** 84:11
- physical** 87:4; 129:1; 130:23; 224:11
- physician** 130:18, 23; 135:15; 138:21; 204:13
- physicians** 85:23; 86:5; 111:14; 139:17; 226:4
- physiologic** 206:20; 207:22
- physiological** 180:25; 183:9
- physiologically** 37:7
- PI** 155:11
- pick** 262:8, 9
- picked** 68:13; 173:6
- picking** 110:13
- picture** 184:15
- piece** 116:6
- Pierre** 73:7
- pillow** 131:17
- pills** 69:9; 70:3
- Pittsburgh** 138:13; 142:6
- pivotal** 18:4, 18; 44:6, 14; 51:11; 90:24
- PK** 160:13
- PK17** 105:9
- place** 26:23; 76:7; 108:17; 160:19; 167:5; 192:19; 213:14; 227:9
- placebo** 42:24, 25; 69:7, 15, 19
- placebos** 71:3
- placed** 77:8; 128:18
- placenta** 38:20; 39:7
- placental** 40:9
- places** 108:9, 113:16; 128:15; 165:13
- plan** 46:15; 82:24; 89:17; 166:6, 8, 10; 167:10; 171:23; 209:13; 231:7, 19; 232:1; 247:5, 22; 250:21, 22; 251:18; 252:1, 18, 19, 22
- planned** 45:3; 63:14; 87:6, 14; 250:20; 261:2; 269:11
- planning** 68:7
- plans** 89:25
- plasma** 106:2
- platelet** 213:22
- platinum/DTIC/interferon** 153:15
- plausibility** 197:4, 8, 16; 198:15; 215:18, 24
- plausible** 120:25
- playing** 109:4
- pleas** 127:21; 128:1
- please** 63:1; 70:8; 72:25; 105:6, 9, 18; 123:2, 8; 127:14, 14; 143:16; 190:25; 200:6; 201:17; 210:17; 214:1; 227:12; 269:16, 18; 270:23
- pleased** 62:21
- pleasure** 113:25; 138:18; 227:18
- pleura** 21:23
- plot** 53:20; 54:8; 55:11
- plotted** 53:23; 55:14
- plural** 255:12
- plus** 142:17; 149:10; 153:9, 12, 15, 19; 160:24, 24; 178:22; 188:23; 189:19; 190:2; 206:1; 208:18; 230:12; 249:4; 250:15; 258:5
- podium** 20:19
- point** 15:24; 22:12; 26:14; 34:18; 63:19; 65:11, 15; 66:23; 67:20; 75:8; 88:2; 103:1; 104:9; 109:2; 116:25; 118:3, 7, 12; 119:16; 139:20; 146:1; 150:10; 199:24; 213:5; 214:19; 222:5; 225:10; 246:4; 248:6; 264:24
- pointed** 64:5; 67:12; 89:15; 109:22; 229:1
- points** 73:17; 98:16, 17, 17; 145:5
- policy** 14:20
- pool** 163:15
- pooled** 146:10; 147:4
- poor** 140:10; 144:25; 145:10; 146:7, 12, 14; 147:2, 6, 11, 18; 153:23; 154:20; 212:1; 225:7; 229:7, 12; 238:25
- poorer** 145:15; 198:20
- poorly** 135:10
- population** 32:3; 49:6, 15; 54:2, 14; 55:17; 82:2; 90:21; 93:25; 94:6; 101:19; 110:11; 113:5, 14, 20; 160:13; 162:1; 163:22; 164:2, 3, 6, 7, 22; 165:3, 4, 11; 167:20; 169:25; 170:4, 7, 17; 172:7; 174:20; 175:14; 177:7; 179:2, 7; 180:11; 182:12, 23; 183:1; 184:9, 11, 14; 185:17, 21; 186:9; 187:11, 15; 189:7, 20; 190:8; 198:11; 201:13, 14; 210:21, 22; 217:14; 218:3; 219:2, 3; 228:14; 232:10; 234:21; 235:1, 12; 237:11, 12; 245:10; 246:18; 248:3, 10, 20, 24; 249:4; 254:5; 256:6; 259:1; 261:1; 267:6
- populations** 165:3; 166:15; 267:6
- portion** 133:22; 224:11
- pose** 115:12
- posing** 115:23
- positive** 45:15; 49:14, 14; 54:11; 55:23; 57:14; 59:5, 6; 62:6; 66:3; 67:21; 75:22; 76:3; 92:9; 97:14; 101:20; 102:3; 119:5; 256:3, 4, 10, 12, 13, 14, 18, 19; 257:1, 16, 21, 25; 258:4, 5, 6, 8, 13, 14, 14, 16
- positives** 265:19; 266:10
- possibility** 26:22; 201:4; 259:18
- possible** 87:3, 5, 5; 106:19; 202:22; 246:5; 254:17
- possibly** 111:13; 146:3; 168:16; 171:5; 175:23; 217:23
- post** 82:23; 259:19
- post-hoc** 82:10; 83:25; 250:22
- post-study** 57:24
- postmenopausal** 16:11; 17:5, 16; 23:25; 27:22; 28:7; 30:11, 23; 31:24; 32:14; 39:2; 43:23; 44:1; 45:12; 57:13; 60:1; 61:12; 62:5, 18; 90:18; 91:1; 92:7; 101:20; 102:2; 119:4; 122:13
- postpone** 87:2
- potencies** 40:5, 6, 10
- potency** 40:7, 20
- potent** 28:17; 29:13; 34:12; 37:12, 16; 40:18; 43:11; 62:12
- potential** 7:8; 19:5; 77:19; 82:11; 104:20; 120:20; 126:4; 190:9; 201:7; 206:20; 248:11
- potentially** 16:24; 201:22
- power** 47:13; 58:5; 218:21, 24; 231:4; 257:22
- powered** 176:12; 257:21
- PR** 46:6, 6; 97:12; 179:25; 180:7
- PR's** 93:11; 96:3, 5; 162:9, 11
- practice** 32:1; 94:4; 116:17; 134:8; 167:25
- practices** 19:12; 20:20, 22
- practicing** 130:17, 23

<p>practitioner 125:8 pre 57:24; 169:24 pre-established 177:8 pre-filled 242:24 pre-study 197:2 pre-treat 181:11 preceded 135:1 preceding 239:6 precisely 136:19 preclinical 19:18; 33:14, 15; 43:12; 62:13; 105:18, 24; 106:9; 198:12; 200:3, 9; 201:7; 207:21, 25 preclude 7:3; 125:24 precludes 245:16 precursor 38:25 precursors 28:2 predefined 47:25 predetermined 63:17 predicted 184:7 predicting 202:14 predictive 75:16; 147:10 predictor 146:7, 11; 147:2, 6; 174:22; 202:20; 229:12 predictors 144:25; 172:17 predominantly 28:10 preference 114:14 preferred 75:5 pregnant 131:9 prejudice 114:7 preliminary 80:1; 112:24; 113:3; 114:6 premalignant 26:19 premature 91:10; 92:1 premenopausal 24:2; 121:13; 122:12 preoperative 18:8; 44:10; 56:23; 75:15 preplanned 104:10; 197:7; 216:2 prerogative 211:20 presence 75:24; 144:7; 157:22; 158:4, 20; 165:14; 166:4; 229:11; 230:24; 238:4; 251:24 present 7:8; 9:2; 11:10; 16:23; 19:8, 20; 20:8; 21:1; 34:2; 43:18; 46:10, 23; 48:19; 49:1; 78:2; 90:14; 91:9; 92:2; 95:10; 119:23; 126:4; 141:23; 143:20; 202:14; 203:6 presentation 16:10, 14; 35:10; 47:2; 90:12; 92:4; 102:7; 109:16; 141:11, 15; 154:25; 202:4; 203:4, 14; 209:4; 212:6; 227:16, 24; 228:11; 246:7; 254:20; 258:19 presented 36:25; 61:8; 64:13; 75:10; 83:2; 95:19; 107:21; 113:4; 114:9, 21; 116:19; 119:20; 151:6;</p>	<p>198:2; 203:2; 246:11; 250:3; 251:10; 254:1; 258:20; 270:16; 271:3 presenters 20:1; 102:9 presenting 45:8; 95:9; 165:17; 227:20 presently 89:19 preserve 66:14; 67:17 President 16:20; 127:7; 141:19 presidential 13:2 prespecified 142:23; 165:11; 171:22; 172:9; 174:14, 16; 189:8; 192:22; 209:14; 232:14; 237:15; 251:24; 252:18, 19 pressed 86:5 pressors 151:10 pressure 153:1; 181:7 prestratification 166:21, 22 prestratify 166:2 prestudy 215:6, 11 presumably 103:10, 12 presumed 32:14 pretty 69:11; 131:5 Prevacid 181:12; 205:17 prevalence 23:10 prevalent 22:6; 34:19 prevent 26:19, 22 prevention 34:7 previous 7:25; 15:21; 27:13; 110:2; 126:23; 136:13; 219:17; 220:11; 264:23 previously 42:8; 43:8; 44:4; 154:10 Prilosec 181:12; 205:16 primarily 28:2; 76:22; 87:10; 91:21; 92:7; 103:6; 151:25; 206:16 primary 18:14; 26:18; 46:3, 10, 19; 47:10; 48:10; 51:12; 56:17; 57:5, 19; 58:2; 64:12; 78:23; 82:25; 91:17; 103:2, 13; 104:13; 106:25; 107:8, 13; 108:15; 111:4; 117:5; 118:11; 135:8; 144:6; 164:23; 189:10; 215:23; 217:15, 24; 231:2, 10, 21; 232:6; 248:13; 253:7, 8; 260:6; 261:3; 266:3, 4; 267:10; 269:11 principal 20:6, 8; 79:4; 155:20 principle 206:12 printer 137:16 printouts 137:14 Prior 45:22; 48:1; 50:23, 25; 51:1, 2; 53:7; 54:10, 23; 56:3; 61:21; 63:5; 85:7; 90:20; 94:14, 18, 19; 111:23; 112:2, 6, 19; 115:15; 150:18, 22; 151:18; 161:21; 168:18,</p>	<p>18; 169:20; 170:11; 172:12, 12; 186:16; 187:3, 4; 212:4; 213:5; 215:8, 13; 220:19; 221:5, 5; 225:18; 231:15; 239:12; 247:19; 250:20, 22; 251:7, 25; 252:4, 8, 20; 257:4 priori 68:14 private 134:8 privilege 141:18 privity 167:6 probability 256:14; 257:4 probably 11:8; 16:2, 3; 87:16; 92:19; 96:15; 102:3; 112:1, 25; 117:22; 122:17; 128:17; 134:12; 176:5; 195:23; 262:10 problem 12:21, 23; 23:1, 13; 34:17; 157:8, 9; 204:4; 225:17; 246:22, 23, 23, 25; 247:2, 17; 249:8, 9; 262:9 problematic 173:11, 12, 13 problems 71:7; 152:22; 183:23; 246:21, 24; 249:7 procedure 65:16; 70:5; 196:5, 15 proceed 64:19 PROCEEDINGS 5:1; 123:11; 271:17 process 26:4, 8; 36:3; 128:19 proclamation 13:2 produce 24:17; 256:3 produced 78:17; 150:6 produces 154:3, 9 product 7:25; 71:6; 126:23; 255:7 production 36:22; 156:5; 158:8, 15; 197:19 products 7:18; 126:16 Professor 19:13; 20:16; 134:6 profile 17:7, 24; 18:20; 19:4; 33:15; 37:1; 110:16; 122:6; 140:22; 208:6, 7; 261:16 progesterone 21:12; 24:17 progestins 34:16 prognoses 235:6 prognosis 140:9; 143:21; 145:1, 11; 146:14; 147:14, 18; 154:20; 156:25; 198:20; 229:2, 7; 238:25 prognostic 144:19; 146:22, 23; 166:22; 172:11; 173:5, 14; 174:7; 195:18; 228:25; 229:6; 230:5, 23; 238:7, 18; 239:5, 7; 241:2, 3, 20; 245:13; 251:5; 253:25; 257:2; 260:11; 268:21, 23 program 19:18, 21, 23;</p>	<p>43:21; 158:19 programs 127:11 progress 29:15; 112:20; 205:1 progressed 30:23; 51:18; 135:7; 204:14; 222:11, 14; 223:16; 237:1 progresser 218:11 progressers 215:3 progresses 135:13 progressing 217:20; 224:12 progression 9:12, 16, 25; 10:3, 12; 11:3; 12:18; 14:10, 12, 14, 23; 15:9, 12; 17:17; 18:13, 22, 24; 26:19; 32:21, 23; 44:18; 45:1; 46:4; 47:13, 24; 48:3; 50:1; 51:12, 14, 15, 18, 21, 22; 52:3, 6; 53:6, 18; 54:5, 9, 16; 56:15, 17; 61:18; 76:21; 77:6; 78:4, 22; 79:7, 10, 13; 80:10, 14, 15, 20, 24; 81:2, 10, 15, 17; 87:3; 90:21; 91:8, 18; 95:16, 18, 22; 100:17; 110:2; 111:3; 112:14; 117:5; 118:9, 11, 18, 22; 137:12; 152:19; 177:15, 20, 21, 23; 178:21; 179:3, 11; 180:4, 12, 15; 188:25; 202:24; 203:3; 212:7; 217:1, 2; 218:1; 219:14; 222:10; 224:1, 9, 24; 236:2, 10, 15, 17, 18, 20, 23, 24, 25; 237:3, 3, 7, 18; 241:10, 16; 242:3, 11; 245:19; 264:16, 17; 268:9 progressive 162:9, 12; 177:17, 25; 178:11, 17, 20; 182:14; 192:13, 16; 216:7, 10, 13, 14, 15; 217:18; 220:23; 221:2, 4, 25; 222:2, 18, 20, 22; 223:1, 9, 19; 264:4, 10, 22; 265:2 projected 68:21 proliferation 156:4 proliferative 158:2 prolongation 152:20 prolonged 51:19; 79:13, 14; 95:19; 128:12 promise 221:11 promising 23:20; 149:6 promote 90:8 proof 206:11 properties 38:19 prophylaxis 151:18 proportion 220:1, 17, 22; 256:11, 11, 13, 17; 258:8, 12; 265:19 proportional 171:24; 174:2; 175:20; 177:5 proposed 90:17; 118:8; 147:22; 161:15; 229:18, 21, 23; 230:10 proposing 190:11 prospective 43:25; 56:21; 61:9; 75:16; 76:17;</p>	<p>86:22; 89:25; 164:17 prospectively 48:23; 50:7; 53:6; 54:22; 58:24; 61:20; 77:8; 82:24; 165:1, 2; 232:6 prospectively-defined 47:20 prostate 22:15 protect 156:9 protein 24:17; 25:8, 9 protocol 46:21; 59:4; 65:7; 78:8; 84:22; 131:14; 132:2, 23; 133:2, 6; 165:12; 186:23; 191:21; 192:9, 23; 196:12; 205:18; 208:21, 25; 212:11; 214:4; 215:12, 13; 219:10; 227:1; 231:9; 232:14; 237:15; 247:3; 248:4; 250:17; 251:17; 259:22 protocols 134:24; 191:22 proton 181:11; 205:16 prove 67:1; 163:17, 21; 164:10; 198:9; 199:6 proven 9:25; 154:6 proves 158:12 provide 30:12; 32:4; 66:2; 68:4; 142:19; 143:9; 183:12; 189:21; 190:3; 224:22; 230:2; 255:8; 262:14 provided 7:6; 9:13; 69:2; 126:2; 160:14; 169:10; 204:17 providers 262:19 provides 66:1; 111:11; 115:8; 137:19 PROVOCIPIORCA 6:5, 5; 62:25; 103:24, 25; 125:5, 5; 210:10, 11, 25; 220:15, 16 PS 239:18 psychological 129:1 PT 213:19 PTT 213:19 public 5:10; 8:4, 5; 127:1, 3, 11; 133:22; 265:21 publication 238:23 Publications 228:23 published 35:17; 144:22; 146:10 pulmonary 60:25; 99:4; 182:1 pulsatile 181:10 pump 181:11; 205:16 pure 23:20 purple 176:18 pursue 136:18 pursued 113:8 put 86:16; 102:3; 121:3; 196:23; 205:4; 226:16; 262:18 putatively 69:24</p>
---	--	--	---	---

puts 195:14
putting 12:19; 136:22
puzzled 194:21
puzzling 194:22; 202:22

Q

Q 173:21
qualifier 121:11
quality 30:6, 13; 86:19, 20, 23, 25; 87:5, 7, 8, 9, 13, 17, 20, 24; 128:13; 129:14; 130:15; 135:24; 139:20, 22; 140:22; 150:6; 164:14; 183:15, 16, 18, 20; 184:8, 10, 13, 16, 17, 25; 185:7; 190:4; 204:3, 7, 25; 205:4, 21; 262:7, 17
quality-adjusted 184:20, 22; 189:2
quarter 85:16
quarters 85:20
queried 77:16
questionable 249:13
questionnaire 183:25; 206:3
quick 88:13; 210:23
quickly 30:18; 65:21; 215:14
quite 13:23; 26:21; 31:10; 40:20; 74:25; 82:21; 100:6; 111:12, 18; 112:10; 122:17; 128:19; 157:1; 159:25; 163:25; 174:17; 193:20; 206:11; 226:5
quote 214:6
quotes--"hormone 102:4
QWB 206:2

R

race 94:24; 172:21; 252:4
radiation 23:17; 45:13; 50:20
radical 197:19
radicals 163:13; 202:8
radiologist 77:9
radiology 77:5
raise 123:2; 269:16, 18; 270:23
raised 189:7; 216:1; 265:13
raises 195:6, 11
Rajeshwari 246:10
raloxifene 34:4
random 78:25
randomize 58:17; 100:16; 83:17; 84:24; 85:4; 173:23, 25; 174:1; 177:16, 24; 194:25; 195:8, 9; 196:1, 5, 5, 8, 13, 21; 220:22; 230:25; 238:6; 239:12; 250:13; 253:8;

268:25
randomize 82:19; 164:21
Randomized 9:9; 10:11; 12:14, 20; 14:8, 9, 12; 18:4, 19; 26:10; 31:1; 32:10, 13, 15; 41:1; 43:25; 48:13, 17, 20, 25; 54:15; 56:7, 22; 59:24; 61:9; 62:16; 79:22; 84:14; 90:25; 93:20; 94:2; 95:14; 101:11; 117:1; 119:11; 143:7; 149:14; 164:17, 21; 166:16, 17; 167:20; 169:13, 18; 184:21, 24; 186:12; 189:4; 193:13; 196:22; 197:2; 215:9, 20; 220:4; 230:22; 231:18; 245:5; 246:15; 248:20; 249:1, 21; 254:25; 255:14; 259:25; 260:4
randomizing 12:22
randomly 44:16; 57:1
range 23:16; 98:14; 152:8, 9
ranged 148:6; 191:20
ranges 188:11
ranitidine 158:10
ranked 73:10
rapid 215:2; 218:10
rapidly 32:2; 223:19
rare 244:9
rate 12:17; 14:7, 22; 26:16; 46:6; 47:24; 48:4; 52:12, 18; 56:16, 16; 57:20, 21, 22; 58:5, 6; 59:14, 19; 60:3, 3; 76:5; 91:21; 96:2, 4, 5, 8, 10, 12, 24; 97:10, 11; 100:15; 116:15; 148:22; 150:3; 152:18; 153:10, 13; 154:13, 15; 179:17, 25; 180:8; 181:8; 201:8; 202:3; 217:3, 4, 10, 13; 225:4; 226:7; 236:2; 241:12; 244:18; 245:18; 268:7
rates 47:21; 59:17; 92:20, 24; 96:13; 97:12; 117:2; 152:7, 8, 11; 178:4, 6; 179:18; 217:25
rather 24:24; 30:18; 67:2; 72:4; 74:11, 21; 86:8; 91:24; 99:23; 106:1; 112:9; 116:24; 121:10, 21; 139:9; 146:19; 155:12; 157:14; 189:25; 225:20
ratio 51:22; 52:7; 53:23, 25; 55:14; 76:6; 95:25; 174:25; 233:9, 10, 15, 17; 240:11, 13
rationale 9:20; 10:23; 31:19; 32:4; 143:5; 155:12; 167:12; 250:5
ratios 53:20, 22; 55:11, 13; 233:22; 240:7
raw 224:4
reach 223:12; 235:3, 15; 237:12; 245:10

reached 18:11; 150:8; 222:5; 247:24
react 25:10; 203:16; 207:2
reacted 207:4
reaction 155:8; 181:9; 202:6; 207:13, 15
reactive 157:13, 14; 159:3; 197:12
read 116:24; 125:19; 237:4
reading 84:8; 112:11
reads 17:14
ready 88:8
real 34:18; 114:25; 121:5; 169:22; 201:18; 263:4
realistic 111:3
reality 86:17; 113:18
realize 25:22; 262:2
realized 64:11
realizing 67:18
really 12:16; 13:14, 23; 26:12; 85:19; 87:6; 88:4; 91:24; 97:23; 101:11; 103:25; 105:2; 107:7; 108:16, 23; 109:4; 110:23; 113:11, 25; 118:11; 132:18, 20; 135:11; 139:23; 156:14; 163:3; 166:5; 173:20; 176:6; 177:21, 23; 178:3; 187:6; 192:17; 197:14; 198:14; 199:24; 207:12; 214:3; 215:25; 217:11, 18; 219:23; 221:15; 263:11; 265:4, 22; 266:3, 16, 17
reanalysis 220:10
reason 70:18, 25; 79:8; 80:16; 86:4; 87:8, 19; 95:17; 97:22, 99:21; 108:6; 119:11; 138:19; 150:5; 203:8, 10; 215:18; 218:5; 223:24; 252:11; 264:10; 265:16
reasonable 30:8; 217:8
reasonably 112:24; 247:12
reasons 22:1; 114:13; 122:4; 163:6; 219:10; 226:9; 255:21
reassured 110:1
reassuring 110:17
rebuttal 203:9
receive 31:1; 44:24; 81:11; 192:10
received 17:20; 48:17; 49:2; 50:25; 51:1, 2, 4, 8; 54:10; 63:5; 79:11; 94:13, 18; 150:5, 18, 22; 187:3; 194:14; 204:11; 212:3; 213:4; 251:25
receiving 102:19; 134:25; 136:8; 182:22
recent 21:7; 229:1; 234:7; 238:23; 245:25
recently 13:7; 24:19, 21;

25:23, 25; 26:21; 27:21; 30:18; 31:10; 32:8; 146:10; 147:22; 153:14; 256:22
receptor 21:12; 24:13, 15, 17, 22, 23; 25:2, 3, 4, 4, 5, 6, 8, 17; 27:6; 35:23, 23; 36:4, 18; 38:15; 39:24; 48:1; 49:12, 14; 53:7; 54:11, 24; 55:24; 61:22; 74:19, 22; 75:1, 4, 19; 76:3; 92:8; 94:12; 97:8, 14; 101:20; 102:3, 4, 18; 112:23; 113:2, 13, 16; 114:8; 119:5, 5; 158:10, 13; 159:1; 167:24; 205:9, 10
receptor--and 36:8
receptor-positive 32:14; 60:1; 94:11; 97:9
receptors 45:15; 49:15; 59:6; 75:19; 76:4; 201:4
Recess 88:10; 227:15
recessed 123:12; 271:18
recognize--and 206:14
recognized 21:7; 28:12; 64:15
recognizing 68:2
recollection 13:8
recommend 102:13; 133:11
recommendation 46:17; 64:18; 102:1; 118:21
recommendations 9:8; 65:22
recommended 66:9, 12; 131:24
reconvene 88:8; 271:15
record 7:3, 22; 124:8; 125:24; 126:9, 20; 142:11; 200:7
recorded 5:11
recorder 70:9; 105:6
records 214:10; 243:5
recovered 42:2
recruit 155:21
recurred 92:13
recurrence 45:13, 21; 173:16
recurrent 45:24; 51:8
red 131:21; 176:23; 248:1; 251:1, 3
REDMAN 6:9, 9; 7:12; 125:10, 10; 194:10, 11, 19; 216:3, 4, 14, 16; 217:1; 219:1; 221:7, 8; 224:4, 13, 16; 225:1; 263:18; 266:23, 24
Redman's 264:1
redness 207:16
reduce 26:18; 36:10; 106:19; 159:22; 161:17
reducing 43:6; 51:21; 73:23
reduction 39:13; 47:13; 52:6; 54:8; 88:16; 89:10;

172:3, 6; 192:2, 20; 199:1; 201:8; 243:11, 12
reductions 191:16, 17; 192:19, 23
reevaluated 178:20
refer 28:5; 129:13; 260:20
reference 188:12; 261:9
referred 25:9; 33:17; 64:22; 137:7
refers 247:17
refining 249:17
reflect 259:21
refresh 13:9; 65:6
refuse 127:16, 17
regard 6:24; 7:2; 46:25; 63:10; 69:21; 77:20; 78:4, 6, 21; 79:3; 80:12, 13; 112:22; 113:7; 125:23; 153:22
regarded 31:2
regarding 66:6; 81:24; 83:21; 85:10; 116:12; 126:11; 216:17; 230:9; 246:22, 23; 248:9; 262:3; 266:25; 267:13
regardless 164:1; 188:10; 220:5; 233:5; 265:25
regimen 92:12; 139:9; 149:5, 15, 19; 150:3, 11; 152:23; 160:23; 161:13; 164:11; 167:12; 177:3; 181:21; 186:8, 12, 14; 201:22; 228:17; 229:21; 230:11, 14; 242:7; 244:13; 245:7
regimens 140:7; 151:24; 152:1, 11, 12; 168:2; 201:19; 242:13
regimes 128:13
region 115:7; 144:6; 252:10
registration 18:15; 105:11; 229:16; 230:4
regression 47:15, 22; 53:18; 55:9; 180:1
regrettably 166:20
regular 47:4; 71:2, 6
regulated 7:7; 126:3
regulations 94:5
regulator 24:24
regulatory 12:5; 16:21; 228:2
reiteration 117:9
relapse 57:9
relapses 150:9
relate 200:9
related 61:2; 99:10, 23, 24; 101:9; 182:16, 18, 19; 183:4, 24; 211:3, 6, 9, 10, 13, 15, 17; 227:2
relates 206:21
Relating 209:10
relationship 262:18;

263:10
relative 25:20; 40:6, 7; 66:1, 6; 146:12; 147:6; 233:13
relatively 25:23; 26:1; 27:4; 30:17; 39:15; 52:2; 99:2, 5, 6; 226:10; 228:20
relevance 35:15; 116:13
relevant 14:22; 51:24; 53:16; 54:17; 55:7; 56:2, 16; 61:20; 67:19; 77:11; 78:15, 20; 112:9, 17; 113:7, 20
reliable 178:4; 204:23; 245:16; 248:7
reliably 217:16; 218:2; 240:14
relied 120:6
relocated 131:9
relying 259:7
remain 34:8; 42:4; 66:5; 67:3; 81:9; 192:2
remainder 59:7; 264:8
remained 30:24; 48:14; 65:25; 95:15; 247:14
remaining 80:21; 151:2; 257:17
remains 62:9; 154:14
remarkable 155:12; 161:3; 168:14
Remarks 141:16
remember 33:23; 83:14; 130:20; 167:13
remembered 78:24
remind 24:9; 27:17; 28:20; 32:9; 80:21; 117:13
remission 30:14; 144:24
removal 177:25
remove 192:14
removed 130:25; 223:23, 25
removing 130:21
renal 151:14; 160:4; 182:2
reoccurring 131:8
rep 108:24; 125:9
repeat 149:23; 259:11
repeated 206:19; 247:18
reply 70:7
report 63:18, 19, 21; 69:17; 103:5; 224:11, 15
reported 7:7; 17:23; 60:9, 14, 17; 63:4; 69:17; 71:17; 114:16; 126:3; 149:6; 152:16; 153:14; 207:22; 209:18; 236:6; 238:19; 244:20, 24; 245:1, 24
reporting 29:4; 60:24; 65:9; 71:22, 23; 214:14
represent 31:22; 218:19; 226:13; 234:20, 25; 238:1; 251:1, 2, 3; 261:4; 269:12, 15, 25; 270:8
representative 6:21;

124:19
represents 51:13; 53:20; 55:11; 143:25; 175:6; 176:6; 188:12; 248:1, 2; 261:11
reproduced 188:4; 259:4
reproducible 143:1; 148:19; 188:20
reproducibly 97:23
request 7:14; 126:13
require 10:17; 11:9; 16:3; 117:22; 181:4
required 9:10, 11; 10:11, 14; 12:10; 47:17; 58:12; 59:4; 84:23; 117:14, 16; 168:22; 214:7; 223:23; 243:11; 255:6, 8, 13
requirement 13:1, 4, 5
requirements 8:19, 21, 22, 23, 25; 9:2, 6, 21; 10:7, 9, 23
requiring 151:10; 153:1
Research 5:25; 7:8; 19:18, 23; 40:24; 105:16; 121:12; 124:25; 126:4; 127:5, 8; 138:12; 139:4
resected 72:9, 11
resection 57:4
resections 72:15
reservoir 28:15
residual 41:17; 42:2; 73:10, 23
resistance 23:1; 34:17; 75:24, 25
resolved 77:17
respect 7:23; 11:12; 15:5, 10, 18; 75:18; 126:21
respectively 51:17; 94:18
respiratory 211:2
respond 22:24; 105:5; 122:16; 157:16; 159:7, 9
responded 53:1
responder 92:21
responders 150:8
responding 22:23; 30:11; 52:14, 20, 23; 55:22; 56:4; 150:9, 23
response 8:9; 9:18, 25; 10:4, 13; 11:3, 18; 12:17; 14:7, 16, 22; 15:6, 6; 18:22; 22:21; 25:12; 30:14; 46:5, 8; 47:21, 24; 48:4; 52:12, 22; 53:1; 54:22; 55:9, 20; 56:2, 15; 57:19, 21; 58:5, 6; 59:14, 17; 60:3; 61:18; 75:12; 76:5, 20; 77:6, 21; 78:4; 79:17, 19; 80:3, 9, 12; 87:10; 89:4; 91:21; 92:20, 22, 24; 93:3, 9, 14; 96:2, 4, 5, 8, 10, 12, 13, 19, 23, 24; 97:3, 5, 8, 9, 11, 12; 100:15, 16; 112:13; 114:7, 8; 115:16, 18; 116:15; 117:1, 4; 119:1; 120:9;

122:24; 123:5; 129:23; 133:17; 138:8; 141:4; 148:22, 23; 150:3, 7, 16, 19; 152:2, 7, 8, 11, 18; 153:10, 13, 16; 154:13, 15; 157:24; 161:5; 162:6; 178:4, 6, 15; 179:17, 18, 22; 180:8; 186:5; 192:11, 16; 193:2, 14; 194:7; 199:10, 24; 202:3, 24; 203:3, 9, 11; 217:3, 4, 10, 13, 25; 219:13; 223:14; 236:2, 4; 237:17; 241:10, 12; 242:2; 245:18; 261:22; 268:7; 269:17, 22; 270:6, 10, 21, 24; 271:8, 13
responses 72:10, 13; 103:3, 3; 114:6; 150:4, 6; 153:3; 154:9; 180:13; 217:17, 18; 241:11
responsible 19:18
responsiveness 75:2, 6; 156:11
rest 104:11; 149:21; 153:17; 168:11; 261:18
restore 156:10; 157:19; 158:2, 23; 198:5
restores 158:14
restricted 175:23
result 27:23; 68:1; 88:21; 95:24; 98:6; 115:20; 142:24, 25; 156:20; 188:4, 19; 189:21; 247:18; 249:21; 256:3, 4; 259:12; 269:9
resulted 52:11, 17; 59:13
resulting 177:25
results 32:3; 34:5; 37:15; 40:4, 24; 42:15; 43:7, 18, 21; 44:14; 45:8; 46:11, 22; 51:11; 52:4; 53:14; 54:2, 13; 55:5; 56:20; 61:9, 14; 67:3, 25; 69:1; 77:4; 78:2; 81:19; 83:2, 8; 84:5; 89:21; 95:9, 10; 100:14; 101:18, 21; 104:7; 105:18; 110:1, 8; 117:1; 141:23; 143:11; 144:22; 149:6; 153:18; 162:2; 165:16; 167:6; 185:13; 189:3; 197:22; 219:23; 229:24; 230:3; 237:11, 23; 248:23; 249:25; 254:9; 259:21, 22; 266:13, 15, 16; 269:5
resumed 123:12; 271:18
reticular 163:14
reticuloendothelial 200:13
retinoids 34:6
retirees 136:15
retrospect 74:24
return 131:5, 204:20; 259:25
returned 242:25
revealed 240:17
reversal 264:15
reverse 156:8; 157:20

reversed 112:1; 158:4
review 16:23; 43:20; 44:13; 60:6, 23; 76:20; 77:3, 5, 11; 101:25; 103:2; 107:15; 114:5; 167:7, 8; 174:10; 175:22; 201:17; 214:12; 217:6; 227:20, 23; 228:4, 12; 232:8; 243:23; 245:21; 250:4, 10; 260:16; 261:18; 263:19; 267:21
reviewed 65:24; 68:9; 70:21; 77:14; 107:13; 268:13
Reviewer 125:16; 246:11
Reviewer's 47:1
reviewers 261:21
reviewing 100:23; 106:25
Revised 231:19
rhinitis 181:13
Richard 5:18; 6:18; 124:15
richer 33:15
Right 71:11; 80:19; 85:3, 6; 110:14; 118:8; 121:12; 129:4; 130:16, 24, 24; 134:17; 135:20; 198:12; 200:17; 207:10; 226:22, 24
Rigs 20:7
risk 47:13; 51:21; 54:9; 144:1; 146:12; 147:7; 170:21; 172:3, 6; 190:7; 233:11, 12, 15
road 218:10
robustness 254:16
rodent 39:11; 40:15
role 19:9; 23:18; 26:7
rookie 133:9
room 5:5, 10; 7:15; 126:14; 133:2; 136:16; 259:8
Rosenberg 151:24
Rosenberg's 134:4
Rotterdam 142:9
rough 23:9
routine 130:23; 132:18, 21; 151:18
rule 66:23, 24, 25; 67:22, 23, 25; 265:23
ruled 67:6
rules 63:17; 82:11
ruling 66:1; 67:14
run 23:1; 87:7; 167:20
Russia 102:18; 103:1; 107:13, 14

S

S 21:15; 127:4, 4, 7; 134:2
safe 19:3; 34:21; 52:2; 62:1; 111:16; 183:10; 185:5; 262:21
safely 139:14; 140:19;

162:17
safer 214:22
safety 11:11; 19:1, 21; 43:21; 46:11; 47:1; 60:6; 67:14; 98:19; 100:25; 101:5; 110:12, 16; 117:20; 118:9; 120:17; 122:1, 5, 9, 20; 155:4; 160:16; 167:4, 5, 8; 180:17; 189:12, 13; 206:17; 208:12, 16, 20, 24; 209:2; 211:24; 214:20; 216:4; 224:17; 229:20; 231:11; 243:9; 245:21, 24; 260:18; 261:15, 16; 262:21; 263:3; 268:13; 270:16; 271:3
said-maybe 78:1
salvage 249:15
same 14:7; 22:17; 38:25; 44:9; 54:22; 55:10; 83:3; 108:4; 110:5; 114:15; 115:25; 119:20; 121:4; 122:17; 128:1, 3; 157:2; 158:8; 170:11; 175:13; 180:12; 182:1; 186:2, 7, 14; 187:14; 192:19; 216:22; 220:9; 221:16; 238:25; 244:13; 253:20
sample 47:17; 58:12; 63:8; 229:23
sampled 41:9
San 75:11
Sandra 6:20
Sanjiv 142:6; 218:12
SANTANA 5:24, 24; 7:12; 120:19; 124:24, 24; 126:8; 206:9, 10; 207:20; 215:17
Sarah 5:13; 124:10
satisfactory 107:14
save 128:8; 154:24; 203:16
saw 70:13; 76:14; 79:9; 82:21; 115:18; 170:7; 185:22; 225:6
saying 15:25; 66:22; 67:1; 78:2; 174:20; 223:15
scale 183:20; 262:9
scaled 248:6
scales 262:9
scan 213:14, 14; 223:18; 224:10; 225:15; 226:11; 264:21, 23, 25
scanned 168:22
scans 197:1; 213:10; 224:5; 236:12
scenario 81:16; 110:19
schedule 229:17
Scheduled 47:4; 138:10; 222:7, 14, 16
schedules 136:14
scheme 74:14; 147:23
school 133:25; 142:8
science 57:23; 198:9
scientific 31:19; 35:7; 197:21; 200:1
scientifically 66:10

18; 173:1; 174:8; 175:12, 21; 176:16; 177:13; 178:13, 24; 179:4, 8, 12, 16; 180:2, 16, 18; 181:14, 25; 182:5, 10, 20; 183:5, 14, 19; 184:6, 12, 18; 185:3, 8, 15, 19, 24; 186:4; 187:5, 13, 18; 188:2, 21; 189:5, 22; 190:10, 15; 198:18; 212:13, 23; 216:8; 223:6; 227:22; 228:4, 6, 10, 11, 18; 229:5, 6, 14; 230:8, 20, 21; 231:8, 17, 24; 232:7, 12, 22, 23; 233:8, 9, 25; 234:3, 6, 11, 14, 17, 19; 235:16, 19, 20, 22, 25; 236:3, 9; 237:5, 6, 9, 19; 238:3, 9, 10; 239:4, 20; 240:10, 11, 16, 21, 22; 241:8, 13, 18, 20; 242:4, 8, 9, 12, 19, 23; 243:8, 9, 18, 25; 244:2, 6, 11, 21; 245:3, 8, 20; 246:13, 20; 247:1, 16; 248:8, 25; 249:5, 11; 250:12, 25; 251:12, 22; 253:10; 254:7; 255:4, 20; 256:20; 257:6; 258:15; 259:5, 13, 20, 24; 260:3, 8, 15; 261:7, 14
slide--with 80:13
slides 83:21; 193:1; 210:11; 231:6; 245:4
slight 58:17; 169:16, 181:7, 10
slightly 178:21; 240:3; 243:16
Sloan-Kettering 5:16; 124:14; 149:14; 229:10
slope 267:16
small 9:15; 30:4; 40:24; 51:7; 73:20; 83:16; 98:23; 99:3, 6, 20; 100:1; 116:14; 140:2; 149:2; 154:10; 187:15; 240:19; 241:25
smaller 14:11, 15; 74:9; 84:9; 218:21
smallest 233:21
snow 137:24
so-called 34:14; 149:5
soaking 131:17
soft 50:8, 8, 10; 95:3; 97:2; 144:6
sole 64:20; 145:14
solid 79:22
solve 157:8, 9
solved 34:17
some-off 264:25
somebody 83:19
somehow 78:18
someone 67:15; 70:22; 119:12; 127:14; 193:17
Somers 6:3; 125:3
sometimes 25:15; 84:21; 108:20; 115:4, 8; 122:4; 138:18; 263:14
somewhat 9:1; 70:15; 173:10; 218:4

son 128:2
soon 40:14; 131:5
sophisticated 24:24
sort 13:4; 27:17; 78:14; 83:17; 107:18; 118:14; 127:23; 164:5; 219:20; 220:2; 224:19; 226:23
soul 142:13
sound 120:1; 256:10
sounds 108:12
source 39:8; 40:10; 243:4
sources 39:6, 10
South 252:10, 11
Soviet 93:22
spacing 92:23
spark 129:3
speak 127:5; 133:21; 137:25; 264:15
speaker 33:18; 130:1; 133:19; 138:10
speakers 8:6
special 21:6; 38:9; 42:17; 160:13
specialists 135:3
specialized 200:19
specialty 134:10
species 39:11; 40:15, 16; 197:12
specific 17:14; 20:4; 24:8; 28:24; 153:23; 197:23; 198:14; 209:11; 244:1, 8, 24; 246:21; 247:4; 267:2, 17
Specifically 16:25; 18:12; 33:5; 64:23; 65:2; 76:10; 162:10; 197:4, 10; 202:11; 261:21
specification 247:20
specificity 29:10
specified 46:21; 78:7; 191:21; 196:12; 210:2, 9; 221:1; 251:17, 18; 252:16, 22
specify 247:3
spectrum 34:3
speculate 73:22
speculation 165:10
speeches 135:1
spelled 65:7
spend 143:7; 160:18
spent 9:5; 89:15
spleen 200:16
Sponsor 16:14; 64:5; 83:19; 88:12; 104:6; 109:15; 141:11, 15; 167:1, 9; 190:22; 196:15; 203:16; 212:16; 247:6; 249:2; 250:3, 22; 251:15; 252:13, 24; 263:25; 264:13
sponsor's 16:10; 95:12; 240:4; 247:22
sponsors 255:13
spontaneous 71:22

spontaneously 17:23
spread 21:22, 25; 135:10
squared 168:4, 6
Sridhara 227:24; 240:1; 246:8, 10, 11
St 5:24; 106:16; 124:24; 133:24; 134:8, 8, 10; 137:24
stabilization 82:7
stabilize 218:10
stabilized 133:5; 218:6
stable 46:7; 132:22; 162:9, 12; 180:1, 7; 203:11; 218:7; 220:24
stacks 137:15, 15
Stacy 5:6; 6:1; 125:1; 205:23
staff 134:4; 135:17; 140:15
stage 44:10; 45:12; 50:19; 57:15; 59:10, 11; 83:10; 92:7, 8; 94:10; 128:4, 14; 138:2; 143:21; 144:4, 17; 147:22; 151:21; 173:19; 174:1; 229:2; 239:6
stages 26:4; 120:5; 135:4
Staging 144:16; 147:22
stance 75:8
stand 259:15; 260:19, 21; 271:14
standard 19:5; 27:14; 31:3, 3; 32:25; 33:9; 62:17; 64:17, 19; 65:3; 67:22; 83:6; 116:17; 121:9; 149:18; 189:24; 217:2; 228:2; 249:19
standard--or 36:10
standardly 82:13
standards 226:8
standing 138:19
standpoint 12:5; 207:5
start 5:3, 9; 16:9; 41:8; 102:10; 109:10, 15; 123:9; 124:7; 184:1; 207:2; 215:10; 220:22; 227:13; 250:21; 257:13; 263:20, 21; 265:24; 267:16
started 41:16, 23, 24; 84:20; 85:3, 17; 93:18; 131:4; 136:22; 139:8; 142:1; 189:11
starting 51:11
State 19:14; 24:18; 95:11; 106:2; 134:1, 3; 144:20; 200:6; 248:15
stated 22:2; 165:13; 203:9; 230:13, 15; 231:10, 20
Statement 6:22, 24; 46:25; 102:13; 125:20, 21; 209:1, 4
statements 7:14; 126:12
States 17:13; 37:21, 25; 70:19; 93:24; 102:17; 107:1; 108:1, 3; 111:22,

25; 112:8, 17; 113:18, 21; 121:9; 143:24; 169:5; 208:18; 248:11; 249:14
stating 230:1
statistical 67:5; 81:24; 97:3; 109:2; 117:15; 135:5; 152:21; 166:6, 8, 10; 167:10; 170:20; 171:23; 174:10, 15; 175:22; 205:3; 206:6; 209:13; 227:25; 231:7, 19; 232:1; 235:3, 15; 237:13; 245:10; 246:9, 11, 14; 247:5, 22; 250:21; 251:18; 252:1, 18, 19; 265:13; 269:6
statistically 9:16; 42:6; 43:3, 5; 51:20; 52:5; 53:11; 54:6; 55:3, 21; 56:11; 81:19; 84:5; 95:24; 97:5; 98:7; 101:22; 104:12; 120:1; 169:17; 171:2, 4, 18; 172:5; 179:6; 184:23; 185:1; 195:4; 241:16; 249:25; 258:23; 259:4, 23; 260:7; 265:18; 269:7
statistician 70:1, 6; 208:18; 227:24; 240:1
statistician--if 133:10
statistics 109:23; 133:9, 10; 137:9
status 21:2; 47:6; 48:2; 49:9, 12; 53:8; 54:24; 57:15; 61:22; 74:19; 88:3; 95:1, 2; 97:8, 17, 20, 25; 98:2, 5, 10, 11, 14, 16; 100:19; 102:18; 113:13; 146:8; 147:17; 150:17, 21; 153:24; 154:11; 169:15; 172:16; 176:6; 178:18, 19, 23; 193:19, 20; 194:2; 201:12; 212:1; 214:9, 11, 14, 17; 215:11; 224:20; 239:11, 14, 16, 18, 23, 23, 24; 251:6; 252:9; 269:1
statuses 224:18
stay 129:2
steady 106:2
step 28:21, 23
steroidal 29:18; 31:10; 38:6
steroidogenesis 17:10
still 44:23; 64:16; 65:15; 66:25; 67:3; 72:7; 76:13; 79:1; 81:4, 4, 18, 19; 85:17; 87:23; 168:1; 171:4; 172:24; 185:17; 206:16; 210:14; 220:6; 229:3; 231:19; 266:3
stimulate 156:7, 19
stimulating 157:23
stimulation 202:9
stimulus 36:1, 3, 18, 20, 22
stood 144:23
stop 133:1
stopping 92:14

story 130:11
Stover 138:10, 11, 12
strata 53:10, 19; 54:3; 55:2, 10, 17; 82:18, 20
strategies 36:5; 116:1
strategy 23:7; 27:8
strates 83:15
stratification 44:21; 81:25; 82:8, 12, 14, 15, 15; 230:24
Stratified 48:3; 53:5; 58:9; 74:5; 165:14, 16; 230:5, 23; 231:14; 238:4, 5; 250:13; 268:25
stratify 83:12; 169:25; 194:23, 25
stratum 230:25
street 134:5
strength 65:5; 249:19
stress 33:24; 163:10, 19; 197:12, 13; 198:6, 21, 23; 199:2, 5, 14, 19, 23; 200:11
striking 97:12; 116:16; 238:13; 258:25
strokes 99:1
strong 74:20; 109:21; 146:23; 176:25; 197:8; 269:7
stronger 85:13
strongly 75:7; 112:25; 133:11; 234:22; 265:14
struck 69:16; 108:24
structures 29:17
struggle 86:18
studied 29:2; 73:9; 93:17 250:1
studies 11:18; 13:22, 24; 14:1, 2; 18:2; 37:9; 44:1; 60:11, 12; 62:6; 63:2; 70:17; 74:4, 9, 10, 11, 21; 77:4; 86:20; 87:7, 8, 20; 91:14; 96:14; 104:2; 105:12, 19; 106:9; 108:10; 121:23; 147:4, 9; 159:11, 12; 160:9, 12, 13, 19, 20, 21; 161:24; 162:16, 17, 25 174:5; 186:11; 188:20; 198:13, 23; 199:12; 204:7 208:3; 217:10; 227:23; 229:10; 230:2, 5; 233:17; 236:8, 13, 18; 237:2; 249:16, 21; 256:9; 262:19
study 12:16; 14:4; 18:4, 5, 6, 7, 11, 12, 14, 15, 18, 19; 20:6, 9; 31:2; 39:20; 40:24; 41:8, 9; 44:6, 6, 9, 9, 14, 16, 20; 45:4, 9, 11; 46:3, 12, 19, 20; 48:7, 22; 49:2, 5, 23; 50:18; 51:11; 54:15, 17; 56:2, 6, 10, 20, 20, 22; 57:1, 12, 17, 19; 58:2, 10, 23; 59:23, 25, 25 60:15, 15, 17; 61:10, 14, 15, 20, 25; 63:4; 64:7, 11; 66:15; 69:9, 12, 21; 70:12 71:21, 25; 72:8; 73:2, 20;

75:11; 77:4; 78:23; 79:7;
81:5, 10; 82:16; 83:10, 19;
84:25; 85:5, 7; 86:17, 21;
7:6, 14, 17; 88:1, 19;
89:19; 91:8, 12, 17; 92:20;
93:18, 21, 25; 94:9; 95:15;
17:99:13, 16, 17; 100:22;
101:13, 15; 103:1; 104:17;
105:16; 107:2; 113:3;
115:13, 14; 119:2; 120:7,
11; 160:15, 22, 23; 161:8,
18, 20; 164:18, 20; 166:7,
16; 167:14, 20; 169:2;
176:12; 177:16; 178:1;
182:16, 19, 22, 22; 183:4,
16, 21; 185:10, 11, 13, 14;
186:5, 6, 7, 12, 13, 14, 17;
187:2, 19, 21; 188:17;
189:11, 16; 191:1, 15;
192:14, 15; 195:1; 197:21,
22; 198:8; 202:1, 5; 204:3,
9, 14; 205:2; 206:25;
208:19; 209:18; 210:17;
211:3, 6, 9, 10, 13, 15, 17,
23; 212:3, 4, 10, 11, 14;
213:11; 215:2, 3, 10, 20;
217:16; 220:18, 19; 221:3,
6, 18, 20; 223:16, 23, 24,
24; 224:1; 225:8, 9, 24;
226:16, 17; 227:4, 8;
228:1, 3, 12; 229:12, 16;
230:10, 11, 16, 21, 22, 25;
231:2, 3, 10, 23; 232:2, 8;
34:19, 20, 24, 25; 235:12;
37:4, 24; 238:5; 239:7, 9;
242:25; 243:16, 20, 21;
244:12, 16, 17; 245:5, 23;
246:9, 11, 15, 16; 249:1,
15, 21; 250:13, 18, 21;
254:19, 21; 255:21; 256:6,
7; 259:1, 2, 9, 11, 16;
260:4, 19; 261:1, 3, 11;
262:4; 263:10; 266:4, 4, 5;
267:9, 22; 268:14, 16;
269:12, 25
studying 32:5
stuff 263:16
sub-class 38:4, 7
sub-Q 147:13, 24;
167:15; 168:1; 177:3;
183:10; 185:5; 190:8;
200:24; 201:7
subcutaneous 82:6;
131:23; 140:12; 151:25;
164:10; 168:2; 242:16, 21
subgroup 54:19; 56:16;
76:2; 142:23; 165:11, 14,
25; 166:3; 174:14, 17;
176:12; 197:7, 15; 215:23;
216:2; 228:15; 231:1, 7,
14, 22, 25; 232:6; 234:15;
235:4, 18; 237:23; 238:1,
6, 11; 239:17; 240:9, 15,
241:15, 17; 245:11;
246:19; 248:16; 249:6, 7,
13; 250:2, 6, 9, 9, 10, 14,
16, 20, 24; 251:13; 254:6,
17, 18; 259:1; 260:11;
261:10; 268:1, 3, 5, 10, 18,
24; 269:24; 270:4, 9

subgroups 53:16; 54:10;
55:7, 21, 24; 56:13; 66:8;
234:18; 237:16; 250:1, 8;
251:5; 254:15
subject 128:17; 255:24
submission 10:17;
35:18; 209:25; 247:8;
250:22
submit 26:9; 27:8; 30:5;
255:13
submitted 7:5; 18:3;
101:12; 126:1; 166:10;
186:18; 232:16; 236:19;
244:14; 245:5; 247:5;
250:21; 251:15; 252:2, 13,
24
submitting 7:14; 126:13
subpopulation 175:24;
177:1
subsequent 41:7;
162:25; 247:13; 259:2
Subsequently 19:16;
84:15; 252:1, 25
subset 22:23, 24; 24:2;
80:3; 82:21; 83:15; 84:1, 2,
9; 109:21; 116:14; 146:2;
195:3, 15, 19; 218:16;
223:8; 231:20, 21; 260:10;
265:24, 25; 266:3, 8, 22,
25; 267:4
subsets 54:17; 56:2;
61:21; 122:18
substantial 43:1; 101:14,
17, 23; 195:18; 220:17;
255:9, 10, 19; 259:15;
260:19, 20, 21, 22; 261:4,
9, 11; 269:12, 16; 270:1, 8
substantially 95:12;
139:23
substrate 29:20
substudy 57:23
subtraction 210:14
subtype 21:6; 25:21
success 137:10
suffered 131:16; 244:7;
245:22
sufficient 10:5; 15:4;
120:3; 249:22
sufficiently 28:17; 66:24,
25; 204:22; 206:8
suggest 22:13; 34:4;
75:8; 89:4; 106:13;
174:13; 198:6; 207:25;
226:23; 249:15
suggested 64:22; 119:9,
15; 175:22; 194:23
suggesting 97:13; 206:5
suggestive 98:1
suggests 66:10; 101:18;
104:18; 105:24; 112:24;
113:4; 173:13; 175:2;
229:8
suitable 44:23; 79:1
suiting 127:24
summarize 8:18; 100:14;
143:11; 171:14; 188:3;

212:13; 231:6
summarized 231:21
summarizes 10:7;
267:22
summary 12:1; 56:6;
59:23; 61:8; 67:9; 147:9;
153:22; 160:16; 188:22;
237:10; 245:4; 249:1;
267:22
summer 13:13
superb 112:21
superior 44:4; 51:20;
52:5; 54:16; 56:1, 11; 60:2;
61:16, 19, 25; 62:15; 66:1;
96:25; 97:10; 100:15;
111:13; 154:6
superiority 47:11; 56:14;
58:3; 110:8; 117:15
supplement 256:23
supplier 130:14
support 18:20; 43:22;
62:7; 101:12, 17; 103:20;
139:16; 153:1; 173:23;
189:18; 228:3; 229:22, 25;
230:14; 245:6; 255:14;
260:23; 263:1
supporting 230:2; 236:1;
237:17; 242:2
supportive 18:7; 44:9;
56:20; 86:7, 8; 120:5;
143:9; 175:18; 177:12;
241:9; 245:17; 248:14
supports 17:23; 19:5;
61:25; 177:6; 202:1
suppose 74:24; 226:19
suppress 155:24; 157:4
suppressed 198:3
suppressing 199:23
suppression 156:14;
157:6
sure 5:5; 70:6; 104:1;
112:1; 132:4; 167:23, 25;
168:22; 207:8; 209:20;
210:18; 252:11; 265:8
surely 129:11, 11
surgeon 134:2; 161:3
surgery 23:17; 27:23;
45:13; 50:19; 57:6, 7, 14,
22; 59:19; 60:4; 130:21;
134:4, 7; 153:11; 168:21
surgical 57:4; 72:15;
133:23
surprised 86:14
surrogate 9:25; 12:18
survival 9:10, 24; 10:1,
14, 16, 18, 19, 20; 11:5, 8,
10, 11, 19; 14:16; 15:16,
17, 18, 21; 16:1, 3, 6; 45:2;
46:9, 14, 15, 21; 47:1, 7;
57:9; 63:9, 18, 19, 21;
64:15, 17, 21; 65:17, 24;
66:1, 2, 7, 14, 19; 67:10;
12, 16; 68:1, 4, 9; 73:18;
92:1, 2, 3; 100:20, 21, 23,
24; 101:1; 109:23, 24, 25;
110:22, 24; 115:24, 25;
117:13, 15, 18, 19, 22, 23;

118:6, 8; 135:22; 136:23;
137:5, 19; 138:2; 142:17;
144:11, 12, 15; 145:15, 20,
22; 146:2; 147:15; 148:6,
19, 24, 25; 149:11, 16;
150:1; 151:1, 5; 152:9, 21;
153:4, 10, 13, 16; 154:3,
14, 16, 21; 161:2, 11, 17,
25, 25; 162:13, 21; 163:21;
164:11, 23; 165:1, 2;
169:8, 9; 170:16, 19;
171:3, 11, 14, 15, 18;
174:22; 176:8, 10, 15, 20,
25; 177:4, 9, 11; 179:19,
21; 180:9; 184:17, 20, 22;
185:1, 5, 16, 18, 20, 22;
187:17, 21, 24; 188:6, 8,
10, 15, 16, 17, 24; 189:2,
4, 9; 190:4; 193:9, 9, 13;
199:11; 202:25; 203:10;
217:11, 13, 15, 24; 218:3,
5, 21; 219:14; 220:5, 13;
221:22; 228:13, 15, 24;
229:13; 230:7, 18; 231:2,
4; 232:5, 9, 13, 15, 23;
233:6, 10, 23; 234:1, 4, 7,
21; 235:1, 6, 8, 13, 17, 20,
23; 236:22; 237:12, 25;
238:19; 240:8, 18, 23;
241:22; 245:9, 11; 246:23;
247:10; 249:3, 8, 12;
253:6, 11; 258:23, 25;
259:4; 260:9; 261:2, 4;
267:24; 268:2, 4; 269:10,
24
suspicious 130:17
Sweden 142:12; 160:20;
200:9
switch 122:3
Switzerland 35:8
SWOG 146:5
symbols 100:4
symptoms 72:4; 132:5;
183:22
synonymous 144:4
synthesis 27:9, 16
syringes 204:20; 242:25
system 29:10; 40:12;
41:22; 163:9, 15; 200:13,
18; 217:21
systematic 255:25
systemic 45:23; 50:25;
72:4; 148:12; 150:18, 22;
169:1
systems 37:14; 40:18,
21; 256:3

T

T 156:5, 9; 157:15; 158:3,
18, 21; 159:4
T2 57:15; 59:7
T3 59:8
T4 59:8
T4c 57:15
table 12:3; 83:21; 84:8;
85:13, 14, 18; 93:15;

114:5; 116:25; 151:23;
174:10; 175:13; 185:25;
202:2; 250:3; 253:13;
254:1; 267:22
tables 220:17
Tablets 8:12; 16:10; 17:3
tachyphylaxis 206:18;
207:9; 208:1
tail 159:15; 258:2
take-home 254:8
talk 117:17, 21; 181:23;
214:20; 246:14
talked 114:5; 130:17;
267:21
talking 26:12; 27:16;
74:13; 88:3; 112:4, 6;
134:19; 194:7, 7; 252:15;
260:20; 262:2; 265:24
Tamofen 91:14
Tamoxifen 11:18; 13:15;
14:1, 6, 8, 10, 13; 15:5, 8,
10; 16:5; 18:6, 7, 21;
24:12, 14; 26:13, 13, 23;
27:2, 5, 12, 13, 19; 30:24;
32:17, 23, 25; 33:3, 9;
34:4, 8; 36:10; 42:24; 43:2,
4, 15, 18; 44:3, 4, 18; 45:5,
21; 47:12; 48:1; 51:2, 4, 5,
6, 15, 16, 21; 52:9, 13, 15,
19; 53:1, 2, 22, 24; 54:11,
16, 24; 55:13, 16; 56:1, 3,
12, 23; 57:3; 58:4, 6, 19;
59:4, 15, 21; 60:3; 61:17,
20, 21; 62:1, 13, 15; 63:3,
5; 66:1; 69:7, 11, 24;
70:12, 13, 16; 71:3, 7;
72:13; 75:25; 76:5, 10;
79:18, 25; 80:2, 4; 81:8;
85:18; 86:2; 90:6; 91:1, 13;
92:13; 94:3, 7, 13, 17, 18;
95:16; 96:6, 7, 14, 21, 25;
97:11; 98:5, 15, 15; 99:9,
21; 100:15; 105:17; 106:5,
10, 11, 21; 110:14; 111:12,
24; 112:3, 7, 13, 13, 18,
20, 25; 114:8, 14; 115:20;
116:5, 12; 117:2; 119:3;
122:15; 149:3, 5, 9, 10;
154:6; 258:18, 22, 24;
259:3
Tannock 256:23, 25;
257:12
target 24:8, 12; 25:13;
28:16, 17, 24; 132:19
targeted 24:6, 7, 11
targeting 29:11
targets 33:17
task 143:20
Taylor 5:12, 13, 13;
124:10, 10; 203:18, 19;
205:7; 219:5, 7
Team 6:16; 77:13;
101:25; 125:17; 227:19;
228:1, 5; 254:23; 261:18
technetium-labeled
200:14
Technical 141:20

technically 247:23	32:6; 34:8, 10, 13; 43:22;	thromboembolic 33:5;	128:10; 136:20; 137:9;	155:13; 164:1, 4, 6, 12;
technique 69:8	44:7, 10; 45:14, 21, 22, 23;	60:25; 99:3	140:22; 151:8, 10, 13;	167:12; 168:11; 172:1, 4,
tells 174:18	50:20, 25; 56:8; 61:12, 16;	thrombophlebitis 99:4	154:14; 161:15, 18;	24; 174:24; 175:6, 6, 8, 14;
Temple 12:24, 25; 16:16;	62:4, 16; 63:5; 67:7; 79:2,	thrombosis 100:1	164:14; 182:13, 14, 16, 17,	177:6, 22, 23; 178:16, 19;
20:24; 70:24, 25; 71:13;	3, 8, 11; 87:12; 90:18, 20;	throughout 26:24	18; 185:6; 192:22, 24;	179:5, 14; 181:4, 20;
88:13; 89:7, 24; 90:4, 7,	92:14; 94:14, 16; 99:19,	Thursday 271:18	212:7; 243:15; 244:8, 9,	183:8; 186:1, 12, 14;
11; 91:7; 104:15, 16;	22; 102:2; 110:17; 111:25;	Thus 43:10; 251:8;	22, 24, 25; 246:6	187:10; 188:10; 189:1, 18,
106:5, 13, 16; 108:7, 20;	112:7; 116:18, 20; 121:22;	254:16	toxicity-related 243:22	19, 25; 190:13; 191:3, 14,
115:3, 4; 116:7; 120:4, 23,	125:6; 135:4; 136:3, 20;	TIA's 98:25	track 187:16; 219:21	18; 193:6; 194:3, 12, 17;
24; 226:18, 19	137:10; 143:5; 148:12;	ticked 224:2	tracking 187:10	195:3, 17, 19; 196:8, 9, 22;
TEMPLETON-SOMERS	150:18, 22; 155:10;	timely 64:16; 65:15	traditional 165:7;	204:21, 22; 206:7; 207:8,
6:3, 23; 125:3, 19, 22	161:21; 168:18; 169:21;	times 27:3; 56:4; 73:4;	173:19; 256:8	14; 216:19; 225:14; 228:8,
Ten 264:5	183:22; 186:16; 187:3;	127:20; 176:11; 188:4;	Traditionally 179:17	21; 229:21; 230:11, 14;
tend 21:13, 16; 24:2;	188:23; 192:3, 10; 216:10,	227:10; 232:24; 251:19	trailing 146:7	231:15; 233:11, 13;
187:16; 207:7	20; 221:5; 222:23; 225:19;	Timewise 209:7	trained 134:1	239:13, 19; 240:14; 241:6,
tendency 122:3	229:4; 242:10; 252:4, 20	timing 207:10; 209:24	traits 83:12	24; 242:6; 247:9; 248:18;
tends 21:21	therapy-naive 44:5, 11;	tissue 28:11; 38:20;	transcription 24:24;	249:4, 23; 250:8; 251:14;
Tennessee 5:25; 124:25	56:24; 60:1	39:12; 50:8, 9, 10; 57:24;	25:11, 11	252:3; 253:16, 18, 20;
tension 67:15	thereafter 34:9; 92:18	72:9, 10; 95:3; 97:2; 144:6;	transfected 39:17; 42:21	254:18; 256:4; 257:5;
term 66:7; 174:12, 15;	therefore 23:12; 25:25;	200:24	transformation 174:3	260:14; 261:5, 12; 262:20;
175:14	26:7; 36:22; 38:6, 21;	tissues 28:10, 10; 35:25;	transformed 174:3	263:23; 267:6, 11; 268:24;
terminal 28:21, 23	40:19; 49:25; 101:2;	200:23; 201:9	transient 181:3	269:14; 270:2, 18; 271:5
terminology 130:20;	117:19; 146:17; 150:12;	today 15:15; 20:8; 33:11;	translated 206:20	treatment-related
208:11	230:25; 238:5; 248:21;	35:10; 61:8; 64:13; 110:6;	translates 25:17; 86:19	151:17
terms 72:23; 75:11;	254:8	127:13; 130:7; 134:16, 19;	transmission 36:17	treatments 14:20; 32:2;
78:15; 93:3; 94:15; 95:9,	thinking 120:25	138:15, 19; 142:11; 164:4;	trauma 128:25	44:7, 10, 17; 46:12, 13;
14; 96:2, 23; 97:8; 100:4,	third 22:25; 29:7; 31:10;	167:18; 168:1; 186:22;	travel 132:11, 15	51:14; 52:2; 56:23; 57:2,
20, 22, 25; 101:5; 135:24;	34:15; 45:4; 74:18; 88:15;	188:10; 189:24; 200:10;	traveled 137:23; 142:10	24; 76:25; 78:3; 96:20;
149:11; 150:16; 191:1, 3,	89:3; 91:5; 93:22; 104:17;	220:12; 227:19; 254:23;	traveling 136:14	100:17; 101:5; 135:9;
13; 193:22; 206:2, 4, 6, 18;	120:16; 146:6, 11; 207:14;	257:10; 264:11	treat 22:10, 15; 24:7;	137:9; 218:10; 265:21
207:21; 209:22; 211:24;	221:9; 242:5	together 129:17; 134:22;	34:19; 53:15; 55:6;	tremendous 266:10
218:15; 234:10; 263:8	Thirdly 195:14	136:22; 160:3; 162:19;	114:10; 134:11; 136:16;	trend 170:18; 176:14, 25;
test 47:15; 58:9; 113:13;	Thirteen 58:21; 161:21	205:4; 212:21; 226:14	139:14; 159:19; 174:20;	180:8, 13, 14; 185:17
131:13; 170:1; 171:21, 24;	Thirty-three 232:18;	told 36:9; 130:25; 137:8,	179:7; 184:9	trends 55:23; 170:5
183:21; 250:5; 256:9	243:19	21; 226:20	treated 27:19; 41:4, 7;	trial 12:19, 20; 26:12;
tested 113:19; 160:2;	Thomas 20:15; 46:19;	tolerability 216:5; 229:21	42:23, 25; 43:1; 44:5;	31:5; 32:9, 10, 20, 24;
166:15; 229:19	63:23	tolerable 214:23	95:23; 98:4, 6; 136:3, 12;	33:2, 4; 34:5; 45:6; 47:10;
testing 231:25; 250:6, 17,	though 68:25; 82:19;	tolerance 128:11	138:25; 146:5; 160:8, 10,	56:8; 62:16; 63:13; 64:19;
19, 23; 256:15; 257:7, 14,	83:25; 116:14; 161:14;	tolerate 207:7	15; 172:6; 180:23; 188:5;	65:8; 66:12, 14; 73:15;
18; 258:11	170:8; 215:21; 219:2;	tolerated 17:24; 19:3;	198:1; 206:25; 212:2;	74:11, 17, 25; 77:8; 79:5;
testosterone 28:3	222:4; 226:9	33:5; 61:5; 62:2; 101:6;	220:18; 231:12; 246:2	80:2, 22; 83:24; 85:17;
tests 206:4	thought 108:16; 131:22;	111:17; 183:11; 228:16;	220:18; 231:12; 246:2	86:25; 89:2, 3; 90:24; 91:1,
Texas 35:22	180:21; 209:6; 256:4	242:6; 246:3	treatment 8:19; 9:7, 22;	3; 92:8; 101:11; 107:16;
textbook 151:24; 256:22	thoughts 201:20	Tom 64:1; 142:7	10:8, 24; 11:6, 15; 13:18;	109:16, 20; 110:16, 22;
thankful 132:25	three 11:23; 30:17, 21,	tomorrow 271:15	16:24; 17:15; 18:8, 23;	111:4, 11, 22; 113:15;
that--all 222:8	21; 37:2; 38:2; 43:2; 47:7,	took 39:5, 6, 10, 12, 14,	19:2, 10, 22; 35:19; 36:6;	114:15; 115:18; 117:1, 5;
the--while 80:13	25; 50:14; 63:14; 65:21;	16, 21, 25; 76:11; 81:16;	44:23, 24, 25; 45:4; 46:5;	118:15, 16, 18; 119:11, 16,
them--my 206:16	72:13; 80:9, 18; 81:23;	84:13; 130:18; 192:19;	47:11, 14; 48:14, 16, 18;	21, 24; 120:2; 134:19, 21,
theory 202:5	85:19; 88:24; 92:18, 23;	227:8	49:5, 13, 19; 50:4, 17, 24;	25; 136:23; 139:24; 143:7,
therapeutic 26:3; 30:8;	93:3; 96:16; 104:11;	top 121:15; 187:8, 24	51:24; 52:3, 4, 8, 11, 17,	10, 11; 149:13; 150:2;
257:5	128:5; 130:5, 21, 22;	total 14:2, 6; 48:7, 20;	24; 53:7, 9, 11, 15; 54:5, 7,	152:15; 153:8, 10, 14, 18;
therapeutically 26:1	131:3, 14, 15; 132:9, 23;	51:1; 58:15, 21; 99:8, 9;	17, 23; 55:1, 4, 6, 15, 19,	164:9; 168:15, 25; 169:13,
therapies 21:9; 23:15;	135:11; 144:23; 147:4;	160:7; 212:25	22; 56:15; 58:3, 8; 59:3,	18; 177:11; 187:8, 10;
27:9; 30:1; 34:2, 11, 50:23;	151:6; 159:18; 161:4;	totally 15:23; 40:13	13, 20; 60:14, 16; 61:2, 18,	188:1, 7; 189:4, 9; 213:2;
57:7; 62:10, 12; 66:6;	188:4, 20; 195:6; 204:3;	touch 67:9; 185:9	23; 62:17; 66:11; 77:1, 10,	217:24; 219:3; 224:19;
80:22; 87:18; 119:10;	208:17; 215:6; 221:15, 17,	toward 111:6; 201:16	15, 24; 78:13, 16, 17, 18,	230:13, 17; 233:11; 243:3,
127:23; 144:13; 148:16,	19; 228:13; 231:6; 232:9,	towards 180:14	20, 23, 24; 80:4; 81:4, 12;	7; 244:13; 245:2, 7, 25;
20; 172:13; 187:4; 215:1;	16, 20; 233:10, 17; 234:9,	Township 124:19	82:4, 7, 20; 84:6; 85:5, 24;	254:25; 255:3, 14, 18, 24;
231:13	18; 238:21; 242:10;	toxic 139:22; 150:11;	87:2, 10, 15; 90:22; 91:12,	258:21; 259:7, 15, 16;
Therapy 6:6; 13:4, 25;	243:20, 21; 246:21; 253:5;	152:25; 265:21	23; 96:3, 15; 98:5; 99:6,	260:1, 2, 5, 5, 5, 21, 24;
16:11; 17:4, 11, 12, 17, 21,	263:23	toxicities 87:15, 16;	23; 102:19; 115:15, 16, 21;	265:23; 266:8, 11, 16;
25; 18:6, 16, 25; 19:6, 12;	three--is 191:25	117:8; 139:12; 244:1, 2, 5,	116:1; 117:12; 118:2;	267:15, 18
20:21; 21:3; 22:11, 24;	three-way 89:1	9; 245:22; 246:1; 268:17	119:4; 120:12; 122:16;	trials 9:10; 10:11; 12:10,
23:12, 17, 23; 24:6, 7, 10,	three-week 215:8;	toxicity 10:2, 5; 11:2, 4;	130:5; 131:2, 3, 12; 133:4;	14; 13:14, 16; 14:8, 9, 12,
11; 25:17; 27:5; 28:24;	225:15	24:8; 29:6; 44:19; 99:11;	134:25; 135:12, 20; 136:7,	15, 16, 17; 19:1; 26:10;
30:24, 25; 31:3, 4, 18, 20;	throes 128:18		8, 24; 137:4; 138:23;	27:11; 30:21; 31:5; 32:11,

120:4; 122:9; 139:5;
146:6; 149:2, 8; 152:5;
53:5, 7; 159:23, 25;
0:6; 168:9; 179:19;
86:10; 229:2; 230:1;
244:3, 10; 256:12, 13, 18,
19; 257:1, 13, 15, 15, 16,
17, 19, 19, 21, 21, 23, 25;
258:1, 3, 6, 6, 7, 13, 14, 16;
259:2; 262:5; 265:15, 16;
267:4
tried 33:23; 38:6; 164:20
trivial 23:13
true 26:23; 110:8; 135:6;
161:16; 182:1; 214:24;
217:14; 219:2; 254:18;
257:16, 19, 20, 22, 25;
258:1, 13; 266:16, 17
truly 83:25; 129:16;
154:18; 226:7; 257:15;
258:11
try 85:24; 127:23; 155:18;
215:21; 226:15
trying 128:16; 156:6;
167:15; 183:22; 198:14;
202:21; 219:17
tumor 9:11, 18, 24, 25;
10:3, 3, 12, 13; 11:2, 3, 17;
14:7, 10, 15; 15:5, 6, 9, 12;
18:13, 22, 22, 24; 32:21;
35:25; 38:15, 24; 40:16;
43:1, 6, 15; 47:5; 52:12;
5, 24; 58:9; 61:2; 92:16,
7; 96:16; 103:7; 130:24;
144:6; 146:20; 154:15;
155:16, 19; 156:2, 23, 25;
159:8, 15, 22; 163:8;
176:4; 178:8, 8, 9, 10, 22;
193:2; 198:8; 199:4;
201:2; 210:13; 217:17, 19,
20; 236:1, 4, 10, 14;
237:17, 18; 239:6; 241:9,
10; 242:2, 3; 245:18, 18
tumor-related 82:3
tumors 21:12, 15; 26:18;
28:14; 39:15; 155:21, 24;
159:17, 19; 161:10;
198:16; 199:3, 16, 19;
201:6
tunnel 128:22
turn 20:19; 131:21;
141:11; 143:14; 265:17
turned 113:2; 130:19
Turning 98:19
turns 157:13
tweak 111:2
Twelve 130:16
Twenty-five 95:3
Twenty-nine 93:20
Twenty-one 99:8
vice 168:4, 6; 238:15;
0:25; 242:16, 17, 21
two 13:2, 24; 14:2, 15;
15:1; 18:2; 22:4; 27:3;
31:5; 32:11, 22; 33:12;
36:7, 14, 16; 39:14; 40:10,
22; 43:25; 45:25; 46:15;

47:15; 49:1; 50:13; 55:21,
23; 58:10, 24; 61:9; 63:2;
68:16; 69:3, 9; 72:13;
73:14; 76:4, 12; 82:5;
83:20; 85:2, 3; 88:4, 14,
24; 92:22; 93:21; 95:7;
96:10, 15, 19; 97:20;
98:12; 99:6, 12; 100:17;
104:2; 105:11, 15, 24;
109:8; 111:24; 113:24;
114:1, 15; 119:9, 18, 21;
130:5; 131:14; 132:7, 22;
134:23; 135:16, 21; 159:6;
160:12, 13; 161:6, 24;
162:7, 8; 165:2, 13;
166:15; 169:14, 16, 23;
170:13; 171:11; 172:16;
173:10; 178:16; 182:4;
183:8; 184:19; 187:1;
191:3, 8, 22; 192:10;
193:5, 23; 194:3; 195:3,
17, 18; 201:16; 203:24;
208:5; 210:7, 11; 213:4;
215:8, 9; 216:21; 222:16;
223:3; 229:10; 230:1, 6;
232:10, 13, 24; 233:6, 24;
236:6; 237:8; 238:11, 14,
21; 241:11, 17, 23; 242:14,
16; 246:17; 247:9; 249:7,
20; 251:23; 254:4; 257:23;
260:17, 18; 265:15, 22;
266:20; 267:11; 268:24
two-arm 90:25
two-tailed 256:9
two-thirds 94:11
type 67:24; 94:15; 139:1;
140:16; 192:24; 244:8, 25;
250:23
types 40:22; 110:3;
136:8; 155:16, 19; 156:23;
192:23; 212:13; 225:23;
244:1
typical 144:15
typically 21:19; 22:2;
164:3; 172:10, 15; 202:9;
214:8

U

U.S. 18:10; 38:3; 70:13;
119:19; 144:2; 225:12
UCLA 142:5; 145:18;
218:14
ultimately 23:1; 34:16
ultrasound 57:21; 59:18
Umea 142:12; 200:9
unable 85:11; 86:6;
100:10
unacceptable 44:19
unadjusted 47:15, 21;
247:14; 248:13, 21;
253:23; 269:8
unanticipated 255:24
unblinding 82:25;
259:18
uncertain 154:14
under 46:18; 99:14;

184:19
undergo 28:9; 57:4
underscore 116:11
understood 15:14;
24:21; 63:10
undertaken 114:24
undetected 255:25
unethical 168:19
unexpected 60:13;
162:1, 13; 183:7
unexpectedly 104:17
unfavorable 66:25
unfortunate 169:24
Unfortunately 135:19;
137:16; 149:8; 150:11;
151:20; 152:22; 197:18
uniformity 248:18, 23
Union 93:22
unique 163:6
unit 129:2; 139:3, 14;
184:4
United 17:13; 37:20, 25;
70:19; 93:24; 102:16;
107:1, 25; 108:3; 111:22,
25; 112:8, 17; 113:18, 21;
121:9; 143:24; 169:5,
208:17
units 149:20; 168:4, 6
units/kg 149:20
univariate 172:1
University 5:14, 20; 6:9,
11; 20:7, 10, 12, 17; 64:2;
70:10; 88:22; 124:11, 17;
125:11, 12, 14; 134:1, 7;
138:12; 139:4; 142:6, 7;
200:8; 238:18
unknown 45:16; 49:16;
55:24; 74:22; 75:1; 92:9;
94:12; 97:13; 102:4, 13;
119:6; 195:23
unless 108:5; 199:25;
222:9; 236:23
Unlike 111:22
unlikely 79:17; 87:20
unlucky 169:24
unquote 214:6
unreproducible 258:16
unsettled 110:15
untreated 154:10
up 15:24; 23:1; 24:18;
31:20; 32:25; 57:15;
62:23; 63:18; 64:4; 83:11;
88:24; 116:10, 12; 130:11;
131:16; 138:19; 143:4;
151:3; 163:2; 166:7;
173:6; 181:8; 185:12;
190:21; 195:2; 199:14;
200:15; 203:15; 210:8;
215:16; 217:17; 219:16,
25; 220:4; 246:8; 252:14;
253:17, 19; 256:16, 16;
258:1, 3, 10, 13, 18;
261:18, 24; 265:9
up-front 82:8, 12; 83:7
update 143:10; 169:9;

185:10, 25; 219:17;
232:15
updated 10:18; 117:13;
185:10; 187:19; 244:14;
247:13; 252:25; 253:19;
254:6
upfront 65:8, 13
upon 8:1; 114:25; 126:24;
207:3; 221:2; 237:14
upper 172:14; 174:6;
211:7
upstream 25:12
urge 75:7; 137:25
us--and 220:20
use 11:22, 24; 12:8;
16:24; 22:19; 23:2, 17;
33:24; 34:20, 20; 37:20;
38:25; 42:20; 73:21; 74:1;
82:13; 84:8, 17; 111:22;
113:25; 116:4, 19; 118:6;
121:9; 122:2, 15; 150:13;
155:13; 168:2; 174:4, 14;
206:16; 258:12; 263:4;
270:18; 271:4
used 22:17; 23:6; 24:25;
26:17, 18, 18; 27:20; 34:8;
39:16; 42:21; 65:18, 19;
70:12, 13, 19; 71:18;
84:15, 21, 24; 85:1;
110:14; 112:19; 114:14;
172:10, 13; 173:12; 174:4;
183:16; 185:14; 196:4, 4;
199:16; 202:9; 207:10;
230:16; 231:20; 232:13,
24; 233:5, 5; 236:16;
245:7; 248:22; 249:19;
251:19; 252:20, 23;
254:11
useful 88:20; 114:22;
116:6; 174:17
uses 230:11
using 23:4; 34:14; 36:12;
47:15; 58:9; 65:3; 70:25;
75:2; 122:19; 150:2;
167:13; 174:3; 186:3, 7,
14; 217:2, 4; 228:2;
232:15; 234:2, 4, 7;
239:21, 23; 244:12;
251:15; 253:20
usual 13:5; 70:25
Usually 10:15; 65:7; 71:9;
74:9; 77:21; 107:23;
119:19; 213:11; 265:15

V

vacation 129:6
vaccine 157:6
vaginal 33:6; 99:14
valid 118:22; 195:8
validate 68:10; 76:23
validated 86:23
validates 101:22
value 153:17; 206:5;
226:12; 233:10, 21;
248:11; 253:18; 268:5, 7

valued 79:7
values 172:14
variability 235:8; 256:2,
5, 6
variable 207:4; 228:24;
229:9; 252:3, 8, 8; 254:11,
12; 268:21
variables 81:25; 82:9, 12;
83:6; 202:20; 252:21, 21
variance 25:2
varied 132:3
variety 104:21; 114:19;
116:3
various 57:25; 155:19;
202:12
vascular 98:19
vasodilator 181:6, 7
vast 79:11; 200:14, 18
vein 159:15
verify 103:14
versus 43:18; 44:2;
72:23; 73:25; 76:6; 80:2;
95:16, 23; 96:4; 98:5, 16,
17; 99:20; 100:16, 18, 19;
112:14; 117:2; 152:17;
165:17; 172:20, 20;
176:23; 210:20, 22;
220:23; 230:12; 231:15;
252:6, 6; 263:8; 267:25;
268:6, 16, 17, 19
viability 197:24
viable 27:7; 111:4; 159:6
vials 204:20; 242:24
vice 13:2; 16:20; 141:19
Victor 5:24; 124:24
view 24:10; 26:23; 34:2;
109:2; 120:16; 232:5;
240:12; 245:15; 256:11;
270:16; 271:2
views 67:10
vinblastine 149:4;
152:17
violations 212:11; 225:5
violent 115:10
viral 199:1
virtually 113:18
visceral 21:24, 50:9, 11;
95:4; 97:4; 144:8; 145:4, 7;
147:10, 15; 148:1; 153:25;
173:8; 238:24, 25
visit 107:22
visitor 107:13
visits 98:12; 107:23
vitro 37:3; 42:21
vivo 37:4; 41:10, 17, 20,
21, 25; 42:2, 4, 9; 73:3, 11;
200:10
volunteered 134:15
vomiting 151:11
Vote 109:12; 126:11;
262:1