WEBVTT

NOTE duration:"00:58:49"

NOTE recognizability:0.922

NOTE language:en-us

NOTE Confidence: 0.924190047058824

00:00:00.000 --> 00:00:03.227 All right. It is my great pleasure

NOTE Confidence: 0.924190047058824

00:00:03.227 --> 00:00:05.677 to introduce Doctor Abner Lucent

NOTE Confidence: 0.924190047058824

00:00:05.677 --> 00:00:08.117 for our grand rounds today.

NOTE Confidence: 0.924190047058824

00:00:08.120 --> 00:00:10.185 Doctor Lucent is a hematopathologist

NOTE Confidence: 0.924190047058824

00:00:10.185 --> 00:00:12.250 at MGH and associate professor

NOTE Confidence: 0.924190047058824

00:00:12.316 --> 00:00:13.920 at Harvard Medical School.

NOTE Confidence: 0.924190047058824

00:00:13.920 --> 00:00:16.160 Upon graduating from college at Wash U,

NOTE Confidence: 0.924190047058824

00:00:16.160 --> 00:00:18.338 he went to Cornell for his MDPHD,

NOTE Confidence: 0.924190047058824

00:00:18.338 --> 00:00:20.846 followed by a PCP residency and

NOTE Confidence: 0.924190047058824

00:00:20.846 --> 00:00:23.599 then Heme Path Fellowship at MGH.

NOTE Confidence: 0.924190047058824

00:00:23.600 --> 00:00:24.440 He has since been there,

NOTE Confidence: 0.924190047058824

00:00:24.440 --> 00:00:26.274 rising to the rank of associate professor.

NOTE Confidence: 0.924190047058824

00:00:26.280 --> 00:00:28.304 He is currently director

NOTE Confidence: 0.924190047058824

00:00:28.304 --> 00:00:30.328 of the Hematology Lab.

NOTE Confidence: 0.924190047058824

00:00:30.330 --> 00:00:32.980 As well as the nascent

NOTE Confidence: 0.924190047058824

00:00:32.980 --> 00:00:35.034 lymphoma tissue repository, Dr.

NOTE Confidence: 0.924190047058824

00:00:35.034 --> 00:00:36.890 Luson has characterized novel

NOTE Confidence: 0.924190047058824

00:00:36.890 --> 00:00:38.746 subtypes of follicular lymphoma

NOTE Confidence: 0.924190047058824

00:00:38.746 --> 00:00:41.237 such as pediatric type follicular

NOTE Confidence: 0.924190047058824

00:00:41.237 --> 00:00:43.530 lymphoma and has defined the genetic

NOTE Confidence: 0.924190047058824

00:00:43.530 --> 00:00:44.970 underpinnings of these tumors.

NOTE Confidence: 0.924190047058824

00:00:44.970 --> 00:00:45.866 So specifically,

NOTE Confidence: 0.924190047058824

00:00:45.866 --> 00:00:48.106 his initial study in blood

NOTE Confidence: 0.924190047058824

00:00:48.106 --> 00:00:50.250 demonstrated the genomic differences

NOTE Confidence: 0.924190047058824

00:00:50.250 --> 00:00:52.575 between pediatric type and the

NOTE Confidence: 0.924190047058824

00:00:52.575 --> 00:00:53.970 traditional follicular lymphoma,

NOTE Confidence: 0.924190047058824

00:00:53.970 --> 00:00:55.614 representing a major advancement

NOTE Confidence: 0.924190047058824

00:00:55.614 --> 00:00:56.847 in the field.

NOTE Confidence: 0.924190047058824

00:00:56.850 --> 00:00:58.518 On the basis of this work

NOTE Confidence: 0.924190047058824

00:00:58.518 --> 00:01:00.200 and also follow up studies.

NOTE Confidence: 0.924190047058824

00:01:00.200 --> 00:01:01.855 PD type molecular lymphoma is

NOTE Confidence: 0.924190047058824

00:01:01.855 --> 00:01:04.142 now a distinct entity in The Who.

NOTE Confidence: 0.924190047058824

00:01:04.142 --> 00:01:04.906 More recently,

NOTE Confidence: 0.924190047058824

00:01:04.906 --> 00:01:06.816 he has characterized the genetic

NOTE Confidence: 0.924190047058824

00:01:06.816 --> 00:01:08.764 landscape of additional lymphoma

NOTE Confidence: 0.924190047058824

00:01:08.764 --> 00:01:10.441 subtypes including primary

NOTE Confidence: 0.924190047058824

00:01:10.441 --> 00:01:12.118 duodenal follicular lymphoma,

NOTE Confidence: 0.924190047058824

00:01:12.120 --> 00:01:13.479 primary cutaneous follicle

NOTE Confidence: 0.924190047058824

00:01:13.479 --> 00:01:14.838 center cell lymphoma,

NOTE Confidence: 0.924190047058824

00:01:14.840 --> 00:01:16.495 primary cutaneous gamma delta T

NOTE Confidence: 0.924190047058824

00:01:16.495 --> 00:01:18.944 cell lymphoma, as well as DLBCL.

NOTE Confidence: 0.924190047058824

00:01:18.944 --> 00:01:21.276 Leg type Doctor Lusan's lab has

NOTE Confidence: 0.924190047058824

00:01:21.276 --> 00:01:23.071 established the first ever PDX

NOTE Confidence: 0.924190047058824

00:01:23.071 --> 00:01:24.889 model of follicular lymphoma.

NOTE Confidence: 0.924190047058824

00:01:24.890 --> 00:01:26.732 He is currently an author for

NOTE Confidence: 0.924190047058824

00:01:26.732 --> 00:01:28.360 five chapters of the upcoming

NOTE Confidence: 0.924190047058824

00:01:28.360 --> 00:01:30.821 5th edition of The Who and lead

NOTE Confidence: 0.924190047058824

00:01:30.821 --> 00:01:33.083 author for four of these chapters.

NOTE Confidence: 0.924190047058824

00:01:33.090 --> 00:01:34.850 He's highly involved in ash,

NOTE Confidence: 0.924190047058824

00:01:34.850 --> 00:01:36.848 working on the Publications committee as

NOTE Confidence: 0.924190047058824

00:01:36.848 --> 00:01:39.170 well as the Abstract Review Committee.

NOTE Confidence: 0.924190047058824

00:01:39.170 --> 00:01:41.130 He has won the Benjamin Councilman Award,

NOTE Confidence: 0.924190047058824

00:01:41.130 --> 00:01:42.658 outstanding paper and pathology

NOTE Confidence: 0.924190047058824

00:01:42.658 --> 00:01:43.804 through use CAP,

NOTE Confidence: 0.924190047058824

00:01:43.810 --> 00:01:46.288 as well as the Berard Dorfman Founders

NOTE Confidence: 0.924190047058824

00:01:46.288 --> 00:01:48.075 Award for Young investigators

NOTE Confidence: 0.924190047058824

00:01:48.075 --> 00:01:50.699 through Society for HEMATOPATHOLOGY.

NOTE Confidence: 0.924190047058824

00:01:50.700 --> 00:01:51.900 I knew of Abner,

NOTE Confidence: 0.924190047058824

00:01:51.900 --> 00:01:54.231 but then got to know him personally

NOTE Confidence: 0.924190047058824

00:01:54.231 --> 00:01:57.815 through a rather epic study that is ongoing,

NOTE Confidence: 0.924190047058824

00:01:57.820 --> 00:02:00.459 and for that I got tasked with

NOTE Confidence: 0.924190047058824

00:02:00.460 --> 00:02:04.848 evaluating 789 potchkin lymphomas

NOTE Confidence: 0.924190047058824

00:02:04.848 --> 00:02:07.236 and I thought.

NOTE Confidence: 0.924190047058824

00:02:07.240 --> 00:02:08.560 Nobody would be willing to work

NOTE Confidence: 0.924190047058824

00:02:08.560 --> 00:02:09.440 on this with me,

NOTE Confidence: 0.924190047058824

00:02:09.440 --> 00:02:13.400 particularly someone with a lab himself.

NOTE Confidence: 0.924190047058824

00:02:13.400 --> 00:02:16.920 But Abner has proved me wrong and has

NOTE Confidence: 0.924190047058824

00:02:16.920 --> 00:02:19.188 helped greatly in that translational study.

NOTE Confidence: 0.924190047058824

00:02:19.188 --> 00:02:21.666 What I didn't know about him until

NOTE Confidence: 0.924190047058824

00:02:21.666 --> 00:02:24.026 very recently is that he started

NOTE Confidence: 0.924190047058824

00:02:24.026 --> 00:02:25.582 his academic faculty position

NOTE Confidence: 0.924190047058824

00:02:25.582 --> 00:02:27.690 focusing on clinical hematopathology.

NOTE Confidence: 0.924190047058824

00:02:27.690 --> 00:02:29.994 And was not in fact in the lab when

NOTE Confidence: 0.924190047058824

00:02:29.994 --> 00:02:32.547 he asked those fundamental questions

NOTE Confidence: 0.924190047058824

00:02:32.547 --> 00:02:34.767 about pediatric type follicular

NOTE Confidence: 0.924190047058824

00:02:34.767 --> 00:02:37.129 lymphoma and that resulted in his Kay Ward.

NOTE Confidence: 0.924190047058824

00:02:37.130 --> 00:02:39.010 He later carried out these

NOTE Confidence: 0.924190047058824

00:02:39.010 --> 00:02:40.890 experiments in David Weinstock's lab.

NOTE Confidence: 0.924190047058824

00:02:40.890 --> 00:02:42.874 And I think it is this unique pathway

NOTE Confidence: 0.924190047058824

00:02:42.874 --> 00:02:44.970 that he has carved that demonstrates

NOTE Confidence: 0.924190047058824

00:02:44.970 --> 00:02:46.900 his scientific queries are truly

NOTE Confidence: 0.924190047058824

00:02:46.900 --> 00:02:48.992 grounded in his own personal clinical

NOTE Confidence: 0.924190047058824

00:02:48.992 --> 00:02:50.642 expertise and that is something

NOTE Confidence: 0.924190047058824

00:02:50.650 --> 00:02:52.490 that I find truly inspiring.

NOTE Confidence: 0.924190047058824

00:02:52.490 --> 00:02:53.918 So thank you so much for coming

NOTE Confidence: 0.924190047058824

00:02:53.918 --> 00:02:56.930 to speak at Yale Grand Rounds.

NOTE Confidence: 0.933544666666667

00:02:56.930 --> 00:02:57.248 Thank you so

NOTE Confidence: 0.94629164

00:02:57.250 --> 00:02:59.794 much for that really kind introduction

NOTE Confidence: 0.94629164

00:02:59.794 --> 00:03:02.468 and it's it's truly an honor and

NOTE Confidence: 0.94629164

00:03:02.468 --> 00:03:04.750 pleasure to be here in the department

NOTE Confidence: 0.94629164

00:03:04.816 --> 00:03:07.049 and thank Doctor Chu and Doctor Lu

NOTE Confidence: 0.94629164

00:03:07.049 --> 00:03:09.249 for hosting me in the department.

NOTE Confidence: 0.94629164

00:03:09.250 --> 00:03:11.274 I'm really happy to talk a little bit

NOTE Confidence: 0.94629164

00:03:11.274 --> 00:03:13.570 about some of the work that we've done

NOTE Confidence: 0.81131856

00:03:15.650 --> 00:03:18.938 just I have no disclosures and.

NOTE Confidence: 0.81131856

00:03:18.938 --> 00:03:21.578 I will talk about different,

NOTE Confidence: 0.81131856

00:03:21.580 --> 00:03:22.380 different efforts,

NOTE Confidence: 0.81131856

00:03:22.380 --> 00:03:24.780 but they all center around a

NOTE Confidence: 0.81131856

00:03:24.780 --> 00:03:27.212 central goal which is if you think

NOTE Confidence: 0.81131856

00:03:27.212 --> 00:03:29.179 about lymphoma or what we do as

NOTE Confidence: 0.81131856

00:03:29.180 --> 00:03:30.636 pathologists and classifying the

NOTE Confidence: 0.81131856

00:03:30.636 --> 00:03:32.456 over hundred types of lymphoma.

NOTE Confidence: 0.909208146153846

00:03:50.820 --> 00:03:53.312 And all the work that I'll be

NOTE Confidence: 0.909208146153846

00:03:53.312 --> 00:03:55.905 presenting has attempted to do is to

NOTE Confidence: 0.909208146153846

00:03:55.905 --> 00:03:57.720 identify biomarkers that can either

NOTE Confidence: 0.909208146153846

00:03:57.720 --> 00:04:00.126 predict or give us a sense of help

NOTE Confidence: 0.909208146153846

00:04:00.126 --> 00:04:03.056 us understand how different lesions,

NOTE Confidence: 0.909208146153846

00:04:03.060 --> 00:04:05.240 why different lesions respond differently

NOTE Confidence: 0.909208146153846

00:04:05.240 --> 00:04:07.420 to therapeutic interventions and the

NOTE Confidence: 0.909208146153846

00:04:07.476 --> 00:04:09.261 heterogeneity responses that we see

NOTE Confidence: 0.909208146153846

00:04:09.261 --> 00:04:11.500 even within a single disease entity.

NOTE Confidence: 0.909208146153846

00:04:11.500 --> 00:04:13.000 And then occasionally when you

NOTE Confidence: 0.909208146153846

00:04:13.000 --> 00:04:13.900 do the investigation,

NOTE Confidence: 0.909208146153846

00:04:13.900 --> 00:04:16.005 you end up finding that what

NOTE Confidence: 0.909208146153846

00:04:16.005 --> 00:04:18.765 was thought to be a part of an

NOTE Confidence: 0.909208146153846

00:04:18.765 --> 00:04:21.418 entity is actually its own entity.

NOTE Confidence: 0.909208146153846

00:04:21.420 --> 00:04:22.980 And so with that I'll start,

NOTE Confidence: 0.909208146153846

00:04:22.980 --> 00:04:24.968 I'll start each of these sections with

NOTE Confidence: 0.909208146153846

00:04:24.968 --> 00:04:27.556 sort of a clinical case that sort of

NOTE Confidence: 0.909208146153846

00:04:27.556 --> 00:04:29.803 represents the impact or of the work.

NOTE Confidence: 0.909208146153846

00:04:29.803 --> 00:04:33.561 So the first is a 25 year old man with

NOTE Confidence: 0.909208146153846

00:04:33.561 --> 00:04:35.653 isolated cervical lymph adenopathy

NOTE Confidence: 0.909208146153846

00:04:35.653 --> 00:04:38.460 limited stage with clonal CD10B cell

NOTE Confidence: 0.909208146153846

00:04:38.460 --> 00:04:40.160 population by flow cytometry and

NOTE Confidence: 0.909208146153846

00:04:40.160 --> 00:04:42.578 you can sort of see a confluence of

NOTE Confidence: 0.909208146153846

00:04:42.580 --> 00:04:45.190 expanded follicles and the sort of

NOTE Confidence: 0.909208146153846

00:04:45.190 --> 00:04:48.019 largest medium to largest sort of cells.

NOTE Confidence: 0.909208146153846

00:04:48.020 --> 00:04:50.540 And there's an architectural pattern to it,

NOTE Confidence: 0.909208146153846

00:04:50.540 --> 00:04:51.610 focular pattern.

NOTE Confidence: 0.909208146153846

00:04:51.610 --> 00:04:54.820 The neoplastic cells are CD10 positive,

NOTE Confidence: 0.909208146153846

00:04:54.820 --> 00:04:57.039 their BCL two mostly negative and have

NOTE Confidence: 0.909208146153846

00:04:57.039 --> 00:04:59.460 a really high proliferation fraction.

NOTE Confidence: 0.9251585

00:05:03.060 --> 00:05:06.684 And so traditionally when this was

NOTE Confidence: 0.9251585

00:05:06.684 --> 00:05:07.874 originally diagnosed, this case,

NOTE Confidence: 0.9251585

00:05:07.874 --> 00:05:10.170 it was diagnosed as a focal lymphoma and

NOTE Confidence: 0.9251585

00:05:10.230 --> 00:05:12.705 I'll talk a little bit about that for those.

NOTE Confidence: 0.9251585

00:05:12.710 --> 00:05:14.470 Not in familiar with lymphoma,

NOTE Confidence: 0.9251585

00:05:14.470 --> 00:05:17.530 but it was diagnosed as a high grade Grade

NOTE Confidence: 0.9251585

00:05:17.530 --> 00:05:21.390 3 focal lymphoma and it was limited stage.

NOTE Confidence: 0.9251585

00:05:21.390 --> 00:05:24.112 And so the question there is do you

NOTE Confidence: 0.9251585

00:05:24.112 --> 00:05:25.918 treat with chemotherapy at the time

NOTE Confidence: 0.9251585

00:05:25.918 --> 00:05:28.470 or do you observe radiation therapy?

NOTE Confidence: 0.9251585

00:05:28.470 --> 00:05:31.070 And so we'll get back to the case,

NOTE Confidence: 0.9251585

00:05:31.070 --> 00:05:32.876 but just as a background focal lymphoma

NOTE Confidence: 0.9251585

00:05:32.876 --> 00:05:35.384 is a neoplasm of germinal center B cells

NOTE Confidence: 0.9251585

00:05:35.384 --> 00:05:37.064 comprised of centrocites and centroblasts,

NOTE Confidence: 0.9251585

00:05:37.070 --> 00:05:39.510 normal cell types within follicles,

NOTE Confidence: 0.9251585

00:05:39.510 --> 00:05:40.962 lymph node follicles.

NOTE Confidence: 0.9251585

00:05:40.962 --> 00:05:42.898 This disease demonstrates a

NOTE Confidence: 0.9251585

00:05:42.898 --> 00:05:44.350 policular growth pattern.

NOTE Confidence: 0.9251585

00:05:44.350 --> 00:05:47.102 The mean age is 6 decade and often

NOTE Confidence: 0.9251585

00:05:47.102 --> 00:05:49.509 presents with advanced stage disease,

NOTE Confidence: 0.9251585

00:05:49.510 --> 00:05:51.838 usually involving lymph nodes

NOTE Confidence: 0.9251585

00:05:51.838 --> 00:05:54.166 can occasionally involve marrow

NOTE Confidence: 0.9251585

00:05:54.166 --> 00:05:55.870 and extranodal sites.

NOTE Confidence: 0.9251585

00:05:55.870 --> 00:05:57.980 These follicular lymphomas can have

NOTE Confidence: 0.9251585

00:05:57.980 --> 00:05:59.668 different contributions of centrocytes,

NOTE Confidence: 0.9251585

00:05:59.670 --> 00:06:02.570 which are smaller cleave cells

NOTE Confidence: 0.9251585

00:06:02.570 --> 00:06:06.390 and larger centroblasts and today.

NOTE Confidence: 0.938134915263158

00:06:10.360 --> 00:06:12.920 Grade one to two would be sort of a lower

NOTE Confidence: 0.938134915263158

00:06:12.992 --> 00:06:15.664 grade and tends to have these smaller cells

NOTE Confidence: 0.938134915263158

00:06:15.664 --> 00:06:19.360 with sort of irregularly shaped nuclei.

NOTE Confidence: 0.938134915263158

00:06:19.360 --> 00:06:22.078 Whereas the central blasts are larger,

NOTE Confidence: 0.938134915263158

00:06:22.080 --> 00:06:24.624 more round with usually nuclear that

NOTE Confidence: 0.938134915263158

00:06:24.624 --> 00:06:27.230 are opposed to the nuclear membrane

NOTE Confidence: 0.938134915263158

00:06:27.230 --> 00:06:29.792 and 3A and 3D split between 3D

NOTE Confidence: 0.938134915263158

00:06:29.792 --> 00:06:31.760 being sheets of these large cells,

NOTE Confidence: 0.938134915263158

00:06:31.760 --> 00:06:34.559 3A being more than 15 per high power field.

NOTE Confidence: 0.938134915263158

00:06:34.560 --> 00:06:36.535 And generally the thought is

NOTE Confidence: 0.938134915263158

00:06:36.535 --> 00:06:38.510 that the grade threes are.

NOTE Confidence: 0.938134915263158

00:06:38.510 --> 00:06:44.590 May have a behave worse and may it may

NOTE Confidence: 0.938134915263158

00:06:44.590 --> 00:06:47.281 require more aggressive chemotherapy

NOTE Confidence: 0.938134915263158

00:06:47.281 --> 00:06:51.552 and the current upcoming WHO grading

NOTE Confidence: 0.938134915263158

00:06:51.552 --> 00:06:54.768 has been removed and and and the ICC

NOTE Confidence: 0.938134915263158

00:06:54.768 --> 00:06:56.605 classification it's still there but

NOTE Confidence: 0.938134915263158

00:06:56.605 --> 00:06:59.042 for the purposes of this just want

NOTE Confidence: 0.938134915263158

00:06:59.042 --> 00:07:02.909 to present the difference so these

NOTE Confidence: 0.938134915263158

00:07:02.909 --> 00:07:05.304 focalformers have a fundamental genetic

NOTE Confidence: 0.938134915263158

00:07:05.304 --> 00:07:08.560 alteration which is BC L2 translocations.

NOTE Confidence: 0.938134915263158

00:07:08.560 --> 00:07:11.974 Which the 1418 which juxtaposes BC

NOTE Confidence: 0.938134915263158

00:07:11.974 --> 00:07:14.244 L2 upon regulatory enhancer elements

NOTE Confidence: 0.938134915263158

00:07:14.244 --> 00:07:17.080 of the heavy chain which causes

NOTE Confidence: 0.938134915263158

00:07:17.080 --> 00:07:19.912 up regulation of BC L2 expression

NOTE Confidence: 0.938134915263158

00:07:19.912 --> 00:07:21.800 which imparts survival advantage

NOTE Confidence: 0.938134915263158

00:07:21.800 --> 00:07:24.440 and it clinically we can see this

NOTE Confidence: 0.933506579166667

00:07:30.520 --> 00:07:31.916 expression representing a germinal

NOTE Confidence: 0.933506579166667

00:07:31.916 --> 00:07:34.519 center cell and you can see that in.

NOTE Confidence: 0.841452866666667

00:07:38.140 --> 00:07:39.552 Folk lympharma, traditional classic,

NOTE Confidence: 0.841452866666667

00:07:39.552 --> 00:07:41.892 folk lympharma, you have BCL two

NOTE Confidence: 0.841452866666667

00:07:41.892 --> 00:07:45.691 expression and traditionally the most

NOTE Confidence: 0.841452866666667

00:07:45.691 --> 00:07:48.793 folk lympharmas have a relatively low

NOTE Confidence: 0.841452866666667

00:07:48.793 --> 00:07:50.672 proliferation fraction and usually

NOTE Confidence: 0.841452866666667

00:07:50.672 --> 00:07:52.868 a reactive general center will have

NOTE Confidence: 0.841452866666667

00:07:52.868 --> 00:07:54.688 a very high proliferation fraction.

NOTE Confidence: 0.841452866666667

00:07:54.688 --> 00:07:58.076 And we can do additional studies to look at

NOTE Confidence: 0.841452866666667

00:07:58.076 --> 00:08:00.872 clonality like PCR for IGHD arrangements,

NOTE Confidence: 0.841452866666667

00:08:00.872 --> 00:08:04.778 fish for for to assess the the BCL

NOTE Confidence: 0.841452866666667

00:08:04.778 --> 00:08:07.720 2 rearrangement and flow cytometry.

NOTE Confidence: 0.841452866666667

00:08:07.720 --> 00:08:10.872 Now early on we had identified there

NOTE Confidence: 0.841452866666667

00:08:10.872 --> 00:08:13.056 were some early series looking at folk

NOTE Confidence: 0.841452866666667

00:08:13.056 --> 00:08:14.971 and plumber and children and there

NOTE Confidence: 0.841452866666667

00:08:14.971 --> 00:08:17.390 there was some common trends noticed.

NOTE Confidence: 0.841452866666667

00:08:17.390 --> 00:08:20.960 So many of these young patients

NOTE Confidence: 0.841452866666667

00:08:20.960 --> 00:08:23.640 were were boys, young young boys.

NOTE Confidence: 0.841452866666667

00:08:23.640 --> 00:08:25.410 And there was they presented with

NOTE Confidence: 0.841452866666667

00:08:25.410 --> 00:08:26.870 limited stage disease often in

NOTE Confidence: 0.841452866666667

00:08:26.870 --> 00:08:28.000 the head and neck region,

NOTE Confidence: 0.841452866666667

00:08:28.000 --> 00:08:30.712 often had what was thought to be high

NOTE Confidence: 0.841452866666667

00:08:30.712 --> 00:08:32.959 histologic grade like more like a Grade 3

NOTE Confidence: 0.841452866666667

00:08:32.960 --> 00:08:37.280 or thought to be and they often lacked BC L2.

NOTE Confidence: 0.841452866666667

00:08:37.280 --> 00:08:37.898 Next question,

NOTE Confidence: 0.841452866666667

00:08:37.898 --> 00:08:39.443 but interestingly in all these

NOTE Confidence: 0.841452866666667

00:08:39.443 --> 00:08:41.320 series there was durable remission.

NOTE Confidence: 0.841452866666667

00:08:41.320 --> 00:08:43.455 Often these patients they'd get

NOTE Confidence: 0.841452866666667

00:08:43.455 --> 00:08:45.163 chemotherapy but sometimes they

NOTE Confidence: 0.841452866666667

00:08:45.163 --> 00:08:48.799 did not and and response was good.

NOTE Confidence: 0.841452866666667

00:08:48.800 --> 00:08:51.216 And so back in 2008 this was considered

NOTE Confidence: 0.841452866666667

00:08:51.216 --> 00:08:52.694 a provisional entity pediatric

NOTE Confidence: 0.841452866666667

00:08:52.694 --> 00:08:55.124 cochlemphoma with where you have these

NOTE Confidence: 0.841452866666667

00:08:55.124 --> 00:08:57.079 folkformers and kids that did well,

NOTE Confidence: 0.841452866666667

00:08:57.080 --> 00:08:59.348 they tended to have what they called

NOTE Confidence: 0.841452866666667

00:08:59.348 --> 00:09:01.559 grade 3 morphology expansive follicles,

NOTE Confidence: 0.841452866666667

00:09:01.560 --> 00:09:03.912 but it was clear that these

NOTE Confidence: 0.841452866666667

00:09:03.912 --> 00:09:04.696 pediatric cochlemphomas.

NOTE Confidence: 0.841452866666667

00:09:04.700 --> 00:09:06.140 Had many features indistinguishable

NOTE Confidence: 0.841452866666667

00:09:06.140 --> 00:09:07.940 from those seen in adults.

NOTE Confidence: 0.841452866666667

00:09:07.940 --> 00:09:10.140 And so at the time when I answered the field,

NOTE Confidence: 0.841452866666667

00:09:10.140 --> 00:09:11.900 there were some questions that came to mind.

NOTE Confidence: 0.841452866666667

00:09:11.900 --> 00:09:14.568 One is that as we got more

NOTE Confidence: 0.841452866666667

00:09:14.568 --> 00:09:15.099 and more experience,

NOTE Confidence: 0.841452866666667

00:09:15.100 --> 00:09:16.913 we realized that many of these patients

NOTE Confidence: 0.841452866666667

00:09:16.913 --> 00:09:18.237 had no progression or occurrence

NOTE Confidence: 0.841452866666667

00:09:18.237 --> 00:09:19.973 even with just excision of the node.

NOTE Confidence: 0.841452866666667

00:09:19.980 --> 00:09:23.380 And I began to see a lot of these cases

NOTE Confidence: 0.841452866666667

00:09:23.380 --> 00:09:25.216 presenting in patients with in their

NOTE Confidence: 0.841452866666667

00:09:25.216 --> 00:09:27.538 20s and 30s with the same features.

NOTE Confidence: 0.841452866666667

00:09:27.540 --> 00:09:28.340 So now the question is,

NOTE Confidence: 0.841452866666667

00:09:28.340 --> 00:09:30.488 are are these Grade 3 folliculars

NOTE Confidence: 0.841452866666667

00:09:30.488 --> 00:09:31.920 or the pediatric folliculars?

NOTE Confidence: 0.841452866666667

00:09:31.920 --> 00:09:33.341 And so we asked the question how

NOTE Confidence: 0.841452866666667

00:09:33.341 --> 00:09:34.493 can we actually distinguish these

NOTE Confidence: 0.841452866666667

00:09:34.493 --> 00:09:35.738 because it's going to actually

NOTE Confidence: 0.841452866666667

00:09:35.738 --> 00:09:37.550 make a big difference in care,

NOTE Confidence: 0.841452866666667

00:09:37.550 --> 00:09:39.320 how can we objectively define these.

NOTE Confidence: 0.841452866666667

00:09:39.320 --> 00:09:41.540 So we started by looking at 27,

NOTE Confidence: 0.841452866666667

00:09:41.540 --> 00:09:43.640 you know all the focal point of

NOTE Confidence: 0.841452866666667

00:09:43.640 --> 00:09:45.964 patients at MGH that were less than 40

NOTE Confidence: 0.841452866666667

00:09:45.964 --> 00:09:47.640 years of age and we found that they

NOTE Confidence: 0.841452866666667

00:09:47.640 --> 00:09:48.760 should have broke into two groups,

NOTE Confidence: 0.841452866666667

00:09:48.760 --> 00:09:51.862 one that were limited stage and

NOTE Confidence: 0.841452866666667

00:09:51.862 --> 00:09:54.154 one with advanced stage disease and

NOTE Confidence: 0.841452866666667

00:09:54.154 --> 00:09:56.461 the ones that were limited stage

NOTE Confidence: 0.841452866666667

00:09:56.461 --> 00:09:59.475 we did see a predominance in in in

NOTE Confidence: 0.841452866666667

00:09:59.475 --> 00:10:00.720 a male predominance.

NOTE Confidence: 0.841452866666667

00:10:00.720 --> 00:10:03.121 And we looked at a whole slew

NOTE Confidence: 0.841452866666667

00:10:03.121 --> 00:10:04.575 of pathological features to

NOTE Confidence: 0.841452866666667

00:10:04.575 --> 00:10:05.999 try to distinguish those.

NOTE Confidence: 0.841452866666667

00:10:06.000 --> 00:10:08.121 We did find that the the limited

NOTE Confidence: 0.841452866666667

00:10:08.121 --> 00:10:09.796 stage ones had large follicles

NOTE Confidence: 0.841452866666667

00:10:09.796 --> 00:10:11.878 and had a star sky pattern,

NOTE Confidence: 0.841452866666667

00:10:11.880 --> 00:10:14.160 but many of the other parameters

NOTE Confidence: 0.841452866666667

00:10:14.160 --> 00:10:16.435 didn't pan out to make a difference.

NOTE Confidence: 0.841452866666667

00:10:16.440 --> 00:10:18.496 But one thing that we noticed really made

NOTE Confidence: 0.841452866666667

00:10:18.496 --> 00:10:20.399 a difference was the BCL 2G arrangements.

NOTE Confidence: 0.841452866666667

00:10:20.400 --> 00:10:22.614 So all of the limited stage ones lacked BCL

NOTE Confidence: 0.841452866666667

00:10:22.614 --> 00:10:24.799 two arrangements and BCL 6 arrangements,

NOTE Confidence: 0.841452866666667

00:10:24.800 --> 00:10:27.056 and had a very high proliferation

NOTE Confidence: 0.841452866666667

00:10:27.056 --> 00:10:28.560 fraction greater than 30%.

NOTE Confidence: 0.841452866666667

00:10:28.560 --> 00:10:30.919 And they had the combination of them

NOTE Confidence: 0.841452866666667

00:10:30.920 --> 00:10:34.076 whereas the the Advanced Age ones,

NOTE Confidence: 0.938241032

00:10:34.080 --> 00:10:36.384 the majority did not have none of them

NOTE Confidence: 0.938241032

00:10:36.384 --> 00:10:38.880 had both and both of those features.

NOTE Confidence: 0.936804341333333

00:10:41.400 --> 00:10:43.416 So we thought well maybe this is something

NOTE Confidence: 0.936804341333333

00:10:43.416 --> 00:10:45.236 maybe maybe these two features the the,

NOTE Confidence: 0.936804341333333

00:10:45.240 --> 00:10:47.928 the BCL 2 gene arrangements and the

NOTE Confidence: 0.936804341333333

00:10:47.928 --> 00:10:49.454 proliferation fraction together could

NOTE Confidence: 0.936804341333333

00:10:49.454 --> 00:10:51.556 could pick these good behaving cases out.

NOTE Confidence: 0.936804341333333

00:10:51.556 --> 00:10:54.330 So then we looked at a second cohort of

NOTE Confidence: 0.936804341333333

00:10:54.330 --> 00:10:56.920 adult patients less than 40 years of age.

NOTE Confidence: 0.936804341333333

00:10:56.920 --> 00:10:58.648 Right. And we've broken them up

NOTE Confidence: 0.936804341333333

00:10:58.648 --> 00:11:00.528 into four categories, you know,

NOTE Confidence: 0.936804341333333

00:11:00.528 --> 00:11:02.040 translocation, no translocation,

NOTE Confidence: 0.936804341333333

00:11:02.040 --> 00:11:04.040 no translocation and high proliferation,

NOTE Confidence: 0.936804341333333

00:11:04.040 --> 00:11:06.100 low proliferation index and the

NOTE Confidence: 0.936804341333333

00:11:06.100 --> 00:11:08.160 ones that had no translocation

NOTE Confidence: 0.936804341333333

00:11:08.231 --> 00:11:10.359 and high proliferation fraction,

NOTE Confidence: 0.936804341333333

00:11:10.360 --> 00:11:14.077 all of them ended up being stage one disease.

NOTE Confidence: 0.936804341333333

00:11:14.080 --> 00:11:15.856 Many of them did get chemotherapy

NOTE Confidence: 0.936804341333333

00:11:15.856 --> 00:11:18.319 and in terms of progression relapse,

NOTE Confidence: 0.936804341333333

00:11:18.320 --> 00:11:20.196 none of them had progression or relapse.

NOTE Confidence: 0.936804341333333

00:11:20.200 --> 00:11:21.551 And actually I remember reading the notes

NOTE Confidence: 0.936804341333333

00:11:21.551 --> 00:11:23.280 and it would be like these surprising notes,

NOTE Confidence: 0.936804341333333

00:11:23.280 --> 00:11:24.471 Oh my gosh,

NOTE Confidence: 0.936804341333333

00:11:24.471 --> 00:11:27.250 this is patients doing really well and.

NOTE Confidence: 0.936804341333333

00:11:27.250 --> 00:11:29.371 And but this trend was really important

NOTE Confidence: 0.936804341333333

00:11:29.371 --> 00:11:31.930 to us and this is just a looking at

NOTE Confidence: 0.936804341333333

00:11:31.930 --> 00:11:34.006 Kaplan Meyer sort of curve showing

NOTE Confidence: 0.936804341333333

00:11:34.006 --> 00:11:35.914 the differences between the the cases

NOTE Confidence: 0.936804341333333

00:11:35.914 --> 00:11:38.163 that have BC L2 arrangements and High

NOTE Confidence: 0.936804341333333

00:11:38.163 --> 00:11:40.410 proliferation index and the ones that didn't.

NOTE Confidence: 0.936804341333333

00:11:40.410 --> 00:11:42.966 At the same time Elaine Jaffe's

NOTE Confidence: 0.936804341333333

00:11:42.966 --> 00:11:45.298 group described that these these

NOTE Confidence: 0.936804341333333

00:11:45.298 --> 00:11:48.850 pediatric follicular lymphoma cases.

NOTE Confidence: 0.936804341333333

00:11:48.850 --> 00:11:50.250 Had a very different morphology.

NOTE Confidence: 0.936804341333333

00:11:50.250 --> 00:11:52.224 So they're the morphology was not

NOTE Confidence: 0.936804341333333

00:11:52.224 --> 00:11:54.232 that of typical Centra blast where

NOTE Confidence: 0.936804341333333

00:11:54.232 --> 00:11:56.416 you can see these larger cells with

NOTE Confidence: 0.936804341333333

00:11:56.416 --> 00:11:58.905 these nucleoli sort of centers sort

NOTE Confidence: 0.936804341333333

00:11:58.905 --> 00:12:00.645 of touching nuclear membranes.

NOTE Confidence: 0.936804341333333

00:12:00.650 --> 00:12:02.974 They were more of a medium sized

NOTE Confidence: 0.936804341333333

00:12:02.974 --> 00:12:05.078 blastoid type phenotype and for that

NOTE Confidence: 0.936804341333333

00:12:05.078 --> 00:12:06.823 reason suggested that we shouldn't

NOTE Confidence: 0.936804341333333

00:12:06.823 --> 00:12:08.289 grade these these these cases.

NOTE Confidence: 0.936804341333333

00:12:08.289 --> 00:12:10.296 And when you look when we looked at

NOTE Confidence: 0.936804341333333

00:12:10.296 --> 00:12:11.943 all of our case at MGH we we found

NOTE Confidence: 0.936804341333333

00:12:12.001 --> 00:12:13.688 that there were two sort of peaks,

NOTE Confidence: 0.936804341333333

00:12:13.690 --> 00:12:16.306 so the pediatric type focal from a peak.

NOTE Confidence: 0.936804341333333

00:12:16.310 --> 00:12:17.417 Peaked in adolescence,

NOTE Confidence: 0.936804341333333

00:12:17.417 --> 00:12:20.000 but you can see that it tailed

NOTE Confidence: 0.936804341333333

00:12:20.071 --> 00:12:22.746 into adulthood versus.

NOTE Confidence: 0.936804341333333

00:12:22.746 --> 00:12:24.882 They took the classic focalforma which

NOTE Confidence: 0.936804341333333

00:12:24.882 --> 00:12:27.390 as we know peaks in the in the 6th,

NOTE Confidence: 0.936804341333333

00:12:27.390 --> 00:12:28.200 7th decade,

NOTE Confidence: 0.936804341333333

00:12:28.200 --> 00:12:30.630 but it's in this intermediate range

NOTE Confidence: 0.936804341333333

00:12:30.630 --> 00:12:33.293 where it becomes important to be

NOTE Confidence: 0.936804341333333

00:12:33.293 --> 00:12:36.710 able to distinguish the difference.

NOTE Confidence: 0.936804341333333

00:12:36.710 --> 00:12:39.419 So from this we proposed that there was a

NOTE Confidence: 0.936804341333333

00:12:39.419 --> 00:12:42.038 highly indolent subset of focalforma which.

NOTE Confidence: 0.936804341333333

00:12:42.040 --> 00:12:44.308 Occurred in patients which were not likely

NOTE Confidence: 0.936804341333333

00:12:44.308 --> 00:12:46.959 to progress and did not require chemotherapy.

NOTE Confidence: 0.936804341333333

00:12:46.960 --> 00:12:48.675 Characterized by the lack of the B,

NOTE Confidence: 0.936804341333333

00:12:48.680 --> 00:12:49.350 CL2B, C,

NOTE Confidence: 0.936804341333333

00:12:49.350 --> 00:12:50.690 L6 arrangements and high

NOTE Confidence: 0.936804341333333

00:12:50.690 --> 00:12:51.360 proliferation fraction,

NOTE Confidence: 0.936804341333333

00:12:51.360 --> 00:12:54.600 and we hypothesize that they were

NOTE Confidence: 0.936804341333333

00:12:54.600 --> 00:12:56.724 biologically distinct and common in

NOTE Confidence: 0.936804341333333

00:12:56.724 --> 00:12:58.116 adolescents and young adults,

NOTE Confidence: 0.936804341333333

00:12:58.120 --> 00:13:01.396 but can occur in older patients.

NOTE Confidence: 0.936804341333333

00:13:01.400 --> 00:13:02.159 At the time,

NOTE Confidence: 0.936804341333333

00:13:02.159 --> 00:13:03.677 we were really excited about this,

NOTE Confidence: 0.936804341333333

00:13:03.680 --> 00:13:07.544 but we realized we saw a phenomenon that.

NOTE Confidence: 0.936804341333333

00:13:07.550 --> 00:13:07.918 You know,

NOTE Confidence: 0.936804341333333

00:13:07.918 --> 00:13:08.470 we hadn't really,

NOTE Confidence: 0.936804341333333

00:13:08.470 --> 00:13:09.875 we they were histologically similar

NOTE Confidence: 0.936804341333333

00:13:09.875 --> 00:13:11.773 to high grateful lymphoma in some ways

NOTE Confidence: 0.936804341333333

00:13:11.773 --> 00:13:13.341 and there was no direct evidence that

NOTE Confidence: 0.936804341333333

00:13:13.341 --> 00:13:15.086 the ones that occurred in adults were

NOTE Confidence: 0.936804341333333

00:13:15.086 --> 00:13:17.394 equivalent to the ones that occurred in kids.

NOTE Confidence: 0.936804341333333

00:13:17.394 --> 00:13:18.387 And practically speaking,

NOTE Confidence: 0.936804341333333

00:13:18.390 --> 00:13:18.928 we noticed,

NOTE Confidence: 0.936804341333333

00:13:18.928 --> 00:13:20.811 I noticed that a lot of patients

NOTE Confidence: 0.936804341333333

00:13:20.811 --> 00:13:22.549 who presented young patients,

NOTE Confidence: 0.936804341333333

00:13:22.550 --> 00:13:23.390 it depended their,

NOTE Confidence: 0.936804341333333

00:13:23.390 --> 00:13:25.350 their therapy depended upon who they saw.

NOTE Confidence: 0.936804341333333

00:13:25.350 --> 00:13:27.415 So if they saw a pediatric pediatric

NOTE Confidence: 0.936804341333333

00:13:27.415 --> 00:13:28.909 oncologist they would be quickly,

NOTE Confidence: 0.936804341333333

00:13:28.910 --> 00:13:30.595 they would be observed and

NOTE Confidence: 0.936804341333333

00:13:30.595 --> 00:13:31.943 they would do fine.

NOTE Confidence: 0.936804341333333

00:13:31.950 --> 00:13:33.630 And if they saw an adult

NOTE Confidence: 0.936804341333333

00:13:33.630 --> 00:13:34.750 oncologist they'd basically be

NOTE Confidence: 0.941930833333333

00:13:34.804 --> 00:13:36.740 given our chop and they would do fine.

NOTE Confidence: 0.941930833333333

00:13:36.740 --> 00:13:39.458 So we I thought it was important to go

NOTE Confidence: 0.941930833333333

00:13:39.458 --> 00:13:42.139 further to define these objectively so that

NOTE Confidence: 0.941930833333333

00:13:42.140 --> 00:13:44.620 basically to avoid unnecessary therapy.

NOTE Confidence: 0.941930833333333

00:13:44.620 --> 00:13:46.456 And so the question hypothesis is

NOTE Confidence: 0.941930833333333

00:13:46.456 --> 00:13:48.108 that pediatric type filial fund

NOTE Confidence: 0.941930833333333

00:13:48.108 --> 00:13:49.818 is biologically distinct and we

NOTE Confidence: 0.941930833333333

00:13:49.818 --> 00:13:51.612 wanted to look at the mutational

NOTE Confidence: 0.941930833333333

00:13:51.612 --> 00:13:53.080 profile differences between the two.

NOTE Confidence: 0.941930833333333

00:13:53.080 --> 00:13:54.060 Now to do this,

NOTE Confidence: 0.941930833333333

00:13:54.060 --> 00:13:56.072 we had to leverage colleagues from

NOTE Confidence: 0.941930833333333

00:13:56.072 --> 00:13:57.768 different institutions across the

NOTE Confidence: 0.941930833333333

00:13:57.768 --> 00:14:00.318 country to get these uncommon cases.

NOTE Confidence: 0.941930833333333

00:14:00.320 --> 00:14:02.816 So we put together 44 cases

NOTE Confidence: 0.941930833333333

00:14:02.816 --> 00:14:04.480 of limited stage disease,

NOTE Confidence: 0.941930833333333

00:14:04.480 --> 00:14:06.330 so we were not including

NOTE Confidence: 0.941930833333333

00:14:06.330 --> 00:14:07.440 advanced stage disease,

NOTE Confidence: 0.941930833333333

00:14:07.440 --> 00:14:09.680 no DLBCL and basically split them up

NOTE Confidence: 0.941930833333333

00:14:09.680 --> 00:14:11.392 into pediatric type focal components

NOTE Confidence: 0.941930833333333

00:14:11.392 --> 00:14:13.793 defined by the BC L2 rearrangement and

NOTE Confidence: 0.941930833333333

00:14:13.793 --> 00:14:15.574 high proliferation fraction versus the

NOTE Confidence: 0.941930833333333

00:14:15.574 --> 00:14:18.341 ones that either had BC L2 arrangement

NOTE Confidence: 0.941930833333333

00:14:18.341 --> 00:14:21.846 or locally low proliferation fraction.

NOTE Confidence: 0.941930833333333

00:14:21.850 --> 00:14:24.055 And we found when we did this again that

NOTE Confidence: 0.941930833333333

00:14:24.055 --> 00:14:26.083 the the ones that we call pediatric

NOTE Confidence: 0.941930833333333

00:14:26.083 --> 00:14:29.142 type had a had a male predominance were

NOTE Confidence: 0.941930833333333

00:14:29.142 --> 00:14:31.410 mostly involving the head and neck.

NOTE Confidence: 0.941930833333333

00:14:31.410 --> 00:14:33.402 And when we looked at the ones above

NOTE Confidence: 0.941930833333333

00:14:33.402 --> 00:14:35.126 older than 18 or younger than 18,

NOTE Confidence: 0.941930833333333

00:14:35.130 --> 00:14:37.839 which is the classic definition of pediatric

NOTE Confidence: 0.941930833333333

00:14:37.839 --> 00:14:40.249 and how sometimes these were defined,

NOTE Confidence: 0.941930833333333

00:14:40.250 --> 00:14:42.482 they had a similar breakdown male

NOTE Confidence: 0.941930833333333

00:14:42.482 --> 00:14:44.788 predominance and head and neck predominance.

NOTE Confidence: 0.941930833333333

00:14:44.788 --> 00:14:47.278 And in terms of therapy,

NOTE Confidence: 0.941930833333333

00:14:47.280 --> 00:14:49.782 a lot of the limited stage

NOTE Confidence: 0.941930833333333

00:14:49.782 --> 00:14:52.000 ones did get chemotherapy,

NOTE Confidence: 0.941930833333333

00:14:52.000 --> 00:14:54.295 the classic folk problems did

NOTE Confidence: 0.941930833333333

00:14:54.295 --> 00:14:55.755 get chemotherapy and radiation.

NOTE Confidence: 0.941930833333333

00:14:55.760 --> 00:14:58.000 A lot of the ones that were

NOTE Confidence: 0.941930833333333

00:14:58.000 --> 00:15:00.640 called PTFL did get excision,

NOTE Confidence: 0.941930833333333

00:15:00.640 --> 00:15:03.240 but the sort of rates were very different.

NOTE Confidence: 0.941930833333333

00:15:03.240 --> 00:15:04.776 So the the patients,

NOTE Confidence: 0.941930833333333

00:15:04.776 --> 00:15:08.412 the PTFL patients did really well with

NOTE Confidence: 0.941930833333333

00:15:08.412 --> 00:15:11.840 with remission no evidence of disease.

NOTE Confidence: 0.941930833333333

00:15:11.840 --> 00:15:14.241 Whereas the the the ones that were

NOTE Confidence: 0.941930833333333

00:15:14.241 --> 00:15:16.853 more classic had a BC L2 arrangement

NOTE Confidence: 0.941930833333333

00:15:16.853 --> 00:15:19.115 or high a low proliferation fraction

NOTE Confidence: 0.941930833333333

00:15:19.120 --> 00:15:21.668 were much more likely to recur and

NOTE Confidence: 0.941930833333333

00:15:21.668 --> 00:15:22.760 transformation events occurred

NOTE Confidence: 0.941930833333333

00:15:22.822 --> 00:15:23.998 solely in that group.

NOTE Confidence: 0.941930833333333

00:15:24.000 --> 00:15:27.405 This is a Kappa Meyer and when you

NOTE Confidence: 0.941930833333333

00:15:27.405 --> 00:15:29.280 looked at the breakdown between

NOTE Confidence: 0.941930833333333

00:15:29.280 --> 00:15:30.996 pediatric type in older patients

NOTE Confidence: 0.941930833333333

00:15:30.996 --> 00:15:33.377 and and less than 18 or older than

NOTE Confidence: 0.941930833333333

00:15:33.377 --> 00:15:36.554 18 the the the the the same trends

NOTE Confidence: 0.941930833333333

00:15:36.554 --> 00:15:40.330 occurred in terms of doing well.

NOTE Confidence: 0.941930833333333

00:15:40.330 --> 00:15:43.252 So we then looked at the the the

NOTE Confidence: 0.941930833333333

00:15:43.252 --> 00:15:45.257 molecular dynamics of these lesions

NOTE Confidence: 0.941930833333333

00:15:45.257 --> 00:15:48.070 and we found that the pediatric

NOTE Confidence: 0.941930833333333

00:15:48.070 --> 00:15:51.101 type colliculum informas had a very

NOTE Confidence: 0.941930833333333

00:15:51.101 --> 00:15:53.458 low genomic complexity with you

NOTE Confidence: 0.941930833333333

00:15:53.458 --> 00:15:55.796 know much fewer genome copy number

NOTE Confidence: 0.941930833333333

00:15:55.796 --> 00:15:57.528 alterations and genomic events

NOTE Confidence: 0.941930833333333

00:15:57.530 --> 00:16:00.290 than the typical for lymphomas.

NOTE Confidence: 0.941930833333333

00:16:00.290 --> 00:16:02.621 And there was a high higher predominance

NOTE Confidence: 0.941930833333333

00:16:02.621 --> 00:16:05.466 of loss of heterozygosity 1P36 and

NOTE Confidence: 0.941930833333333

00:16:05.466 --> 00:16:09.270 deletions at that site of TNFRSF 14.

NOTE Confidence: 0.941930833333333

00:16:09.270 --> 00:16:11.376 But the most striking thing was

NOTE Confidence: 0.941930833333333

00:16:11.376 --> 00:16:13.633 when we looked at the pediatric

NOTE Confidence: 0.941930833333333

00:16:13.633 --> 00:16:16.342 type whether lower than 18 or older

NOTE Confidence: 0.941930833333333

00:16:16.342 --> 00:16:17.835 than 18 that the classic.

NOTE Confidence: 0.941930833333333

00:16:17.835 --> 00:16:20.353 So we we did a targeted panel that

NOTE Confidence: 0.941930833333333

00:16:20.353 --> 00:16:22.143 included pretty much every gene

NOTE Confidence: 0.941930833333333

00:16:22.143 --> 00:16:23.774 that had been mutated reported to be

NOTE Confidence: 0.941930833333333

00:16:23.774 --> 00:16:25.269 mutated in focal form at the time

NOTE Confidence: 0.938815971428571

00:16:27.390 --> 00:16:31.470 and which was much more than here almost 100

NOTE Confidence: 0.94312881

00:16:33.670 --> 00:16:34.922 I think 100 genes.

NOTE Confidence: 0.94312881

00:16:34.922 --> 00:16:37.236 These these on the left are sort

NOTE Confidence: 0.94312881

00:16:37.236 --> 00:16:39.402 of the ones that are classically

NOTE Confidence: 0.94312881

00:16:39.402 --> 00:16:41.170 mutated in full lymphoma.

NOTE Confidence: 0.94312881

00:16:41.170 --> 00:16:43.502 And you can see that the even limited

NOTE Confidence: 0.94312881

00:16:43.502 --> 00:16:46.268 stage ones that had BC L2 arrangement

NOTE Confidence: 0.94312881

00:16:46.268 --> 00:16:48.224 or low proliferation fraction had a

NOTE Confidence: 0.94312881

00:16:48.224 --> 00:16:50.247 high frequency of these mutations.

NOTE Confidence: 0.94312881

00:16:50.250 --> 00:16:51.690 But they were essentially

NOTE Confidence: 0.94312881

00:16:51.690 --> 00:16:53.490 not present in the PTF,

NOTE Confidence: 0.94312881

00:16:53.490 --> 00:16:56.087 the pediatric type full lymphomas other than

NOTE Confidence: 0.94528522

00:16:58.130 --> 00:17:00.530 TNFTNFTNFRSF 14.

NOTE Confidence: 0.94528522

00:17:00.530 --> 00:17:02.750 We also did helexome on a on a on on

NOTE Confidence: 0.94528522

00:17:02.821 --> 00:17:05.245 six of the cases and we didn't find

NOTE Confidence: 0.94528522

00:17:05.245 --> 00:17:07.278 any recurrent mutations at the time.

NOTE Confidence: 0.94528522

00:17:07.280 --> 00:17:09.902 And this histogram just shows the purple

NOTE Confidence: 0.94528522

00:17:09.902 --> 00:17:12.219 and the blue represents 2 big subsets

NOTE Confidence: 0.94528522

00:17:12.219 --> 00:17:14.853 of typical classic focal FOMA and the

NOTE Confidence: 0.94528522

00:17:14.853 --> 00:17:17.640 most common mutations including ML,

NOTE Confidence: 0.94528522

00:17:17.640 --> 00:17:19.340 L2, probably PA,

NOTE Confidence: 0.94528522

00:17:19.340 --> 00:17:21.040 lot of chromatin modifying genes.

NOTE Confidence: 0.94528522

00:17:21.040 --> 00:17:22.608 And you can see that the the low

NOTE Confidence: 0.94528522

00:17:22.608 --> 00:17:23.871 frequency in the pediatric type

NOTE Confidence: 0.94528522

00:17:23.871 --> 00:17:25.236 focalforma other than the Tina,

NOTE Confidence: 0.94528522

00:17:25.240 --> 00:17:26.494 Tina, RSF 14.

NOTE Confidence: 0.94528522

00:17:26.494 --> 00:17:29.002 So we thought that they suggested

NOTE Confidence: 0.94528522

00:17:29.002 --> 00:17:31.797 definitely these were biologically distinct

NOTE Confidence: 0.94528522

00:17:31.800 --> 00:17:34.558 and we were pretty happy with that.

NOTE Confidence: 0.94528522

00:17:34.560 --> 00:17:36.576 And but we weren't clear what was driving

NOTE Confidence: 0.94528522

00:17:36.576 --> 00:17:38.101 the the pediatric type proliferation

NOTE Confidence: 0.94528522

00:17:38.101 --> 00:17:40.341 but at the same time we submitted

NOTE Confidence: 0.94528522

00:17:40.393 --> 00:17:42.199 to to blood and we're very excited.

NOTE Confidence: 0.94528522

00:17:42.200 --> 00:17:45.297 We we received a review saying well you

NOTE Confidence: 0.94528522

00:17:45.297 --> 00:17:47.033 only looked at six cases of whole EXIM.

NOTE Confidence: 0.94528522

00:17:47.040 --> 00:17:48.867 We think you should look up more

NOTE Confidence: 0.94528522

00:17:48.867 --> 00:17:50.616 and that was a little depressing

NOTE Confidence: 0.94528522

00:17:50.616 --> 00:17:52.620 at the time but it was turned

NOTE Confidence: 0.94528522

00:17:52.620 --> 00:17:54.770 out to be very fruitful and maybe

NOTE Confidence: 0.94528522

00:17:54.770 --> 00:17:56.960 appreciate the review process because

NOTE Confidence: 0.94528522

00:17:56.960 --> 00:17:59.000 we we basically sequenced all,

NOTE Confidence: 0.94528522

00:17:59.000 --> 00:18:01.200 the whole EXIM and all we found that.

NOTE Confidence: 0.94528522

00:18:01.200 --> 00:18:02.916 About 60% of these cases had

NOTE Confidence: 0.94528522

00:18:02.916 --> 00:18:04.999 mutations in the MAP kinase pathway,

NOTE Confidence: 0.94528522

00:18:05.000 --> 00:18:07.655 particularly MAP 2K1 at a

NOTE Confidence: 0.94528522

00:18:07.655 --> 00:18:10.300 a targeted hotspot site,

NOTE Confidence: 0.94528522

00:18:10.300 --> 00:18:13.708 which is present in this negative

NOTE Confidence: 0.94528522

00:18:13.708 --> 00:18:16.786 regulatory region of map 2K1 and represents

NOTE Confidence: 0.94528522

00:18:16.786 --> 00:18:19.144 a mutation that's commonly seen in

NOTE Confidence: 0.94528522

00:18:19.144 --> 00:18:21.199 other neoplasms including melanomas,

NOTE Confidence: 0.94528522

00:18:21.200 --> 00:18:23.208 ****** hand cell hysterocytosis,

NOTE Confidence: 0.94528522

00:18:23.208 --> 00:18:25.718 B rap negative hairy cells,

NOTE Confidence: 0.94528522

00:18:25.720 --> 00:18:26.002 etcetera.

NOTE Confidence: 0.94528522

00:18:26.002 --> 00:18:28.258 So we were very excited about this and

NOTE Confidence: 0.94528522

00:18:28.258 --> 00:18:30.365 we thought this clearly demonstrated

NOTE Confidence: 0.94528522

00:18:30.365 --> 00:18:32.575 that these were biologically distinct.

NOTE Confidence: 0.94528522

00:18:32.580 --> 00:18:35.492 And at the time three groups were

NOTE Confidence: 0.94528522

00:18:35.492 --> 00:18:38.100 working on this simultaneously.

NOTE Confidence: 0.94528522

00:18:38.100 --> 00:18:40.260 And this is sort of a summary of

NOTE Confidence: 0.94528522

00:18:40.260 --> 00:18:42.759 all the cases in those three groups.

NOTE Confidence: 0.94528522

00:18:42.760 --> 00:18:45.707 You can see that again the common

NOTE Confidence: 0.94528522

00:18:45.707 --> 00:18:47.895 mutations typical and full lymphoma

NOTE Confidence: 0.94528522

00:18:47.895 --> 00:18:50.842 are very lowly are very rare in

NOTE Confidence: 0.94528522

00:18:50.842 --> 00:18:53.336 pediatric type and the map 2K1 and

NOTE Confidence: 0.94528522

00:18:53.336 --> 00:18:55.056 the MAP kinase pathway mutations

NOTE Confidence: 0.94528522

00:18:55.056 --> 00:18:57.485 really seem to be to drive the

NOTE Confidence: 0.94528522

00:18:57.485 --> 00:18:58.833 pediatric type molecular ones.

NOTE Confidence: 0.94528522

00:18:58.840 --> 00:19:00.940 The the one that is shared is

NOTE Confidence: 0.94528522

00:19:00.940 --> 00:19:03.440 the mutation of TNFRSF 14.

NOTE Confidence: 0.94528522

00:19:03.440 --> 00:19:05.744 So from this we you know we use

NOTE Confidence: 0.94528522

00:19:05.744 --> 00:19:07.633 the term pediatric type lymphoma

NOTE Confidence: 0.94528522

00:19:07.633 --> 00:19:10.510 to to include the fact that these

NOTE Confidence: 0.94528522

00:19:10.587 --> 00:19:12.319 occur in older patients.

NOTE Confidence: 0.94528522

00:19:12.320 --> 00:19:14.581 And you know from that that sort

NOTE Confidence: 0.94528522

00:19:14.581 --> 00:19:16.945 of helped define the current our

NOTE Confidence: 0.94528522

00:19:16.945 --> 00:19:18.713 current understanding of pediatric

NOTE Confidence: 0.94528522

00:19:18.713 --> 00:19:21.480 type of lymphoma and and in the

NOTE Confidence: 0.94528522

00:19:21.480 --> 00:19:23.905 DOUBLECHILD 2016 that was the help

NOTE Confidence: 0.94528522

00:19:23.905 --> 00:19:25.557 define the the characteristics.

NOTE Confidence: 0.94528522

00:19:25.560 --> 00:19:27.390 Some of the important features are

NOTE Confidence: 0.94528522

00:19:27.390 --> 00:19:29.555 that grading is not used for these

NOTE Confidence: 0.94528522

00:19:29.555 --> 00:19:31.768 for the reasons I mentioned there's

NOTE Confidence: 0.94528522

00:19:31.768 --> 00:19:34.960 never any advantage disease and

NOTE Confidence: 0.94528522

00:19:34.960 --> 00:19:36.584 there's no component of the LBCL.

NOTE Confidence: 0.94528522

00:19:36.584 --> 00:19:38.600 So if there is a if you see the

NOTE Confidence: 0.94528522

00:19:38.600 --> 00:19:41.420 LBCL that excludes this diagnosis.

NOTE Confidence: 0.94528522

00:19:41.420 --> 00:19:43.020 And the clinical implications that

NOTE Confidence: 0.94528522

00:19:43.020 --> 00:19:44.944 both children and adults with PTFL

NOTE Confidence: 0.94528522

00:19:44.944 --> 00:19:46.888 do not likely need chemotherapy when

NOTE Confidence: 0.94528522

00:19:46.888 --> 00:19:48.546 they're when they're diagnosed that

NOTE Confidence: 0.94528522

00:19:48.546 --> 00:19:51.898 way and the map kinase mutation may help,

NOTE Confidence: 0.94528522

00:19:51.900 --> 00:19:53.460 may help with the diagnosis.

NOTE Confidence: 0.94528522

00:19:53.460 --> 00:19:55.315 So going back to the patient I

NOTE Confidence: 0.94528522

00:19:55.315 --> 00:19:56.480 described that was originally

NOTE Confidence: 0.94528522

00:19:56.480 --> 00:19:58.334 diagnosed as grade three O 3,

NOTE Confidence: 0.94528522

00:19:58.340 --> 00:20:01.735 this was re diagnosed by Elaine Jaffe

NOTE Confidence: 0.924502703333334

00:20:01.740 --> 00:20:04.820 at at, at, at as pediatric type

NOTE Confidence: 0.924502703333334

00:20:04.820 --> 00:20:07.560 for lymphoma but at the site where

NOTE Confidence: 0.924502703333334

00:20:07.560 --> 00:20:09.420 the patient was being treated.

NOTE Confidence: 0.924502703333334

00:20:09.420 --> 00:20:10.440 They were still going to give

NOTE Confidence: 0.924502703333334

00:20:10.440 --> 00:20:11.388 our chop because they weren't

NOTE Confidence: 0.924502703333334

00:20:11.388 --> 00:20:12.296 familiar with this entity.

NOTE Confidence: 0.924502703333334

00:20:12.300 --> 00:20:14.708 And so I received a call from the

NOTE Confidence: 0.924502703333334

00:20:14.708 --> 00:20:17.231 mom about this and had seen the paper

NOTE Confidence: 0.924502703333334

00:20:17.231 --> 00:20:20.152 and I refer them to our ecology team

NOTE Confidence: 0.924502703333334

00:20:20.152 --> 00:20:22.172 who who basically were suggested

NOTE Confidence: 0.924502703333334

00:20:22.180 --> 00:20:23.885 observation and the patient's doing

NOTE Confidence: 0.924502703333334

00:20:23.885 --> 00:20:26.255 well and I still occasionally get calls

NOTE Confidence: 0.924502703333334

00:20:26.255 --> 00:20:29.193 from families about this where the

NOTE Confidence: 0.924502703333334

00:20:29.193 --> 00:20:31.540 the thought is to treat aggressively

NOTE Confidence: 0.924502703333334

00:20:31.540 --> 00:20:34.428 and they're always actually happy

NOTE Confidence: 0.924502703333334

00:20:34.428 --> 00:20:36.920 to to to feel like I've made some

NOTE Confidence: 0.924502703333334

00:20:36.920 --> 00:20:39.279 impact on the care of these patients.

NOTE Confidence: 0.924502703333334

00:20:39.280 --> 00:20:40.984 I just wanted to emphasize that

NOTE Confidence: 0.924502703333334

00:20:40.984 --> 00:20:43.140 it's really important to to follow

NOTE Confidence: 0.924502703333334

00:20:43.140 --> 00:20:46.656 all the criteria and this this

NOTE Confidence: 0.924502703333334

00:20:46.656 --> 00:20:48.712 case sort of demonstrates why.

NOTE Confidence: 0.924502703333334

00:20:48.712 --> 00:20:52.273 So this is a 25 year old with

NOTE Confidence: 0.924502703333334

00:20:52.273 --> 00:20:53.599 cervical lymphadenopathy,

NOTE Confidence: 0.924502703333334

00:20:53.600 --> 00:20:56.414 the nice space dot star sky pattern

NOTE Confidence: 0.924502703333334

00:20:56.414 --> 00:20:59.096 and the sort of blastoid type

NOTE Confidence: 0.924502703333334

00:20:59.096 --> 00:21:02.725 cells and these are CD10 positive

NOTE Confidence: 0.924502703333334

00:21:02.725 --> 00:21:06.250 with B cells with a relatively

NOTE Confidence: 0.924502703333334

00:21:06.250 --> 00:21:08.562 high proliferation fraction and.

NOTE Confidence: 0.924502703333334

00:21:08.570 --> 00:21:10.202 No BC L2 expression.

NOTE Confidence: 0.924502703333334

00:21:10.202 --> 00:21:12.446 So this was brought to me as a as a

NOTE Confidence: 0.924502703333334

00:21:12.446 --> 00:21:14.144 consult as whether this could be a

NOTE Confidence: 0.924502703333334

00:21:14.144 --> 00:21:15.685 nice classic case of pediatric type

NOTE Confidence: 0.924502703333334

00:21:15.685 --> 00:21:17.540 lymphoma and I asked you know did

NOTE Confidence: 0.924502703333334

00:21:17.540 --> 00:21:20.998 you do the fish for B CL2B C L6 and

NOTE Confidence: 0.924502703333334

00:21:20.998 --> 00:21:23.291 they didn't and it was frustrating

NOTE Confidence: 0.924502703333334

00:21:23.291 --> 00:21:25.440 for them but it after came back

NOTE Confidence: 0.924502703333334

00:21:25.505 --> 00:21:27.410 with ABC L6 gene rearrangement.

NOTE Confidence: 0.924502703333334

00:21:27.410 --> 00:21:30.182 So this is essentially a conventional

NOTE Confidence: 0.924502703333334

00:21:30.182 --> 00:21:31.964 BC L2 negative lymphoma.

NOTE Confidence: 0.924502703333334

00:21:31.964 --> 00:21:34.328 So it's not a pediatric type

NOTE Confidence: 0.924502703333334

00:21:34.330 --> 00:21:36.510 which and these do occur.

NOTE Confidence: 0.924502703333334

00:21:36.510 --> 00:21:38.790 And interestingly later there was

NOTE Confidence: 0.924502703333334

00:21:38.790 --> 00:21:40.456 you know months later there was a

NOTE Confidence: 0.924502703333334

00:21:40.456 --> 00:21:41.622 axillary lymph adenopathy and they

NOTE Confidence: 0.924502703333334

00:21:41.622 --> 00:21:43.036 re biopsied it because they were a

NOTE Confidence: 0.924502703333334

00:21:43.036 --> 00:21:44.234 little concerned by the diagnosis

NOTE Confidence: 0.924502703333334

00:21:44.234 --> 00:21:46.083 that it was not called pediatric type

NOTE Confidence: 0.924502703333334

00:21:46.083 --> 00:21:49.695 this time the the Falcons were much smaller.

NOTE Confidence: 0.924502703333334

00:21:49.695 --> 00:21:52.785 There was this eosinophil deposits and

NOTE Confidence: 0.924502703333334

00:21:52.790 --> 00:21:55.184 deposits that looked a little bit like

NOTE Confidence: 0.924502703333334

00:21:55.184 --> 00:21:57.350 Dutcher bodies and some of the cells,

NOTE Confidence: 0.924502703333334

00:21:57.350 --> 00:22:00.520 the cells were relatively small.

NOTE Confidence: 0.924502703333334

00:22:00.520 --> 00:22:02.806 The follicles were or small smaller

NOTE Confidence: 0.924502703333334

00:22:02.806 --> 00:22:05.152 again CD10 positive but this time

NOTE Confidence: 0.924502703333334

00:22:05.152 --> 00:22:07.027 the proliferation fraction was low

NOTE Confidence: 0.924502703333334

00:22:07.027 --> 00:22:09.318 and there was BC L2 expression.

NOTE Confidence: 0.924502703333334

00:22:09.320 --> 00:22:12.116 So clearly a case of classic

NOTE Confidence: 0.924502703333334

00:22:12.116 --> 00:22:13.514 classic folk lymphoma.

NOTE Confidence: 0.924502703333334

00:22:13.520 --> 00:22:15.050 So it's really important to follow

NOTE Confidence: 0.924502703333334

00:22:15.050 --> 00:22:16.385 all those guidelines and make

NOTE Confidence: 0.924502703333334

00:22:16.385 --> 00:22:17.720 the diagnosis of pediatric type.

NOTE Confidence: 0.924502703333334

00:22:17.720 --> 00:22:19.799 It's not just the BC L2 negativity.

NOTE Confidence: 0.933963975

00:22:22.400 --> 00:22:24.745 So from that you know we looked

NOTE Confidence: 0.933963975

00:22:24.745 --> 00:22:26.568 at several subtypes of folk

NOTE Confidence: 0.933963975

00:22:26.568 --> 00:22:28.800 lymphoma to to try to understand.

NOTE Confidence: 0.933963975

00:22:28.800 --> 00:22:32.160 Them and sort of the variation in in

NOTE Confidence: 0.933963975

00:22:32.160 --> 00:22:34.160 their behavior and I'll just mention

NOTE Confidence: 0.933963975

00:22:34.160 --> 00:22:36.781 while the other one which is the primary

NOTE Confidence: 0.933963975

00:22:36.781 --> 00:22:38.425 utaneous follicle central lymphoma

NOTE Confidence: 0.933963975

00:22:38.425 --> 00:22:40.600 which are localized skin lesions.

NOTE Confidence: 0.933963975

00:22:40.600 --> 00:22:43.600 They by definition don't are not

NOTE Confidence: 0.933963975

00:22:43.600 --> 00:22:45.845 systemic disease and they often

NOTE Confidence: 0.933963975

00:22:45.845 --> 00:22:47.560 occur in the head and the trunk.

NOTE Confidence: 0.933963975

00:22:47.560 --> 00:22:49.640 They have an excellent prognosis.

NOTE Confidence: 0.933963975

00:22:49.640 --> 00:22:52.118 Again they're negative for BC L2,

NOTE Confidence: 0.933963975

00:22:52.120 --> 00:22:54.600 they lack BC L2 rearrangements.

NOTE Confidence: 0.933963975

00:22:54.600 --> 00:22:57.060 So they're clear similarities to

NOTE Confidence: 0.933963975

00:22:57.060 --> 00:22:59.520 to pediatric type of lymphoma.

NOTE Confidence: 0.933963975

00:22:59.520 --> 00:23:02.560 So we wanted to investigate to see if

NOTE Confidence: 0.933963975

00:23:02.560 --> 00:23:05.120 we can understand understand these.

NOTE Confidence: 0.933963975

00:23:05.120 --> 00:23:09.236 We did, we did a study where we

NOTE Confidence: 0.933963975

00:23:09.240 --> 00:23:13.240 basically got primary continuous,

NOTE Confidence: 0.933963975

00:23:13.240 --> 00:23:15.630 continuous focal pharma and and

NOTE Confidence: 0.933963975

00:23:15.630 --> 00:23:17.542 secondary primarily being ones

NOTE Confidence: 0.933963975

00:23:17.542 --> 00:23:19.853 that occurred in the skin and

NOTE Confidence: 0.933963975

00:23:19.853 --> 00:23:21.518 actually and and not systemically.

NOTE Confidence: 0.933963975

00:23:21.520 --> 00:23:23.355 Initially there were four cases

NOTE Confidence: 0.933963975

00:23:23.355 --> 00:23:25.565 and we occasionally see this where

NOTE Confidence: 0.933963975

00:23:25.565 --> 00:23:27.707 it it fulfills the features of of.

NOTE Confidence: 0.933963975

00:23:27.710 --> 00:23:29.630 A primary utanous follicle center lymphoma,

NOTE Confidence: 0.933963975

00:23:29.630 --> 00:23:31.550 but then years later, months later,

NOTE Confidence: 0.933963975

00:23:31.550 --> 00:23:34.150 years later has systemic dissemination.

NOTE Confidence: 0.933963975

00:23:34.150 --> 00:23:36.388 So we had four of those.

NOTE Confidence: 0.933963975

00:23:36.390 --> 00:23:38.868 And then we also had secondary utanous

NOTE Confidence: 0.933963975

00:23:38.868 --> 00:23:40.691 follicle center lymphoma where there

NOTE Confidence: 0.933963975

00:23:40.691 --> 00:23:42.436 was a previous systemic disease

NOTE Confidence: 0.933963975

00:23:42.436 --> 00:23:44.609 involving the skin or they currently

NOTE Confidence: 0.933963975

00:23:44.609 --> 00:23:46.745 presented systemically and in the skin.

NOTE Confidence: 0.933963975

00:23:46.750 --> 00:23:49.654 And so the hypothesis that these

NOTE Confidence: 0.933963975

00:23:49.654 --> 00:23:52.100 would be genetically distinct and

NOTE Confidence: 0.933963975

00:23:52.100 --> 00:23:54.650 there may be initial differences.

NOTE Confidence: 0.933963975

00:23:54.650 --> 00:23:57.242 So you can see here that the median range,

NOTE Confidence: 0.933963975

00:23:57.250 --> 00:23:58.950 age range was approximately

NOTE Confidence: 0.933963975

00:23:58.950 --> 00:24:00.650 similar across these groups

NOTE Confidence: 0.942266216

00:24:03.330 --> 00:24:08.387 and in terms of therapeutic therapy

NOTE Confidence: 0.942266216

00:24:08.387 --> 00:24:10.889 was pretty it was pretty similar

NOTE Confidence: 0.942266216

00:24:10.890 --> 00:24:13.438 as well and the the patients with

NOTE Confidence: 0.942266216

00:24:13.438 --> 00:24:14.923 primary continuous fossil center

NOTE Confidence: 0.942266216

00:24:14.923 --> 00:24:17.240 of course did much better and but

NOTE Confidence: 0.942266216

00:24:17.240 --> 00:24:19.585 they they did they did recur as

NOTE Confidence: 0.942266216

00:24:19.585 --> 00:24:22.193 these as these cases do recur but

NOTE Confidence: 0.942266216

00:24:22.193 --> 00:24:24.480 the patients still do very well.

NOTE Confidence: 0.942266216

00:24:24.480 --> 00:24:26.482 One of the interesting things we noted

NOTE Confidence: 0.942266216

00:24:26.482 --> 00:24:28.540 was that the recurrences tended to

NOTE Confidence: 0.942266216

00:24:28.540 --> 00:24:31.520 occur at the similar same location.

NOTE Confidence: 0.942266216

00:24:31.520 --> 00:24:32.672 So you can see.

NOTE Confidence: 0.942266216

00:24:32.672 --> 00:24:34.976 You can see that here where the

NOTE Confidence: 0.942266216

00:24:34.976 --> 00:24:37.635 recurrences occurred pretty much at the

NOTE Confidence: 0.942266216

00:24:37.635 --> 00:24:40.304 same sites as the primary location,

NOTE Confidence: 0.942266216

00:24:40.304 --> 00:24:42.345 even the secondary recurrences.

NOTE Confidence: 0.942266216

00:24:42.345 --> 00:24:46.095 Whereas the the four cases that

NOTE Confidence: 0.942266216

00:24:46.095 --> 00:24:49.816 actually eventually recurred in a

NOTE Confidence: 0.942266216

00:24:49.816 --> 00:24:52.000 in a different site or were more.

NOTE Confidence: 0.942266216

00:24:52.000 --> 00:24:53.800 Groups presented systemically

NOTE Confidence: 0.942266216

00:24:53.800 --> 00:24:56.142 had quite interesting locations

NOTE Confidence: 0.942266216

00:24:56.142 --> 00:24:59.280 such as the dura breast and

NOTE Confidence: 0.950317

00:25:01.640 --> 00:25:04.744 bone marrow, and so one of

NOTE Confidence: 0.950317

00:25:04.744 --> 00:25:06.700 the things we noted was that

NOTE Confidence: 0.950317

00:25:06.787 --> 00:25:09.199 these secondary cutaneous folk,

NOTE Confidence: 0.950317

00:25:09.200 --> 00:25:11.680 the secondary cutaneous folk lymphomas,

NOTE Confidence: 0.950317

00:25:11.680 --> 00:25:13.912 harbored a lot of the mutations

NOTE Confidence: 0.950317

00:25:13.912 --> 00:25:15.850 in the chromatin modifying genes.

NOTE Confidence: 0.950317

00:25:15.850 --> 00:25:18.070 Whereas again the primary cutaneous had

NOTE Confidence: 0.950317

00:25:18.070 --> 00:25:20.768 fewer although they were more they were they,

NOTE Confidence: 0.950317

00:25:20.770 --> 00:25:22.178 they occurred more frequently.

NOTE Confidence: 0.950317

00:25:22.178 --> 00:25:25.024 I mean they they they had there were

NOTE Confidence: 0.950317

00:25:25.024 --> 00:25:27.039 more cases than in primary pediatric

NOTE Confidence: 0.950317

00:25:27.039 --> 00:25:29.831 type and that that had these but they

NOTE Confidence: 0.950317

00:25:29.831 --> 00:25:32.646 were definitely much fewer than the

NOTE Confidence: 0.950317

00:25:32.646 --> 00:25:34.900 secondary cutaneous folk lymphomas,

NOTE Confidence: 0.950317

00:25:34.900 --> 00:25:38.762 the few cases that actually presented

NOTE Confidence: 0.950317

00:25:38.762 --> 00:25:41.290 like primary cutaneous falcal,

NOTE Confidence: 0.950317

00:25:41.290 --> 00:25:44.070 center lymphoma but then.

NOTE Confidence: 0.950317

00:25:44.070 --> 00:25:45.918 Showed systemic involvement

NOTE Confidence: 0.950317

00:25:45.918 --> 00:25:47.150 interestingly showed

NOTE Confidence: 0.9462458875

00:25:49.350 --> 00:25:51.850 more frequent mutations in these

NOTE Confidence: 0.9462458875

00:25:51.850 --> 00:25:53.350 chromatin modifying genes.

NOTE Confidence: 0.91897162

00:25:55.390 --> 00:25:59.990 So we proposed an algorithm to try to

NOTE Confidence: 0.91897162

00:25:59.990 --> 00:26:03.630 predict cases or to to help support

NOTE Confidence: 0.91897162

00:26:03.630 --> 00:26:07.122 cases that we that would potentially

NOTE Confidence: 0.91897162

00:26:07.122 --> 00:26:10.020 behave either at the time of diagnosis

NOTE Confidence: 0.91897162

00:26:10.020 --> 00:26:12.534 or later with systemic disease and.

NOTE Confidence: 0.91897162

00:26:12.534 --> 00:26:15.662 Basically the way it works is 1

NOTE Confidence: 0.91897162

00:26:15.662 --> 00:26:18.776 criteria is having both mutations in

NOTE Confidence: 0.91897162

00:26:18.776 --> 00:26:22.882 KMTTD and Kreb BP or having more than

NOTE Confidence: 0.91897162

00:26:22.882 --> 00:26:25.347 three chromatin modifier gene mutate,

NOTE Confidence: 0.91897162

00:26:25.350 --> 00:26:28.101 more than 3 mutations and chromatin modifier

NOTE Confidence: 0.91897162

00:26:28.101 --> 00:26:30.710 genes or the presence of BCLTG arrangement.

NOTE Confidence: 0.91897162

00:26:30.710 --> 00:26:33.986 And we found that if you had more than two

NOTE Confidence: 0.937570026666667

00:26:37.110 --> 00:26:39.406 of these two or more of these criteria

NOTE Confidence: 0.937570026666667

00:26:39.406 --> 00:26:41.277 that there was a very high risk.

NOTE Confidence: 0.937570026666667

00:26:41.280 --> 00:26:43.572 That this represented a lesion that

NOTE Confidence: 0.937570026666667

00:26:43.572 --> 00:26:46.235 was going to behave more systemically.

NOTE Confidence: 0.937570026666667

00:26:46.235 --> 00:26:48.760 And just to demonstrate this,

NOTE Confidence: 0.937570026666667

00:26:48.760 --> 00:26:50.312 these are few cases.

NOTE Confidence: 0.937570026666667

00:26:50.312 --> 00:26:53.220 This is 1 case of Prime Minister

NOTE Confidence: 0.937570026666667

00:26:53.220 --> 00:26:55.536 Falcon Center Oklahoma with that was

NOTE Confidence: 0.937570026666667

00:26:55.536 --> 00:26:57.960 had no BC L2 generated in the 74

NOTE Confidence: 0.937570026666667

00:26:57.960 --> 00:27:01.238 year old in the scalp and this had

NOTE Confidence: 0.937570026666667

00:27:01.238 --> 00:27:03.794 classic there was CD20 positive cells,

NOTE Confidence: 0.937570026666667

00:27:03.800 --> 00:27:06.716 somewhat of a high proliferation fraction.

NOTE Confidence: 0.937570026666667

00:27:06.720 --> 00:27:09.457 Again the cells were BC L2 negative.

NOTE Confidence: 0.937570026666667

00:27:09.460 --> 00:27:11.300 There was a relatively high,

NOTE Confidence: 0.937570026666667

00:27:11.300 --> 00:27:12.956 like I mentioned,

NOTE Confidence: 0.937570026666667

00:27:12.956 --> 00:27:14.670 proliferation fraction and there

NOTE Confidence: 0.937570026666667

00:27:14.670 --> 00:27:16.805 was no mutations in these in the

NOTE Confidence: 0.937570026666667

00:27:16.805 --> 00:27:18.740 common chromatin modifier genes.

NOTE Confidence: 0.937570026666667

00:27:18.740 --> 00:27:22.188 There was no B CL2B C L6 arrangement

NOTE Confidence: 0.937570026666667

00:27:22.188 --> 00:27:25.470 and this patient to the end of follow

NOTE Confidence: 0.937570026666667

00:27:25.470 --> 00:27:27.678 up never had any systemic disease,

NOTE Confidence: 0.937570026666667

00:27:27.678 --> 00:27:28.896 but there was.

NOTE Confidence: 0.937570026666667

00:27:28.900 --> 00:27:31.350 Here's another case of a 47 year

NOTE Confidence: 0.937570026666667

00:27:31.350 --> 00:27:34.976 old male who had a forehead lesion.

NOTE Confidence: 0.937570026666667

00:27:34.980 --> 00:27:37.220 The I HC showed terminal Center B cells,

NOTE Confidence: 0.937570026666667

00:27:37.220 --> 00:27:40.480 but these were BC L2.

NOTE Confidence: 0.937570026666667

00:27:40.480 --> 00:27:42.676 Positive there was no BC L2,

NOTE Confidence: 0.937570026666667

00:27:42.680 --> 00:27:44.910 B CL6GG arrangements.

NOTE Confidence: 0.937570026666667

00:27:44.910 --> 00:27:47.721 It was signed out as possible cutaneous

NOTE Confidence: 0.937570026666667

00:27:47.721 --> 00:27:50.526 falcocenter lymphoma primary but these

NOTE Confidence: 0.937570026666667

00:27:50.526 --> 00:27:53.762 this turned out to have mutations

NOTE Confidence: 0.937570026666667

00:27:53.762 --> 00:28:00.000 prebby P and KTM2D No B CL2B C L6

NOTE Confidence: 0.937570026666667

00:28:00.000 --> 00:28:02.064 arrangements and then imaging at

NOTE Confidence: 0.937570026666667

00:28:02.064 --> 00:28:03.944 the time showed concurrent nodal

NOTE Confidence: 0.937570026666667

00:28:03.944 --> 00:28:06.186 involvement and then there was a 45

NOTE Confidence: 0.937570026666667

00:28:06.186 --> 00:28:08.950 year old with a male scalp lesion.

NOTE Confidence: 0.937570026666667

00:28:08.950 --> 00:28:11.270 Again,

NOTE Confidence: 0.937570026666667

00:28:11.270 --> 00:28:13.238 no B CL2B C L6 arrangement

NOTE Confidence: 0.937570026666667

00:28:13.238 --> 00:28:15.162 signed out as possible primary

NOTE Confidence: 0.937570026666667

00:28:15.162 --> 00:28:17.306 cutaneous Falco Center lymphoma.

NOTE Confidence: 0.937570026666667

00:28:17.310 --> 00:28:20.710 Again this had Kreb BPKTMTD

NOTE Confidence: 0.937570026666667

00:28:20.710 --> 00:28:23.310 mutations and ABC L2 arrangement.

NOTE Confidence: 0.937570026666667

00:28:23.310 --> 00:28:25.431 The imaging at the time should not

NOTE Confidence: 0.937570026666667

00:28:25.431 --> 00:28:27.070 no concurrent nodal involvement,

NOTE Confidence: 0.937570026666667

00:28:27.070 --> 00:28:29.254 so it was thought to be a primary

NOTE Confidence: 0.937570026666667

00:28:29.254 --> 00:28:30.750 cutaneous Falco center lymphoma.

NOTE Confidence: 0.937570026666667

00:28:30.750 --> 00:28:32.268 But thirteen months later there was

NOTE Confidence: 0.937570026666667

00:28:32.268 --> 00:28:33.947 involvement of the bone marrow and

NOTE Confidence: 0.937570026666667

00:28:33.947 --> 00:28:35.179 axillary lymph node involvement.

NOTE Confidence: 0.937570026666667

00:28:35.180 --> 00:28:35.762 So I think,

NOTE Confidence: 0.937570026666667

00:28:35.762 --> 00:28:36.926 I mean there's still has to

NOTE Confidence: 0.937570026666667

00:28:36.926 --> 00:28:38.100 be validation for this,

NOTE Confidence: 0.937570026666667

00:28:38.100 --> 00:28:42.139 but I think these parameters can help

NOTE Confidence: 0.937570026666667

00:28:42.140 --> 00:28:45.668 in what can sometimes be a difficult,

NOTE Confidence: 0.937570026666667

00:28:45.668 --> 00:28:47.388 in some difficult cases and

NOTE Confidence: 0.937570026666667

00:28:47.388 --> 00:28:48.420 trying to predict,

NOTE Confidence: 0.937570026666667

00:28:48.420 --> 00:28:50.675 maybe even help support when

NOTE Confidence: 0.937570026666667

00:28:50.675 --> 00:28:52.930 these patients should be followed

NOTE Confidence: 0.937570026666667

00:28:53.004 --> 00:28:55.260 carefully for systemic disease.

NOTE Confidence: 0.937570026666667

00:28:55.260 --> 00:28:58.536 So to summarize some of these

NOTE Confidence: 0.937570026666667

00:28:58.540 --> 00:28:59.716 subsets that I've described,

NOTE Confidence: 0.937570026666667

00:28:59.716 --> 00:29:01.620 you have classic focal Pharma with B,

NOTE Confidence: 0.937570026666667

00:29:01.620 --> 00:29:03.384 CL2B, C L6 arrangements.

NOTE Confidence: 0.937570026666667

00:29:03.384 --> 00:29:06.348 And krubby P mutations and KTMTD mutations,

NOTE Confidence: 0.937570026666667

00:29:06.348 --> 00:29:08.243 other chromatin modifying G mutations

NOTE Confidence: 0.937570026666667

00:29:08.243 --> 00:29:10.790 with a low proliferation fraction.

NOTE Confidence: 0.937570026666667

00:29:10.790 --> 00:29:12.866 And then you have which is

NOTE Confidence: 0.937570026666667

00:29:12.866 --> 00:29:13.904 classic focal FOMA.

NOTE Confidence: 0.937570026666667

00:29:13.910 --> 00:29:15.840 You have pediatric focal FOMA

NOTE Confidence: 0.937570026666667

00:29:15.840 --> 00:29:18.344 which lacks the BCL two BCL 6 and

NOTE Confidence: 0.937570026666667

00:29:18.344 --> 00:29:20.016 lacks these chromatin modifying G

NOTE Confidence: 0.937570026666667

00:29:20.016 --> 00:29:21.771 mutations but has kinase mutations

NOTE Confidence: 0.937570026666667

00:29:21.771 --> 00:29:24.309 has a high proliferation fraction.

NOTE Confidence: 0.937570026666667

00:29:24.310 --> 00:29:26.613 These are most likely not arising

NOTE Confidence: 0.937570026666667

00:29:26.613 --> 00:29:27.642 from the typical.

NOTE Confidence: 0.937570026666667

00:29:27.642 --> 00:29:29.700 Recursive cell in the bone marrow

NOTE Confidence: 0.937570026666667

00:29:29.766 --> 00:29:31.381 and where which derives the

NOTE Confidence: 0.937570026666667

00:29:31.381 --> 00:29:32.673 systemic form of this,

NOTE Confidence: 0.937570026666667

00:29:32.680 --> 00:29:34.680 but it's probably represents

NOTE Confidence: 0.937570026666667

00:29:34.680 --> 00:29:36.680 a locally stimulated clonal

NOTE Confidence: 0.937570026666667

00:29:36.680 --> 00:29:38.103 follicular proliferation and

NOTE Confidence: 0.937570026666667

00:29:38.103 --> 00:29:39.372 similarly primary containers.

NOTE Confidence: 0.937570026666667

00:29:39.372 --> 00:29:41.910 Falconceno FOMA is is most likely

NOTE Confidence: 0.937570026666667

00:29:41.973 --> 00:29:44.117 locally stimulated focal lymphoma,

NOTE Confidence: 0.937570026666667

00:29:44.120 --> 00:29:46.682 but a subset of these that appear

NOTE Confidence: 0.937570026666667

00:29:46.682 --> 00:29:49.524 to be this way may actually be more

NOTE Confidence: 0.937570026666667

00:29:49.524 --> 00:29:52.094 have a more of a systemic behavior

NOTE Confidence: 0.937570026666667

00:29:52.094 --> 00:29:54.602 and I think looking at these

NOTE Confidence: 0.937570026666667

00:29:54.602 --> 00:29:56.418 mutations these underlying mutations

NOTE Confidence: 0.937570026666667

00:29:56.418 --> 00:29:58.889 may help predict those few cases.

NOTE Confidence: 0.937570026666667

00:29:58.890 --> 00:30:01.878 So you know,

NOTE Confidence: 0.937570026666667

00:30:01.878 --> 00:30:05.030 one runs against the one runs against the

NOTE Confidence: 0.934890693333333

00:30:05.117 --> 00:30:07.752 wall when really trying to identify

NOTE Confidence: 0.934890693333333

00:30:07.752 --> 00:30:10.240 biomarkers with basically pieces

NOTE Confidence: 0.934890693333333

00:30:10.240 --> 00:30:12.100 of tissue and characterizing,

NOTE Confidence: 0.934890693333333

00:30:12.100 --> 00:30:13.930 we can look at mutational profiles,

NOTE Confidence: 0.934890693333333

00:30:13.930 --> 00:30:18.259 but I began to think about ways that

NOTE Confidence: 0.934890693333333

00:30:18.259 --> 00:30:20.727 we can get around that in terms of

NOTE Confidence: 0.934890693333333

00:30:20.730 --> 00:30:23.740 looking at snapshots of mutational

NOTE Confidence: 0.934890693333333

00:30:23.740 --> 00:30:26.148 landscapes or expression profiles.

NOTE Confidence: 0.934890693333333

00:30:26.150 --> 00:30:28.350 Wanted to do more functional,

NOTE Confidence: 0.934890693333333

00:30:28.350 --> 00:30:30.094 be able to look at the more functional

NOTE Confidence: 0.934890693333333

00:30:30.094 --> 00:30:31.958 behavior of these cells in a context

NOTE Confidence: 0.934890693333333

00:30:31.958 --> 00:30:33.930 of microenvironment or be able to

NOTE Confidence: 0.934890693333333

00:30:33.930 --> 00:30:35.705 assess responses in therapy directly.

NOTE Confidence: 0.934890693333333

00:30:35.710 --> 00:30:37.684 And so began to think about models

NOTE Confidence: 0.934890693333333

00:30:37.684 --> 00:30:40.614 to do this and we started to develop

NOTE Confidence: 0.934890693333333

00:30:40.614 --> 00:30:42.652 patient derived xenograft models and

NOTE Confidence: 0.934890693333333

00:30:42.652 --> 00:30:44.762 we initially developed a repository

NOTE Confidence: 0.934890693333333

00:30:44.762 --> 00:30:47.249 where you know the lymphoma cases

NOTE Confidence: 0.934890693333333

00:30:47.249 --> 00:30:50.422 go to the frozen lab and we have a

NOTE Confidence: 0.934890693333333

00:30:50.422 --> 00:30:52.450 pipeline where tissues that are large

NOTE Confidence: 0.934890693333333

00:30:52.519 --> 00:30:54.835 enough that are not small biopsies.

NOTE Confidence: 0.934890693333333

00:30:54.840 --> 00:30:57.101 We can set aside some tissue and

NOTE Confidence: 0.934890693333333

00:30:57.101 --> 00:30:59.626 viably freeze that tissue and consent

NOTE Confidence: 0.934890693333333

00:30:59.626 --> 00:31:02.956 the patients and then in a very non.

NOTE Confidence: 0.934890693333333

00:31:02.956 --> 00:31:04.630 So we're not targeting any particular

NOTE Confidence: 0.934890693333333

00:31:04.683 --> 00:31:06.398 Histology or anything like that.

NOTE Confidence: 0.934890693333333

00:31:06.400 --> 00:31:09.704 We've done this for about 200 cases to

NOTE Confidence: 0.934890693333333

00:31:09.704 --> 00:31:12.578 date and it's been a very fruitful effort.

NOTE Confidence: 0.934890693333333

00:31:12.578 --> 00:31:14.672 It allows us because we're not

NOTE Confidence: 0.934890693333333

00:31:14.672 --> 00:31:16.199 going after specific histhologies

NOTE Confidence: 0.934890693333333

00:31:16.199 --> 00:31:18.503 to occasional to capture rare cases

NOTE Confidence: 0.934890693333333

00:31:18.503 --> 00:31:20.933 that if you were going to try to

NOTE Confidence: 0.934890693333333

00:31:20.933 --> 00:31:23.938 target that would be hard to do.

NOTE Confidence: 0.934890693333333

00:31:23.940 --> 00:31:25.720 And diagnostic challenging cases

NOTE Confidence: 0.934890693333333

00:31:25.720 --> 00:31:28.803 and the the viably frozen being able

NOTE Confidence: 0.934890693333333

00:31:28.803 --> 00:31:31.190 to viably freeze them allows us to

NOTE Confidence: 0.934890693333333

00:31:31.190 --> 00:31:33.329 then thaw them out and generate

NOTE Confidence: 0.934890693333333

00:31:33.329 --> 00:31:35.820 PDX models or try to culture them.

NOTE Confidence: 0.934890693333333

00:31:35.820 --> 00:31:37.420 So it's been great.

NOTE Confidence: 0.934890693333333

00:31:37.420 --> 00:31:40.340 So that's sort of our resource for this.

NOTE Confidence: 0.934890693333333

00:31:40.340 --> 00:31:43.294 And then the way we generate these

NOTE Confidence: 0.934890693333333

00:31:43.294 --> 00:31:45.870 PDX models is we use NSG immunity

NOTE Confidence: 0.934890693333333

00:31:45.870 --> 00:31:47.940 deficient mice and we initially we

NOTE Confidence: 0.934890693333333

00:31:47.940 --> 00:31:49.866 take those little pieces of tissue

NOTE Confidence: 0.934890693333333

00:31:49.866 --> 00:31:51.618 which you can see on the.

NOTE Confidence: 0.934890693333333

00:31:51.620 --> 00:31:53.580 On the on the right here that we

NOTE Confidence: 0.934890693333333

00:31:53.580 --> 00:31:55.435 viably freeze and we implant them

NOTE Confidence: 0.934890693333333

00:31:55.435 --> 00:31:56.416 underneath the capsule,

NOTE Confidence: 0.934890693333333

00:31:56.420 --> 00:31:57.540 the the renal capsule.

NOTE Confidence: 0.934890693333333

00:31:57.540 --> 00:31:59.220 So we pop out the kidney,

NOTE Confidence: 0.934890693333333

00:31:59.220 --> 00:32:01.317 we make a little hole and we stick the

NOTE Confidence: 0.934890693333333

00:32:01.317 --> 00:32:03.548 tissue in there and then eventually it

NOTE Confidence: 0.934890693333333

00:32:03.548 --> 00:32:05.840 grows into something on the bottom now.

NOTE Confidence: 0.934890693333333

00:32:05.840 --> 00:32:08.562 So you can see it just becomes a tumor

NOTE Confidence: 0.934890693333333

00:32:08.562 --> 00:32:11.212 and we can then take that and we

NOTE Confidence: 0.934890693333333

00:32:11.212 --> 00:32:13.534 can keep propagating that over time.

NOTE Confidence: 0.934890693333333

00:32:13.540 --> 00:32:15.472 And these models are very helpful because

NOTE Confidence: 0.934890693333333

00:32:15.472 --> 00:32:18.067 you can use them to test different therapies.

NOTE Confidence: 0.934890693333333

00:32:18.070 --> 00:32:20.398 And you basically are growing more

NOTE Confidence: 0.934890693333333

00:32:20.398 --> 00:32:24.590 tissue that you can then study live

NOTE Confidence: 0.934890693333333

00:32:24.590 --> 00:32:29.188 and so we use this recently for in in a

NOTE Confidence: 0.934890693333333

00:32:29.188 --> 00:32:31.277 more aggressive disease and again I'll,

NOTE Confidence: 0.934890693333333

00:32:31.277 --> 00:32:33.720 I'll I'll start with the case of

NOTE Confidence: 0.934890693333333

00:32:33.797 --> 00:32:36.110 a 42 year old man presented to the

NOTE Confidence: 0.934890693333333

00:32:36.110 --> 00:32:37.990 Ed with junction night sweats,

NOTE Confidence: 0.934890693333333

00:32:37.990 --> 00:32:42.150 anemia and basically a lot of

NOTE Confidence: 0.934890693333333

00:32:42.150 --> 00:32:43.376 disease lymphadenopathy.

NOTE Confidence: 0.934890693333333

00:32:43.376 --> 00:32:47.054 A biopsy was rendered and basically

NOTE Confidence: 0.934890693333333

00:32:47.054 --> 00:32:50.453 we have these sheets of very large

NOTE Confidence: 0.934890693333333

00:32:50.453 --> 00:32:53.871 cells with a lot of areas of necrosis

NOTE Confidence: 0.934890693333333

00:32:53.871 --> 00:32:57.000 and apoptosis and the cells had were

NOTE Confidence: 0.934890693333333

00:32:57.089 --> 00:32:59.879 large and had plasma blastic sort

NOTE Confidence: 0.934890693333333

00:32:59.879 --> 00:33:02.224 of phenotype with very prominent

NOTE Confidence: 0.934890693333333

00:33:02.224 --> 00:33:04.650 nucleoli and essentially placed nuclei.

NOTE Confidence: 0.934890693333333

00:33:04.650 --> 00:33:07.650 The cells were strongly out positive

NOTE Confidence: 0.934890693333333

00:33:07.650 --> 00:33:10.492 and lacked CD20 and CD3B cell and

NOTE Confidence: 0.934890693333333

00:33:10.492 --> 00:33:14.020 T cell markers and had some CD138.

NOTE Confidence: 0.934890693333333

00:33:14.020 --> 00:33:16.828 So essentially this was the diagnostic

NOTE Confidence: 0.934890693333333

00:33:16.828 --> 00:33:19.780 of positive large B cell lymphoma

NOTE Confidence: 0.934689750909091

00:33:19.780 --> 00:33:23.344 which is driven by overexpression of

NOTE Confidence: 0.934689750909091

00:33:23.344 --> 00:33:25.980 anaplastic lymphoma kinase which is

NOTE Confidence: 0.934689750909091

00:33:25.980 --> 00:33:29.116 which was reported fairly recently in 97.

NOTE Confidence: 0.934689750909091

00:33:29.116 --> 00:33:32.276 These are extremely rare lymphoma cases.

NOTE Confidence: 0.934689750909091

00:33:32.276 --> 00:33:35.216 They often do express plasma

NOTE Confidence: 0.934689750909091

00:33:35.216 --> 00:33:36.980 cell plasoblastic markers.

NOTE Confidence: 0.934689750909091

00:33:36.980 --> 00:33:39.860 They lack typical B cell T cell markers.

NOTE Confidence: 0.934689750909091

00:33:39.860 --> 00:33:41.018 The patients tend to be young,

NOTE Confidence: 0.934689750909091

00:33:41.020 --> 00:33:42.160 the median age.

NOTE Confidence: 0.934689750909091

00:33:42.160 --> 00:33:44.356 In the 40s, one third of them

NOTE Confidence: 0.934689750909091

00:33:44.356 --> 00:33:45.940 are in the pediatric age group.

NOTE Confidence: 0.934689750909091

00:33:45.940 --> 00:33:47.872 The the patient, the the prognosis

NOTE Confidence: 0.934689750909091

00:33:47.872 --> 00:33:50.020 is dismal and many patients die,

NOTE Confidence: 0.934689750909091

00:33:50.020 --> 00:33:51.460 especially in advanced stage

NOTE Confidence: 0.934689750909091

00:33:51.460 --> 00:33:53.260 with within a few years.

NOTE Confidence: 0.934689750909091

00:33:53.260 --> 00:33:55.492 And because of the rarity of the disease

NOTE Confidence: 0.934689750909091

00:33:55.492 --> 00:33:57.857 and the aggressiveness of the disease,

NOTE Confidence: 0.934689750909091

00:33:57.860 --> 00:33:59.332 it's essentially impossible to

NOTE Confidence: 0.934689750909091

00:33:59.332 --> 00:34:01.540 to set up a clinical trial.

NOTE Confidence: 0.934689750909091

00:34:01.540 --> 00:34:04.528 The the ALC anaplastic lymphoma kinase

NOTE Confidence: 0.934689750909091

00:34:04.528 --> 00:34:07.853 is a receptive tyrosine kinase originally

NOTE Confidence: 0.934689750909091

00:34:07.853 --> 00:34:10.045 discovered in anaplastic large cell

NOTE Confidence: 0.934689750909091

00:34:10.045 --> 00:34:11.935 lymphoma which is an op positive.

NOTE Confidence: 0.934689750909091

00:34:11.940 --> 00:34:14.523 T cell from a 94 and these

NOTE Confidence: 0.934689750909091

00:34:14.523 --> 00:34:16.460 are driven by fusions.

NOTE Confidence: 0.934689750909091

00:34:16.460 --> 00:34:19.260 The alcos of a LC L's driven by

NOTE Confidence: 0.934689750909091

00:34:19.260 --> 00:34:22.988 NPM fusions with with the kinase

NOTE Confidence: 0.934689750909091

00:34:22.988 --> 00:34:24.785 part of the ALC protein.

NOTE Confidence: 0.934689750909091

00:34:24.785 --> 00:34:27.385 But the alcosa large B cell from us

NOTE Confidence: 0.934689750909091

00:34:27.385 --> 00:34:29.883 tend to have the partner tends to

NOTE Confidence: 0.934689750909091

00:34:29.883 --> 00:34:31.889 be clathrin so different than the

NOTE Confidence: 0.934689750909091

00:34:31.889 --> 00:34:34.030 ALC L's and these lead to downstream

NOTE Confidence: 0.934689750909091

00:34:34.030 --> 00:34:36.159 signaling and Jack stat and P cell

NOTE Confidence: 0.934689750909091

00:34:36.159 --> 00:34:41.800 gamma and Ras irk Pi through kinase pathways.

NOTE Confidence: 0.934689750909091

00:34:41.800 --> 00:34:43.837 But you can see that the prognosis

NOTE Confidence: 0.934689750909091

00:34:43.837 --> 00:34:46.052 is pretty dismal for patients that

NOTE Confidence: 0.934689750909091

00:34:46.052 --> 00:34:49.840 particularly in advanced stage disease

NOTE Confidence: 0.934689750909091

00:34:49.840 --> 00:34:52.780 and there has been as you probably

NOTE Confidence: 0.934689750909091

00:34:52.780 --> 00:34:55.056 know ALK inhibitors developed for

NOTE Confidence: 0.934689750909091

00:34:55.056 --> 00:34:57.840 these malignancies all kinds of lung,

NOTE Confidence: 0.934689750909091

00:34:57.840 --> 00:35:01.172 all kinds of with without fusions and

NOTE Confidence: 0.934689750909091

00:35:01.172 --> 00:35:04.638 that have been fairly effective so

NOTE Confidence: 0.934689750909091

00:35:04.638 --> 00:35:07.984 soon after the discovery of these fusions.

NOTE Confidence: 0.934689750909091

00:35:07.990 --> 00:35:10.348 The the first generation OP inhibitor

NOTE Confidence: 0.934689750909091

00:35:10.350 --> 00:35:13.087 was was was generated and and and

NOTE Confidence: 0.934689750909091

00:35:13.087 --> 00:35:16.716 shown to be effective in in different

NOTE Confidence: 0.934689750909091

00:35:16.716 --> 00:35:18.838 positive neoplasms and then then

NOTE Confidence: 0.934689750909091

00:35:18.838 --> 00:35:21.130 there was second and third generation

NOTE Confidence: 0.934689750909091

00:35:21.198 --> 00:35:23.440 inhibitors that had higher potency.

NOTE Confidence: 0.934689750909091

00:35:23.440 --> 00:35:26.590 So interestingly in in AL positive

NOTE Confidence: 0.934689750909091

00:35:26.590 --> 00:35:28.054 anaplastic large cell lymphoma

NOTE Confidence: 0.934689750909091

00:35:28.054 --> 00:35:31.074 there has been that you you get a

NOTE Confidence: 0.934689750909091

00:35:31.074 --> 00:35:32.867 significant response right and to

NOTE Confidence: 0.934689750909091

00:35:32.867 --> 00:35:34.529 this to chrosatini which is the

NOTE Confidence: 0.934689750909091

00:35:34.529 --> 00:35:36.130 first generation OP inhibitor but.

NOTE Confidence: 0.934689750909091

00:35:36.130 --> 00:35:38.314 Where the out positive large B cell

NOTE Confidence: 0.934689750909091

00:35:38.314 --> 00:35:40.816 from is you actually these patients

NOTE Confidence: 0.934689750909091

00:35:40.816 --> 00:35:43.714 often go through a several sequential

NOTE Confidence: 0.934689750909091

00:35:43.714 --> 00:35:45.484 highly aggressive chemotherapy

NOTE Confidence: 0.934689750909091

00:35:45.484 --> 00:35:47.758 regimens and don't do well.

NOTE Confidence: 0.934689750909091

00:35:47.758 --> 00:35:49.693 And anecdotally people have tried

NOTE Confidence: 0.934689750909091

00:35:49.693 --> 00:35:52.082 the chrysotonyb and basically the

NOTE Confidence: 0.934689750909091

00:35:52.082 --> 00:35:54.497 patients have maybe had partial

NOTE Confidence: 0.934689750909091

00:35:54.497 --> 00:35:56.220 response and then essentially failure.

NOTE Confidence: 0.934689750909091

00:35:56.220 --> 00:35:58.660 And so the few cases that have been

NOTE Confidence: 0.934689750909091

00:35:58.721 --> 00:36:00.846 reported in the literature anecdotally.

NOTE Confidence: 0.934689750909091

00:36:00.850 --> 00:36:03.818 Have have have shown like a a

NOTE Confidence: 0.934689750909091

00:36:03.818 --> 00:36:05.090 very short response,

NOTE Confidence: 0.934689750909091

00:36:05.090 --> 00:36:07.250 a transit partial response and then

NOTE Confidence: 0.934689750909091

00:36:07.250 --> 00:36:09.610 failure and that's only been a couple.

NOTE Confidence: 0.934689750909091

00:36:09.610 --> 00:36:12.076 So that that had been the status of the

NOTE Confidence: 0.934689750909091

00:36:12.076 --> 00:36:14.724 field and these patients just don't do well.

NOTE Confidence: 0.934689750909091

00:36:14.730 --> 00:36:17.130 So the rationale for PDX modeling

NOTE Confidence: 0.934689750909091

00:36:17.130 --> 00:36:19.505 is that you know to to look at the

NOTE Confidence: 0.934689750909091

00:36:19.505 --> 00:36:20.925 efficacy of these OP inhibitors and

NOTE Confidence: 0.934689750909091

00:36:20.925 --> 00:36:23.409 the the fact is we can't do clinical trials.

NOTE Confidence: 0.934689750909091

00:36:23.410 --> 00:36:26.250 So could we use these models to test

NOTE Confidence: 0.934689750909091

00:36:26.250 --> 00:36:29.118 these OP inhibitors in this disease.

NOTE Confidence: 0.934689750909091

00:36:29.120 --> 00:36:31.520 So again this is just another image

NOTE Confidence: 0.934689750909091

00:36:31.520 --> 00:36:32.920 of how we make these.

NOTE Confidence: 0.934689750909091

00:36:32.920 --> 00:36:34.852 So you can see the small tumor

NOTE Confidence: 0.934689750909091

00:36:34.852 --> 00:36:35.680 and and basically

NOTE Confidence: 0.935222009285714

00:36:37.720 --> 00:36:39.488 we pop that back in and then we

NOTE Confidence: 0.935222009285714

00:36:39.488 --> 00:36:41.038 generate a tumor on the kidney,

NOTE Confidence: 0.935222009285714

00:36:41.040 --> 00:36:44.800 this actually is a tumor and out tumor.

NOTE Confidence: 0.935222009285714

00:36:44.800 --> 00:36:46.969 So on the left here you can see the

NOTE Confidence: 0.935222009285714

00:36:46.969 --> 00:36:48.609 normal kidney on the right these

NOTE Confidence: 0.935222009285714

00:36:48.609 --> 00:36:50.352 go pretty quickly and you can sort

NOTE Confidence: 0.935222009285714

00:36:50.352 --> 00:36:52.371 of see the size of the tumor and

NOTE Confidence: 0.935222009285714

00:36:52.371 --> 00:36:54.197 this is bivalve then you can see

NOTE Confidence: 0.935222009285714

00:36:54.197 --> 00:36:55.787 the the consistency of the tumor.

NOTE Confidence: 0.935222009285714

00:36:55.790 --> 00:36:58.118 You can see here that the PDX tumor

NOTE Confidence: 0.935222009285714

00:36:58.118 --> 00:36:59.903 actually expresses ALC and maintains the

NOTE Confidence: 0.935222009285714

00:36:59.903 --> 00:37:02.287 mean of phenotype of the native and the

NOTE Confidence: 0.935222009285714

00:37:02.287 --> 00:37:03.822 similarities between the Histology of

NOTE Confidence: 0.935222009285714

00:37:03.822 --> 00:37:07.550 the PDX ALC and the original patient.

NOTE Confidence: 0.935222009285714

00:37:07.550 --> 00:37:10.494 So this was originally we did this with

NOTE Confidence: 0.935222009285714

00:37:10.494 --> 00:37:13.258 the with a case that we captured through

NOTE Confidence: 0.935222009285714

00:37:13.258 --> 00:37:15.632 our pipeline and then we consent to

NOTE Confidence: 0.935222009285714

00:37:15.632 --> 00:37:17.338 the patient who agreed to only do this

NOTE Confidence: 0.935222009285714

00:37:17.338 --> 00:37:19.268 if we if we named the mask after him,

NOTE Confidence: 0.935222009285714

00:37:19.270 --> 00:37:20.962 which we did.

NOTE Confidence: 0.935222009285714

00:37:20.962 --> 00:37:25.620 So our approach was to implant the tumor

NOTE Confidence: 0.935222009285714

00:37:25.620 --> 00:37:28.063 and we we use ultrasound to actually

NOTE Confidence: 0.935222009285714

00:37:28.063 --> 00:37:30.215 check for engrassmans and then we we

NOTE Confidence: 0.935222009285714

00:37:30.215 --> 00:37:32.387 check at a second time point to to

NOTE Confidence: 0.935222009285714

00:37:32.387 --> 00:37:34.740 assess for growth and then we sort of

NOTE Confidence: 0.935222009285714

00:37:34.740 --> 00:37:37.059 split the mice between vehicle and latinum.

NOTE Confidence: 0.935222009285714

00:37:37.060 --> 00:37:38.740 So the question is we know that chrosotinum,

NOTE Confidence: 0.935222009285714

00:37:38.740 --> 00:37:40.618 we knew that Chrosotinum wasn't working,

NOTE Confidence: 0.935222009285714

00:37:40.620 --> 00:37:43.574 could second and third generation be helpful

NOTE Confidence: 0.935222009285714

00:37:43.574 --> 00:37:46.739 and so that's what we initially did so.

NOTE Confidence: 0.935222009285714

00:37:46.740 --> 00:37:47.760 So what we found,

NOTE Confidence: 0.935222009285714

00:37:47.760 --> 00:37:49.290 so this is ultrasound imaging and

NOTE Confidence: 0.935222009285714

00:37:49.344 --> 00:37:51.104 it's it's hard to tell but this is

NOTE Confidence: 0.935222009285714

00:37:51.104 --> 00:37:52.698 all tumor and this is all tumor.

NOTE Confidence: 0.935222009285714

00:37:52.700 --> 00:37:55.045 So there was large tumors at the

NOTE Confidence: 0.935222009285714

00:37:55.045 --> 00:37:57.360 time when we started therapy and you

NOTE Confidence: 0.935222009285714

00:37:57.360 --> 00:38:00.013 can see within within a week this on

NOTE Confidence: 0.935222009285714

00:38:00.013 --> 00:38:01.915 the right this is responsive therapy

NOTE Confidence: 0.935222009285714

00:38:01.985 --> 00:38:04.218 with most of this is like fibrotic

NOTE Confidence: 0.935222009285714

00:38:04.218 --> 00:38:07.486 tissue and on the left that's the

NOTE Confidence: 0.935222009285714

00:38:07.486 --> 00:38:09.414 disease and so on the right here

NOTE Confidence: 0.935222009285714

00:38:09.414 --> 00:38:11.011 you can see sort of the difference.

NOTE Confidence: 0.935222009285714

00:38:11.011 --> 00:38:13.090 So at day zero this is the time of

NOTE Confidence: 0.935222009285714

00:38:13.143 --> 00:38:14.844 therapy and you can see the ones

NOTE Confidence: 0.935222009285714

00:38:14.844 --> 00:38:16.220 that didn't get therapy.

NOTE Confidence: 0.935222009285714

00:38:16.220 --> 00:38:16.570 Grew,

NOTE Confidence: 0.935222009285714

00:38:16.570 --> 00:38:17.620 continued to grow.

NOTE Confidence: 0.935222009285714

00:38:17.620 --> 00:38:19.720 The ones that got therapy responded

NOTE Confidence: 0.935222009285714

00:38:19.786 --> 00:38:21.931 well and and and you can see by

NOTE Confidence: 0.935222009285714

00:38:21.931 --> 00:38:23.579 Western that the activity is,

NOTE Confidence: 0.935222009285714

00:38:23.580 --> 00:38:26.574 is is functional in terms on the access

NOTE Confidence: 0.935222009285714

00:38:26.574 --> 00:38:29.544 in terms of eliminating phosphorylation

NOTE Confidence: 0.935222009285714

00:38:29.544 --> 00:38:33.285 of ALK and some downstream signaling.

NOTE Confidence: 0.935222009285714

00:38:33.285 --> 00:38:35.725 And so then we went back to look

NOTE Confidence: 0.935222009285714

00:38:35.725 --> 00:38:37.930 at chrysatinib versus latinib and

NOTE Confidence: 0.935222009285714

00:38:37.930 --> 00:38:40.215 interestingly we found that yes

NOTE Confidence: 0.935222009285714

00:38:40.220 --> 00:38:42.380 in comparison to the vehicle which

NOTE Confidence: 0.935222009285714

00:38:42.380 --> 00:38:44.304 could grew after after therapy

NOTE Confidence: 0.935222009285714

00:38:44.304 --> 00:38:46.409 chrysatnib did have this little.

NOTE Confidence: 0.935222009285714

00:38:46.410 --> 00:38:47.284 Temporary stalling,

NOTE Confidence: 0.935222009285714

00:38:47.284 --> 00:38:49.906 but then grew out afterwards and

NOTE Confidence: 0.935222009285714

00:38:49.906 --> 00:38:52.290 then the Latin showed growth.

NOTE Confidence: 0.935222009285714

00:38:52.290 --> 00:38:54.534 So we're excited that the model

NOTE Confidence: 0.935222009285714

00:38:54.534 --> 00:38:57.112 was sort of mimicking what we were

NOTE Confidence: 0.935222009285714

00:38:57.112 --> 00:38:58.506 seeing in patients.

NOTE Confidence: 0.935222009285714

00:38:58.506 --> 00:39:01.209 We also tried a lectin A,

NOTE Confidence: 0.935222009285714

00:39:01.209 --> 00:39:03.610 which is another ALK inhibitor

NOTE Confidence: 0.935222009285714

00:39:03.610 --> 00:39:06.170 and found similar effect.

NOTE Confidence: 0.935222009285714

00:39:06.170 --> 00:39:08.090 So this is Jake Soumerai,

NOTE Confidence: 0.935222009285714

00:39:08.090 --> 00:39:10.268 who I work closely with as

NOTE Confidence: 0.935222009285714

00:39:10.268 --> 00:39:11.357 a clinical colleague.

NOTE Confidence: 0.935222009285714

00:39:11.360 --> 00:39:14.492 From our data we then he reached out

NOTE Confidence: 0.935222009285714

00:39:14.492 --> 00:39:16.312 to colleagues at different institutions

NOTE Confidence: 0.935222009285714

00:39:16.312 --> 00:39:18.400 who happened to have patients without

NOTE Confidence: 0.935222009285714

00:39:18.400 --> 00:39:21.369 B cell lymphomas for patients and

NOTE Confidence: 0.935222009285714

00:39:21.369 --> 00:39:23.681 they all had the ones that we could

NOTE Confidence: 0.935222009285714

00:39:23.681 --> 00:39:25.576 had the classerin alk fusion,

NOTE Confidence: 0.935222009285714

00:39:25.576 --> 00:39:28.200 many of them had been on prior therapies,

NOTE Confidence: 0.935222009285714

00:39:28.200 --> 00:39:30.408 a couple of them had been

NOTE Confidence: 0.935222009285714

00:39:30.408 --> 00:39:31.512 not responsive resotinip.

NOTE Confidence: 0.928512966666667

00:39:31.520 --> 00:39:36.160 So we put them on this therapy.

NOTE Confidence: 0.928512966666667

00:39:36.160 --> 00:39:41.170 So the one of the patients actually.

NOTE Confidence: 0.928512966666667

00:39:41.170 --> 00:39:46.930 Respond responded and is now in that

NOTE Confidence: 0.928512966666667

00:39:46.930 --> 00:39:50.905 at this point almost three years in

NOTE Confidence: 0.928512966666667

00:39:50.905 --> 00:39:52.915 clinical remission on the right you

NOTE Confidence: 0.928512966666667

00:39:52.915 --> 00:39:55.419 can sort of see what the patient

NOTE Confidence: 0.928512966666667

00:39:55.419 --> 00:39:59.978 initial disease and sort of after we

NOTE Confidence: 0.928512966666667

00:39:59.978 --> 00:40:02.946 had one patient who you know that the

NOTE Confidence: 0.928512966666667

00:40:02.946 --> 00:40:04.230 initial actually I should say the

NOTE Confidence: 0.928512966666667

00:40:04.281 --> 00:40:06.810 initial patient that we made the PDX

NOTE Confidence: 0.928512966666667

00:40:06.810 --> 00:40:10.818 out of responded and then recurred.

NOTE Confidence: 0.928512966666667

00:40:10.818 --> 00:40:14.012 And basically the transplants could

NOTE Confidence: 0.928512966666667

00:40:14.012 --> 00:40:17.118 not be performed in time and he passed.

NOTE Confidence: 0.928512966666667

00:40:17.120 --> 00:40:19.208 But since then the team has sort of

NOTE Confidence: 0.928512966666667

00:40:19.208 --> 00:40:20.824 realized the importance of getting

NOTE Confidence: 0.928512966666667

00:40:20.824 --> 00:40:22.554 the transplant done up front.

NOTE Confidence: 0.928512966666667

00:40:22.560 --> 00:40:24.877 So in summary, one of the patients,

NOTE Confidence: 0.928512966666667

00:40:24.880 --> 00:40:27.208 it's three years out and there's

NOTE Confidence: 0.928512966666667

00:40:27.208 --> 00:40:29.184 another young patient who was

NOTE Confidence: 0.928512966666667

00:40:29.184 --> 00:40:33.185 transferred to us who's now about

NOTE Confidence: 0.928512966666667

00:40:33.185 --> 00:40:35.880 one one year out in clinical remission,

NOTE Confidence: 0.928512966666667

00:40:35.880 --> 00:40:39.440 one of the patients had a partial remission.

NOTE Confidence: 0.928512966666667

00:40:39.440 --> 00:40:44.768 So from this we've initiated a small

NOTE Confidence: 0.928512966666667

00:40:44.768 --> 00:40:48.032 clinical trial to to get more cases

NOTE Confidence: 0.928512966666667

00:40:48.032 --> 00:40:50.180 and generate more PDX models to

NOTE Confidence: 0.928512966666667

00:40:50.256 --> 00:40:52.578 study this and other agents further

NOTE Confidence: 0.928512966666667

00:40:52.578 --> 00:40:55.753 and to also begin to look do some

NOTE Confidence: 0.928512966666667

00:40:55.753 --> 00:40:58.075 functional studies on on these cases.

NOTE Confidence: 0.928512966666667

00:40:58.080 --> 00:41:00.090 Interestingly I also really fascinated

NOTE Confidence: 0.928512966666667

00:41:00.090 --> 00:41:02.100 by class of plastic lymphoma

NOTE Confidence: 0.928512966666667

00:41:02.160 --> 00:41:03.900 because they were discovered.

NOTE Confidence: 0.928512966666667

00:41:03.900 --> 00:41:06.404 Around the same time in actually 1997,

NOTE Confidence: 0.928512966666667

00:41:06.404 --> 00:41:07.796 they, they have,

NOTE Confidence: 0.928512966666667

00:41:07.796 --> 00:41:10.580 they both have plasma blocks morphology,

NOTE Confidence: 0.928512966666667

00:41:10.580 --> 00:41:12.873 they have a very similar expression

NOTE Confidence: 0.928512966666667

00:41:12.873 --> 00:41:15.111 profile with the difference being the

NOTE Confidence: 0.928512966666667

00:41:15.111 --> 00:41:17.059 ALC because they're driven by ALC.

NOTE Confidence: 0.928512966666667

00:41:17.060 --> 00:41:18.460 The ALC largely cell phones

NOTE Confidence: 0.928512966666667

00:41:18.460 --> 00:41:19.580 drive by ALC fusions,

NOTE Confidence: 0.928512966666667

00:41:19.580 --> 00:41:21.044 the the plasma blocks forms are

NOTE Confidence: 0.928512966666667

00:41:21.044 --> 00:41:22.340 driven by Epstein Barr virus.

NOTE Confidence: 0.928512966666667

00:41:22.340 --> 00:41:24.286 So but I actually think that the

NOTE Confidence: 0.928512966666667

00:41:24.286 --> 00:41:25.939 biologies are probably pretty similar.

NOTE Confidence: 0.928512966666667

00:41:25.940 --> 00:41:28.232 There have been some evidence of

NOTE Confidence: 0.928512966666667

00:41:28.232 --> 00:41:29.760 the similar downstream signaling

NOTE Confidence: 0.928512966666667

00:41:29.819 --> 00:41:31.229 pathways being involved.

NOTE Confidence: 0.928512966666667

00:41:31.230 --> 00:41:34.093 So we we've started to view these

NOTE Confidence: 0.928512966666667

00:41:34.093 --> 00:41:36.429 as class obelastic type of fomas

NOTE Confidence: 0.928512966666667

00:41:36.430 --> 00:41:38.985 that have that both have sort of

NOTE Confidence: 0.928512966666667

00:41:38.985 --> 00:41:40.058 clinical clinically disciplined

NOTE Confidence: 0.928512966666667

00:41:40.058 --> 00:41:41.828 prognosis and no clinical trials.

NOTE Confidence: 0.928512966666667

00:41:41.830 --> 00:41:44.541 And we've actually set up models

NOTE Confidence: 0.928512966666667

00:41:44.541 --> 00:41:46.998 of these of class obelastic FOMA as

NOTE Confidence: 0.928512966666667

00:41:46.998 --> 00:41:49.879 well to begin to understand the the

NOTE Confidence: 0.928512966666667

00:41:49.879 --> 00:41:51.984 biology and develop new targets.

NOTE Confidence: 0.928512966666667

00:41:51.990 --> 00:41:54.059 And if you think about B cell develop

NOTE Confidence: 0.928512966666667

00:41:54.059 --> 00:41:55.804 B cell development starting with

NOTE Confidence: 0.928512966666667

00:41:55.804 --> 00:41:58.468 the Pro B cell and the bone marrow

NOTE Confidence: 0.928512966666667

00:41:58.470 --> 00:42:00.530 going into mature B cell.

NOTE Confidence: 0.928512966666667

00:42:00.530 --> 00:42:02.966 And then before you get to plasma

NOTE Confidence: 0.928512966666667

00:42:02.966 --> 00:42:04.779 cell where myelomas are derived

NOTE Confidence: 0.928512966666667

00:42:04.779 --> 00:42:07.530 from most of our mature B cell

NOTE Confidence: 0.928512966666667

00:42:07.530 --> 00:42:09.108 lymphomas are coming from you know

NOTE Confidence: 0.928512966666667

00:42:09.108 --> 00:42:10.969 the more mature B cell phenotype.

NOTE Confidence: 0.928512966666667

00:42:10.970 --> 00:42:13.420 There is a a very transient plastoblast

NOTE Confidence: 0.928512966666667

00:42:13.420 --> 00:42:15.221 phase where probably the plastoblast

NOTE Confidence: 0.928512966666667

00:42:15.221 --> 00:42:17.629 lymphomas and the up large B cell

NOTE Confidence: 0.928512966666667

00:42:17.629 --> 00:42:19.945 lymphomas arise and it it may be

NOTE Confidence: 0.928512966666667

00:42:19.945 --> 00:42:21.560 because these are so transient

NOTE Confidence: 0.928512966666667

00:42:21.628 --> 00:42:23.686 why these are are less common.

NOTE Confidence: 0.928512966666667

00:42:23.690 --> 00:42:25.769 But a very interested in sort of

NOTE Confidence: 0.928512966666667

00:42:25.769 --> 00:42:27.344 characterizing these in our models

NOTE Confidence: 0.928512966666667

00:42:27.344 --> 00:42:28.596 and understanding biology and

NOTE Confidence: 0.928512966666667

00:42:28.596 --> 00:42:30.330 coming up with new targets.

NOTE Confidence: 0.928512966666667

00:42:30.330 --> 00:42:33.130 Some of the questions we'd like to answer

NOTE Confidence: 0.928512966666667

00:42:33.130 --> 00:42:35.255 are what mediates these crozotinib

NOTE Confidence: 0.928512966666667

00:42:35.255 --> 00:42:38.490 failures in out large B cell lymphoma.

NOTE Confidence: 0.928512966666667

00:42:38.490 --> 00:42:41.622 We think that it may have to do with

NOTE Confidence: 0.928512966666667

00:42:41.622 --> 00:42:44.430 P glycoprotein where we know that

NOTE Confidence: 0.928512966666667

00:42:44.430 --> 00:42:47.588 crozotinib may be a a target for that.

NOTE Confidence: 0.928512966666667

00:42:47.588 --> 00:42:50.901 And then also what mediates resistance

NOTE Confidence: 0.928512966666667

00:42:50.901 --> 00:42:53.613 downstream after some time with

NOTE Confidence: 0.928512966666667

00:42:53.613 --> 00:42:56.031 the with the second and third

NOTE Confidence: 0.928512966666667

00:42:56.031 --> 00:42:57.240 generation OP inhibitors.

NOTE Confidence: 0.928324273333333

00:42:57.240 --> 00:42:58.640 And and it's interesting,

NOTE Confidence: 0.928324273333333

00:42:58.640 --> 00:43:00.740 I think it's fascinating that the

NOTE Confidence: 0.928324273333333

00:43:00.801 --> 00:43:02.756 ALK fusions actually are actually

NOTE Confidence: 0.928324273333333

00:43:02.760 --> 00:43:04.916 in part a better prognosis in the

NOTE Confidence: 0.928324273333333

00:43:04.916 --> 00:43:06.498 anaplastic large cell infomas better

NOTE Confidence: 0.928324273333333

00:43:06.498 --> 00:43:08.874 than the ones that don't have the ALK,

NOTE Confidence: 0.928324273333333

00:43:08.880 --> 00:43:10.398 whereas in the B cell infomas,

NOTE Confidence: 0.928324273333333

00:43:10.400 --> 00:43:12.440 it's in parts of dismal prognosis.

NOTE Confidence: 0.928324273333333

00:43:12.440 --> 00:43:15.200 So we're beginning to look

NOTE Confidence: 0.928324273333333

00:43:15.200 --> 00:43:17.408 at trying to understand.

NOTE Confidence: 0.928324273333333

00:43:17.410 --> 00:43:18.890 Whether those differences are different

NOTE Confidence: 0.928324273333333

00:43:18.890 --> 00:43:21.018 by the differences in in the fusion

NOTE Confidence: 0.928324273333333

00:43:21.018 --> 00:43:22.818 partners versus whether it's the native

NOTE Confidence: 0.928324273333333

00:43:22.818 --> 00:43:24.487 environment of B cell versus T cells.

NOTE Confidence: 0.928324273333333

00:43:24.490 --> 00:43:27.990 We have some experiments there to to

NOTE Confidence: 0.928324273333333

00:43:27.990 --> 00:43:31.040 look at that and and again trying to

NOTE Confidence: 0.928324273333333

00:43:31.040 --> 00:43:32.590 understand the silicon pathways that

NOTE Confidence: 0.928324273333333

00:43:32.643 --> 00:43:34.554 may be in parallel to plasma blast

NOTE Confidence: 0.928324273333333

00:43:34.554 --> 00:43:36.409 lymphomas to begin to develop some

NOTE Confidence: 0.928324273333333

00:43:36.409 --> 00:43:38.034 targeted therapies for that disease

NOTE Confidence: 0.928324273333333

00:43:38.034 --> 00:43:40.810 which there are none at the time.

NOTE Confidence: 0.928324273333333

00:43:40.810 --> 00:43:45.250 So for this part we you know we we basically.

NOTE Confidence: 0.928324273333333

00:43:45.250 --> 00:43:47.650 I found the the use of the second,

NOTE Confidence: 0.928324273333333

00:43:47.650 --> 00:43:50.074 the high the next generation of

NOTE Confidence: 0.928324273333333

00:43:50.074 --> 00:43:52.258 inhibitors in this disease and

NOTE Confidence: 0.928324273333333

00:43:52.258 --> 00:43:54.986 illustrate the potential of PDX

NOTE Confidence: 0.928324273333333

00:43:54.986 --> 00:43:57.266 models to inform therapeutic options

NOTE Confidence: 0.928324273333333

00:43:57.266 --> 00:43:59.090 for patients with REMALIGNANCIES.

NOTE Confidence: 0.909565391578947

00:44:02.530 --> 00:44:04.636 And you know more efforts are

NOTE Confidence: 0.909565391578947

00:44:04.636 --> 00:44:06.790 currently needed to look at adding

NOTE Confidence: 0.909565391578947

00:44:06.790 --> 00:44:09.170 electinim to low Latin to first line.

NOTE Confidence: 0.909565391578947

00:44:09.170 --> 00:44:11.290 So currently the NCCN guidelines

NOTE Confidence: 0.909565391578947

00:44:11.290 --> 00:44:13.410 have been modified to include.

NOTE Confidence: 0.909565391578947

00:44:13.410 --> 00:44:15.699 This as a go to after failure

NOTE Confidence: 0.909565391578947

00:44:15.699 --> 00:44:17.490 with first line therapies,

NOTE Confidence: 0.909565391578947

00:44:17.490 --> 00:44:20.106 but we're looking to begin to look at

NOTE Confidence: 0.909565391578947

00:44:20.106 --> 00:44:22.436 setting up a trial where these are

NOTE Confidence: 0.909565391578947

00:44:22.436 --> 00:44:25.409 included as part of the first line therapy.

NOTE Confidence: 0.909565391578947

00:44:25.410 --> 00:44:27.330 And then we've set up multiple

NOTE Confidence: 0.909565391578947

00:44:27.330 --> 00:44:29.242 lines of these at large B cell

NOTE Confidence: 0.909565391578947

00:44:29.242 --> 00:44:30.943 infomas and a plast cell infomas of

NOTE Confidence: 0.909565391578947

00:44:30.943 --> 00:44:32.504 Plast blast infomas to begin to do

NOTE Confidence: 0.909565391578947

00:44:32.504 --> 00:44:34.239 some of these functional studies.

NOTE Confidence: 0.909565391578947

00:44:34.240 --> 00:44:36.291 So I won't go through in detail

NOTE Confidence: 0.909565391578947

00:44:36.291 --> 00:44:37.560 with this last part,

NOTE Confidence: 0.909565391578947

00:44:37.560 --> 00:44:39.792 but one of the issues with lymphoma is

NOTE Confidence: 0.909565391578947

00:44:39.792 --> 00:44:42.275 that it's not a sheet of neoplastic cells,

NOTE Confidence: 0.909565391578947

00:44:42.280 --> 00:44:44.114 but there is a lot of microenvironmental

NOTE Confidence: 0.909565391578947

00:44:44.114 --> 00:44:45.703 cells that are actively interacting

NOTE Confidence: 0.909565391578947

00:44:45.703 --> 00:44:47.199 with the neoplastic cells.

NOTE Confidence: 0.909565391578947

00:44:47.200 --> 00:44:49.083 We know the landscape very well of

NOTE Confidence: 0.909565391578947

00:44:49.083 --> 00:44:51.159 the perform as I described initially,

NOTE Confidence: 0.909565391578947

00:44:51.160 --> 00:44:53.404 but we still can't explain the

NOTE Confidence: 0.909565391578947

00:44:53.404 --> 00:44:55.416 heterogeneity of the disease and the

NOTE Confidence: 0.909565391578947

00:44:55.416 --> 00:44:57.464 one thing that we can at this point

NOTE Confidence: 0.909565391578947

00:44:57.464 --> 00:44:59.699 know that is important is if patients.

NOTE Confidence: 0.909565391578947

00:44:59.700 --> 00:45:01.752 For this the proportion of patients

NOTE Confidence: 0.909565391578947

00:45:01.752 --> 00:45:03.739 that need therapy if they are,

NOTE Confidence: 0.909565391578947

00:45:03.740 --> 00:45:05.900 if they progress or relapse within

NOTE Confidence: 0.909565391578947

00:45:05.900 --> 00:45:08.103 two unit therapy they do really

NOTE Confidence: 0.909565391578947

00:45:08.103 --> 00:45:10.179 poorly and others do really well.

NOTE Confidence: 0.909565391578947

00:45:10.180 --> 00:45:11.908 But trying to find biomarkers earlier

NOTE Confidence: 0.909565391578947

00:45:11.908 --> 00:45:13.779 on to produce that is important.

NOTE Confidence: 0.909565391578947

00:45:13.780 --> 00:45:15.946 We think that understanding some elements

NOTE Confidence: 0.909565391578947

00:45:15.946 --> 00:45:18.379 of the micro environment may be important.

NOTE Confidence: 0.909565391578947

00:45:18.380 --> 00:45:20.660 So we begin to set up,

NOTE Confidence: 0.909565391578947

00:45:20.660 --> 00:45:22.634 we've we've set up models of focal

NOTE Confidence: 0.909565391578947

00:45:22.634 --> 00:45:25.146 fellow which are much harder than some of

NOTE Confidence: 0.909565391578947

00:45:25.146 --> 00:45:27.419 the aggressive lymphomas to begin to look at.

NOTE Confidence: 0.909565391578947

00:45:27.420 --> 00:45:29.135 The impact of genetic alterations in in

NOTE Confidence: 0.909565391578947

00:45:29.135 --> 00:45:30.770 the context of the microenvironment and

NOTE Confidence: 0.909565391578947

00:45:30.770 --> 00:45:32.744 what the interplay may be between the

NOTE Confidence: 0.909565391578947

00:45:32.793 --> 00:45:34.658 neoplastic cells and the microenvironment

NOTE Confidence: 0.945844377777778

00:45:37.020 --> 00:45:39.336 and the barriers again are having

NOTE Confidence: 0.945844377777778

00:45:39.336 --> 00:45:41.328 models for this and I'll just show

NOTE Confidence: 0.945844377777778

00:45:41.328 --> 00:45:43.141 you some of the pictures of the full

NOTE Confidence: 0.945844377777778

00:45:43.141 --> 00:45:44.456 and final model we've generated.

NOTE Confidence: 0.945844377777778

00:45:44.460 --> 00:45:46.416 So again this is a image

NOTE Confidence: 0.945844377777778

00:45:46.416 --> 00:45:48.699 of the tumor on the kidney.

NOTE Confidence: 0.945844377777778

00:45:48.700 --> 00:45:51.898 It's much more well circumscribed than

NOTE Confidence: 0.945844377777778

00:45:51.900 --> 00:45:53.208 some of the aggressive models here

NOTE Confidence: 0.945844377777778

00:45:53.208 --> 00:45:54.980 you can see that the cells are small,

NOTE Confidence: 0.945844377777778

00:45:54.980 --> 00:45:56.930 they look more like centrosized but.

NOTE Confidence: 0.945844377777778

00:45:56.930 --> 00:45:58.085 Mixed mixed morphology,

NOTE Confidence: 0.945844377777778

00:45:58.085 --> 00:46:01.131 one of the exciting things is that when

NOTE Confidence: 0.945844377777778

00:46:01.131 --> 00:46:03.642 you do when we look at the cells they

NOTE Confidence: 0.945844377777778

00:46:03.711 --> 00:46:06.564 include both B cells and the human T cells.

NOTE Confidence: 0.945844377777778

00:46:06.570 --> 00:46:08.607 So they they those two are present

NOTE Confidence: 0.945844377777778

00:46:08.607 --> 00:46:10.860 in the the tumor giving us an

NOTE Confidence: 0.945844377777778

00:46:10.860 --> 00:46:12.834 opportunity to begin to under to

NOTE Confidence: 0.945844377777778

00:46:12.907 --> 00:46:15.169 look at their interactions in vivo.

NOTE Confidence: 0.945844377777778

00:46:15.170 --> 00:46:18.166 This is just the immune chemistry showing

NOTE Confidence: 0.945844377777778

00:46:18.170 --> 00:46:22.013 the B cells and and T cells in the.

NOTE Confidence: 0.945844377777778

00:46:22.020 --> 00:46:24.288 In the tissue we do interestingly get

NOTE Confidence: 0.945844377777778

00:46:24.288 --> 00:46:25.702 some plasma acidic differentiation

NOTE Confidence: 0.945844377777778

00:46:25.702 --> 00:46:27.994 which you don't typically get in

NOTE Confidence: 0.945844377777778

00:46:27.994 --> 00:46:29.999 folk lymphoma but occurs in these

NOTE Confidence: 0.945844377777778

00:46:29.999 --> 00:46:31.334 models and we do get,

NOTE Confidence: 0.945844377777778

00:46:31.340 --> 00:46:33.349 we do get CD21 meshworks in this

NOTE Confidence: 0.945844377777778

00:46:33.349 --> 00:46:34.925 model although they don't persist

NOTE Confidence: 0.945844377777778

00:46:34.925 --> 00:46:36.555 and we believe that's because

NOTE Confidence: 0.945844377777778

00:46:36.555 --> 00:46:38.699 they're non non hematopoietic cells.

NOTE Confidence: 0.945844377777778

00:46:38.700 --> 00:46:40.086 So they persist for a period

NOTE Confidence: 0.945844377777778

00:46:40.086 --> 00:46:41.340 of time and go away.

NOTE Confidence: 0.945844377777778

00:46:41.340 --> 00:46:45.288 We we do get in NSG mice which don't

NOTE Confidence: 0.945844377777778

00:46:45.288 --> 00:46:47.172 have lymph nodes by definition.

NOTE Confidence: 0.945844377777778

00:46:47.172 --> 00:46:48.436 When we do the,

NOTE Confidence: 0.945844377777778

00:46:48.440 --> 00:46:49.952 when we do the PDX as we begin

NOTE Confidence: 0.945844377777778

00:46:49.952 --> 00:46:51.707 to see the generation of lymph

NOTE Confidence: 0.945844377777778

00:46:51.707 --> 00:46:53.357 nodes which is really interesting.

NOTE Confidence: 0.945844377777778

00:46:53.360 --> 00:46:56.144 So these these cells are tracking

NOTE Confidence: 0.945844377777778

00:46:56.144 --> 00:46:58.403 and into some residual primordial

NOTE Confidence: 0.945844377777778

00:46:58.403 --> 00:47:00.418 structure and generating lymph nodes

NOTE Confidence: 0.945844377777778

00:47:00.418 --> 00:47:02.953 and this just shows the B cells and

NOTE Confidence: 0.945844377777778

00:47:02.953 --> 00:47:04.690 the T cells within that and you do see

NOTE Confidence: 0.945844377777778

00:47:04.743 --> 00:47:06.675 some of this plasma state differentiation.

NOTE Confidence: 0.91997488

00:47:08.760 --> 00:47:12.160 We we do imaging to to to look at these.

NOTE Confidence: 0.91997488

00:47:12.160 --> 00:47:14.400 So this is normal kidney on

NOTE Confidence: 0.91997488

00:47:14.400 --> 00:47:15.840 the left and on the right.

NOTE Confidence: 0.9402536

00:47:18.700 --> 00:47:19.420 We'll see

NOTE Confidence: 0.946962533333333

00:47:23.580 --> 00:47:25.512 this, this dark thing is the tumor

NOTE Confidence: 0.946962533333333

00:47:25.512 --> 00:47:27.673 and we we developed this because

NOTE Confidence: 0.946962533333333

00:47:27.673 --> 00:47:29.778 unlike the large aggressive tumors

NOTE Confidence: 0.946962533333333

00:47:29.778 --> 00:47:32.260 where you can clinically sense when

NOTE Confidence: 0.946962533333333

00:47:32.260 --> 00:47:34.815 when the when the tumor is there,

NOTE Confidence: 0.946962533333333

00:47:34.820 --> 00:47:35.696 these are indolent.

NOTE Confidence: 0.946962533333333

00:47:35.696 --> 00:47:38.011 So we need some imaging to be able

NOTE Confidence: 0.946962533333333

00:47:38.011 --> 00:47:40.975 to detect engraftment and we're now

NOTE Confidence: 0.946962533333333

00:47:40.975 --> 00:47:44.280 working at colleagues at the road.

NOTE Confidence: 0.946962533333333

00:47:44.280 --> 00:47:46.840 Wignesh Shanmugam is close colleague.

NOTE Confidence: 0.946962533333333

00:47:46.840 --> 00:47:49.110 I'm working on spatial transcriptomics

NOTE Confidence: 0.946962533333333

00:47:49.110 --> 00:47:52.334 to begin to ask questions around the

NOTE Confidence: 0.946962533333333

00:47:52.334 --> 00:47:54.604 microenvironment and and the spatial

NOTE Confidence: 0.946962533333333

00:47:54.604 --> 00:47:56.420 relationships between the neoplastic

NOTE Confidence: 0.946962533333333

00:47:56.484 --> 00:47:58.782 cells and different subsets of the

NOTE Confidence: 0.946962533333333

00:47:58.782 --> 00:48:01.248 microenvironments and how that plays both

NOTE Confidence: 0.946962533333333

00:48:01.248 --> 00:48:04.496 in real patients but ultimately in the

NOTE Confidence: 0.946962533333333

00:48:04.496 --> 00:48:08.437 PD X's where we can do some manipulation.

NOTE Confidence: 0.946962533333333

00:48:08.440 --> 00:48:09.413 So I just want to make sure

NOTE Confidence: 0.946962533333333

00:48:09.413 --> 00:48:10.159 I don't out of time.

NOTE Confidence: 0.946962533333333

00:48:10.160 --> 00:48:14.038 So yeah, so in conclusion here we.

NOTE Confidence: 0.946962533333333

00:48:14.040 --> 00:48:16.080 We are,

NOTE Confidence: 0.946962533333333

00:48:16.080 --> 00:48:18.544 we are using you know paired human

NOTE Confidence: 0.946962533333333

00:48:18.544 --> 00:48:21.702 focal FOMA and focal PDX samples that

NOTE Confidence: 0.946962533333333

00:48:21.702 --> 00:48:23.918 characterize the the microenvironment,

NOTE Confidence: 0.946962533333333

00:48:23.920 --> 00:48:26.128 the clonal populations and to explore

NOTE Confidence: 0.946962533333333

00:48:26.128 --> 00:48:28.605 their nature and roll the crosstalk

NOTE Confidence: 0.946962533333333

00:48:28.605 --> 00:48:30.477 between these cell populations.

NOTE Confidence: 0.946962533333333

00:48:30.480 --> 00:48:32.286 And we anticipate that the INTRIVIAL

NOTE Confidence: 0.946962533333333

00:48:32.286 --> 00:48:34.888 model will serve as an ideal system to

NOTE Confidence: 0.946962533333333

00:48:34.888 --> 00:48:36.558 really interrogate focal formal biology

NOTE Confidence: 0.946962533333333

00:48:36.558 --> 00:48:39.016 and understand the mechanism mechanisms

NOTE Confidence: 0.946962533333333

00:48:39.016 --> 00:48:42.876 of targeted therapies and resistance.

NOTE Confidence: 0.946962533333333

00:48:42.876 --> 00:48:47.260 So with that I want to thank you for,

NOTE Confidence: 0.946962533333333

00:48:47.260 --> 00:48:48.720 for coming in person and

NOTE Confidence: 0.946962533333333

00:48:48.720 --> 00:48:50.580 for those who are on zoom,

NOTE Confidence: 0.946962533333333

00:48:50.580 --> 00:48:53.100 thank you for for listening

NOTE Confidence: 0.946962533333333

00:48:53.100 --> 00:48:54.220 and I'll take any questions.

NOTE Confidence: 0.94025356

00:49:02.660 --> 00:49:03.020 Very nice.

NOTE Confidence: 0.901673494

00:49:05.260 --> 00:49:08.700 Two questions Chris really like getting.

NOTE Confidence: 0.94025356

00:49:14.010 --> 00:49:14.210 It's

NOTE Confidence: 0.933544608333333

00:49:29.770 --> 00:49:34.690 about is now we know that uniquely

NOTE Confidence: 0.933544608333333

00:49:34.690 --> 00:49:37.606 starts by in that general center.

NOTE Confidence: 0.94780115

00:49:44.390 --> 00:49:46.694 Yeah, I mean presumably like the

NOTE Confidence: 0.94780115

00:49:46.694 --> 00:49:48.736 potentially the map kinase might

NOTE Confidence: 0.94780115

00:49:48.736 --> 00:49:50.906 be driving proliferation in those,

NOTE Confidence: 0.94780115

00:49:50.910 --> 00:49:52.758 that's one possibility and

NOTE Confidence: 0.94780115

00:49:52.758 --> 00:49:55.068 you know there have been

NOTE Confidence: 0.902829309090909

00:49:57.790 --> 00:50:00.334 you know people looking at micro

NOTE Confidence: 0.902829309090909

00:50:00.334 --> 00:50:02.990 RNAs and other other downstream.

NOTE Confidence: 0.902829309090909

00:50:02.990 --> 00:50:05.078 But we don't have a clear clearly that

NOTE Confidence: 0.902829309090909

00:50:05.078 --> 00:50:07.140 not it's not the same mechanism as

NOTE Confidence: 0.902829309090909

00:50:07.140 --> 00:50:09.152 having BCL two over express but that

NOTE Confidence: 0.902829309090909

00:50:09.152 --> 00:50:11.352 also may may be part of the reason why

NOTE Confidence: 0.902829309090909

00:50:11.352 --> 00:50:13.326 we never see systemic involvement by we

NOTE Confidence: 0.902829309090909

00:50:13.326 --> 00:50:15.644 don't see you know long term systemic

NOTE Confidence: 0.902829309090909

00:50:15.644 --> 00:50:17.344 involvement by these pediatric type.

NOTE Confidence: 0.902829309090909

00:50:17.350 --> 00:50:19.042 They're pretty limited and the you

NOTE Confidence: 0.902829309090909

00:50:19.042 --> 00:50:21.065 know to the point where there was

NOTE Confidence: 0.902829309090909

00:50:21.065 --> 00:50:23.004 a lot of debate about whether these

NOTE Confidence: 0.902829309090909

00:50:23.063 --> 00:50:24.990 should even be called lymphoma, right.

NOTE Confidence: 0.950317

00:50:33.030 --> 00:50:37.736 Maybe I wonder where it's in

NOTE Confidence: 0.950317

00:50:37.736 --> 00:50:40.470 on the OR the machinery. Yeah,

NOTE Confidence: 0.94629164

00:50:43.470 --> 00:50:44.550 yeah. There's no direct. Yeah.

NOTE Confidence: 0.938423890909091

00:50:45.110 --> 00:50:46.250 Second question I wanted to

NOTE Confidence: 0.938423890909091

00:50:46.250 --> 00:50:47.630 ask is on the latter app,

NOTE Confidence: 0.938423890909091

00:50:47.630 --> 00:50:50.504 the PDX is really pretty exciting

NOTE Confidence: 0.938423890909091

00:50:50.504 --> 00:50:53.549 to be able to use those.

NOTE Confidence: 0.938423890909091

00:50:53.550 --> 00:50:55.726 But you brought up from the end that

NOTE Confidence: 0.938423890909091

00:50:55.726 --> 00:50:59.310 you also want to look at the micro.

NOTE Confidence: 0.938423890909091

00:50:59.310 --> 00:51:01.630 Yes, you do get to. Have some of it

NOTE Confidence: 0.850840825

00:51:01.630 --> 00:51:03.390 in the future planted,

NOTE Confidence: 0.92767435

00:51:03.790 --> 00:51:05.350 but I think a lot of you guys,

NOTE Confidence: 0.92767435

00:51:05.350 --> 00:51:08.626 some of the issues are that for

NOTE Confidence: 0.92767435

00:51:08.626 --> 00:51:10.686 multiple passages that sort of

NOTE Confidence: 0.92767435

00:51:10.686 --> 00:51:12.982 leave that and you start winding up.

NOTE Confidence: 0.92767435

00:51:12.990 --> 00:51:16.410 Yes, yes. So, so I'm wondering if

NOTE Confidence: 0.92767435

00:51:16.410 --> 00:51:19.654 a lot of you guys explore which

NOTE Confidence: 0.92767435

00:51:19.654 --> 00:51:22.150 types of humanized type models.

NOTE Confidence: 0.950317

00:51:24.360 --> 00:51:25.965 We're we're starting to to to

NOTE Confidence: 0.950317

00:51:25.965 --> 00:51:27.210 look at the humanized models

NOTE Confidence: 0.9408825625

00:51:27.259 --> 00:51:28.597 we've had it's a little bit,

NOTE Confidence: 0.9408825625

00:51:28.600 --> 00:51:30.168 they're a little bit tricky to to

NOTE Confidence: 0.9408825625

00:51:30.168 --> 00:51:31.800 use and they're extremely expensive.

NOTE Confidence: 0.9408825625

00:51:31.800 --> 00:51:33.825 So you have to like you have to temper

NOTE Confidence: 0.9408825625

00:51:33.825 --> 00:51:36.036 how you do things get this jump into it.

NOTE Confidence: 0.9408825625

00:51:36.040 --> 00:51:38.632 And then we also in terms of match and

NOTE Confidence: 0.9408825625

00:51:38.632 --> 00:51:41.078 we've tried to attempt to in our bank,

NOTE Confidence: 0.9408825625

00:51:41.080 --> 00:51:42.444 we actually can prospectively

NOTE Confidence: 0.9408825625

00:51:42.444 --> 00:51:44.490 collect blood from the patients who

NOTE Confidence: 0.9408825625

00:51:44.552 --> 00:51:46.500 consent and so we've actually tried

NOTE Confidence: 0.9408825625

00:51:46.500 --> 00:51:48.393 to think about matching those which

NOTE Confidence: 0.9408825625

00:51:48.393 --> 00:51:50.433 takes some time and then you have to

NOTE Confidence: 0.9408825625

00:51:50.433 --> 00:51:52.408 you know so we're working on that.

NOTE Confidence: 0.9408825625

00:51:52.410 --> 00:51:54.130 It's a much harder experiment.

NOTE Confidence: 0.9408825625

00:51:54.130 --> 00:51:55.274 Yeah. And you're right.

NOTE Confidence: 0.9408825625

00:51:55.274 --> 00:51:56.670 Over time, it's a, you know,

NOTE Confidence: 0.9408825625

00:51:56.670 --> 00:51:57.900 we do run into, you know,

NOTE Confidence: 0.9408825625

00:51:57.900 --> 00:51:59.130 you lose like environment and how.

NOTE Confidence: 0.9408825625

00:51:59.130 --> 00:52:00.890 Yeah.

NOTE Confidence: 0.9408825625

00:52:00.890 --> 00:52:01.250 Thank you.

NOTE Confidence: 0.9301902

00:52:04.930 --> 00:52:06.246 Hi, can I ask you a question?

NOTE Confidence: 0.9301902

00:52:06.250 --> 00:52:08.008 This is Jeff Sklar on Zoom

NOTE Confidence: 0.94427896

00:52:11.210 --> 00:52:14.764 A2 part question. You know, I wonder

NOTE Confidence: 0.94427896

00:52:14.764 --> 00:52:17.249 about selection that's going on.

NOTE Confidence: 0.95534863

00:52:22.680 --> 00:52:25.280 Murders once they're established

NOTE Confidence: 0.95534863

00:52:25.280 --> 00:52:26.918 and compare the sequences of the

NOTE Confidence: 0.92683568

00:52:30.640 --> 00:52:32.116 yeah, we we do do that,

NOTE Confidence: 0.92683568

00:52:32.120 --> 00:52:37.408 we we do sequence them and do RN A/C

NOTE Confidence: 0.92683568

00:52:37.408 --> 00:52:41.104 to to compare and the the mutations

NOTE Confidence: 0.92683568

00:52:41.104 --> 00:52:43.192 that are present in the patient

NOTE Confidence: 0.92683568

00:52:43.192 --> 00:52:44.432 are typically present in the,

NOTE Confidence: 0.92683568

00:52:44.440 --> 00:52:47.040 although there are some.

NOTE Confidence: 0.92683568

00:52:47.040 --> 00:52:48.630 They're not 100% but they're

NOTE Confidence: 0.92683568

00:52:48.630 --> 00:52:50.220 pretty similar the the main

NOTE Confidence: 0.92683568

00:52:50.277 --> 00:52:51.639 chromatin modifying gene

NOTE Confidence: 0.9301903

00:52:57.040 --> 00:53:00.365 and so one of the points I was

NOTE Confidence: 0.9301903

00:53:00.365 --> 00:53:02.936 kind of getting at is do you ever

NOTE Confidence: 0.9301903

00:53:02.936 --> 00:53:05.076 see transformation to large cell

NOTE Confidence: 0.9301903

00:53:05.080 --> 00:53:08.240 in the rafted folliculars? Yes,

NOTE Confidence: 0.900959729473684

00:53:08.240 --> 00:53:10.974 we have. We have seen that in a in a few

NOTE Confidence: 0.900959729473684

00:53:10.974 --> 00:53:13.678 cases we can't get it to recurrently occur.

NOTE Confidence: 0.900959729473684

00:53:13.680 --> 00:53:15.390 So we'll have it as a.

NOTE Confidence: 0.900959729473684

00:53:15.390 --> 00:53:17.374 As an event and you know we're excited

NOTE Confidence: 0.900959729473684

00:53:17.374 --> 00:53:19.254 about the possibility of leveraging

NOTE Confidence: 0.900959729473684

00:53:19.254 --> 00:53:21.026 that to understand transformation,

NOTE Confidence: 0.900959729473684

00:53:21.030 --> 00:53:24.335 but it's it's hard to get as a

NOTE Confidence: 0.900959729473684

00:53:24.335 --> 00:53:25.985 recurrent issue as a you know,

NOTE Confidence: 0.900959729473684

00:53:25.990 --> 00:53:29.270 as a model of that transformation. Thanks.

NOTE Confidence: 0.94025356

00:53:38.470 --> 00:53:38.590 Yeah,

NOTE Confidence: 0.59691423

00:53:41.870 --> 00:53:42.030 very.

NOTE Confidence: 0.933544666666667

00:53:51.690 --> 00:53:54.450 Yes, yeah. Yes. Yeah,

NOTE Confidence: 0.9402536

00:53:57.450 --> 00:53:57.650 yeah,

NOTE Confidence: 0.9352219

00:54:02.450 --> 00:54:03.474 yeah. And that's also

NOTE Confidence: 0.9352219

00:54:03.474 --> 00:54:05.010 in my bucket in my mind.

NOTE Confidence: 0.9352219

00:54:05.010 --> 00:54:05.900 But I never really talked

NOTE Confidence: 0.9352219

00:54:05.900 --> 00:54:07.050 about it because no one knows,

NOTE Confidence: 0.9352219

00:54:07.050 --> 00:54:08.650 you know, it's so rare.

NOTE Confidence: 0.9352219

00:54:08.650 --> 00:54:10.340 But I really think that

NOTE Confidence: 0.9352219

00:54:10.340 --> 00:54:12.030 ultimately we're going to find

NOTE Confidence: 0.9352219

00:54:12.094 --> 00:54:13.909 that these have very similar.

NOTE Confidence: 0.9352219

00:54:13.910 --> 00:54:17.682 Analogy and if targets and in one,

NOTE Confidence: 0.9352219

00:54:17.682 --> 00:54:18.906 then my other question

NOTE Confidence: 0.948879371428571

00:54:27.590 --> 00:54:30.075 what are your thoughts really

NOTE Confidence: 0.948879371428571

00:54:30.075 --> 00:54:31.949 about this grading versus not.

NOTE Confidence: 0.9402536

00:54:35.230 --> 00:54:38.070 Yeah. So to be honest when

NOTE Confidence: 0.9402536

00:54:38.070 --> 00:54:40.110 I when I first joined

NOTE Confidence: 0.937157169230769

00:54:40.215 --> 00:54:42.874 the committee and having trained.

NOTE Confidence: 0.937157169230769

00:54:42.874 --> 00:54:44.380 With Nancy Harris.

NOTE Confidence: 0.937157169230769

00:54:44.380 --> 00:54:45.772 And I got onto the committee

NOTE Confidence: 0.937157169230769

00:54:45.772 --> 00:54:46.980 and the committee was like,

NOTE Confidence: 0.937157169230769

00:54:46.980 --> 00:54:48.500 we need to get rid of this grading.

NOTE Confidence: 0.937157169230769

00:54:48.500 --> 00:54:49.460 And my eyes were like,

NOTE Confidence: 0.83735318

00:54:51.860 --> 00:54:54.060 yeah, because that was like,

NOTE Confidence: 0.83735318

00:54:54.060 --> 00:54:55.500 yeah, I was like, wow.

NOTE Confidence: 0.83735318

00:54:55.500 --> 00:54:57.747 And I found myself defending really trying

NOTE Confidence: 0.83735318

00:54:57.747 --> 00:54:59.978 to defend the the point of grading.

NOTE Confidence: 0.83735318

00:54:59.980 --> 00:55:03.050 But then they made me see that, you know,

NOTE Confidence: 0.83735318

00:55:03.050 --> 00:55:05.115 with some of the newer targeted therapies

NOTE Confidence: 0.83735318

00:55:05.115 --> 00:55:08.450 that are being used, there is no.

NOTE Confidence: 0.83735318

00:55:08.450 --> 00:55:10.585 There's no difference really in in the

NOTE Confidence: 0.83735318

00:55:10.585 --> 00:55:12.487 patients that are 3A versus 1 to 2.

NOTE Confidence: 0.83735318

00:55:12.490 --> 00:55:14.058 And then the other thing is like

NOTE Confidence: 0.83735318

00:55:14.058 --> 00:55:15.939 I mentioned the POD24 where where

NOTE Confidence: 0.83735318

00:55:15.939 --> 00:55:17.954 patients that relapse or occur

NOTE Confidence: 0.83735318

00:55:17.954 --> 00:55:20.386 within two years they do much worse.

NOTE Confidence: 0.83735318

00:55:20.386 --> 00:55:22.210 And then the patients who don't,

NOTE Confidence: 0.83735318

00:55:22.210 --> 00:55:24.010 if you look at some of those papers

NOTE Confidence: 0.83735318

00:55:24.010 --> 00:55:26.010 they they they show you like in the

NOTE Confidence: 0.83735318

00:55:26.010 --> 00:55:27.885 supplements like the the the breakdown of

NOTE Confidence: 0.83735318

00:55:27.885 --> 00:55:29.810 these cases and there's an even number

NOTE Confidence: 0.83735318

00:55:29.810 --> 00:55:32.123 of grade one to two grade 3A in those.

NOTE Confidence: 0.83735318

00:55:32.130 --> 00:55:34.398 So it's actually not predictive of that.

NOTE Confidence: 0.83735318

00:55:34.400 --> 00:55:36.866 So I actually think there's a pretty

NOTE Confidence: 0.83735318

00:55:36.866 --> 00:55:40.192 good argument of not doing grading.

NOTE Confidence: 0.83735318

00:55:40.192 --> 00:55:43.524 I think the consensus of 3B is

NOTE Confidence: 0.83735318

00:55:43.524 --> 00:55:45.252 really more like DLBCL essentially,

NOTE Confidence: 0.83735318

00:55:45.252 --> 00:55:47.480 which is basically sheets of large cells.

NOTE Confidence: 0.83735318

00:55:47.480 --> 00:55:49.480 This happens to have follicles.

NOTE Confidence: 0.83735318

00:55:49.480 --> 00:55:51.160 So what the decision was was

NOTE Confidence: 0.83735318

00:55:51.160 --> 00:55:52.280 we would lose it.

NOTE Confidence: 0.83735318

00:55:52.280 --> 00:55:53.810 But usually when you think about

NOTE Confidence: 0.83735318

00:55:53.810 --> 00:55:55.678 making a change in a different way,

NOTE Confidence: 0.83735318

00:55:55.680 --> 00:55:57.156 show there's sort of this unwritten

NOTE Confidence: 0.83735318

00:55:57.156 --> 00:55:58.778 rule that you have to have data.

NOTE Confidence: 0.83735318

00:55:58.780 --> 00:56:00.257 To support it and interestingly for that,

NOTE Confidence: 0.83735318

00:56:00.260 --> 00:56:02.126 there is no data to talk

NOTE Confidence: 0.83735318

00:56:02.126 --> 00:56:03.059 about removing something,

NOTE Confidence: 0.83735318

00:56:03.060 --> 00:56:05.472 but it's almost like when you look at the

NOTE Confidence: 0.83735318

00:56:05.472 --> 00:56:07.660 origins of grading which was a little bit,

NOTE Confidence: 0.83735318

00:56:07.660 --> 00:56:09.620 there's not much data there.

NOTE Confidence: 0.83735318

00:56:09.620 --> 00:56:11.020 So it's and then the idea was

NOTE Confidence: 0.83735318

00:56:11.020 --> 00:56:12.338 like over time we'll figure it

NOTE Confidence: 0.83735318

00:56:12.338 --> 00:56:13.899 out but it never got figured out.

NOTE Confidence: 0.83735318

00:56:13.900 --> 00:56:15.300 So it's almost removing something

NOTE Confidence: 0.83735318

00:56:15.300 --> 00:56:16.140 that was never.

NOTE Confidence: 0.83735318

00:56:16.140 --> 00:56:17.220 So I think that's the,

NOTE Confidence: 0.83735318

00:56:17.220 --> 00:56:19.866 well what we did do is was

NOTE Confidence: 0.83735318

00:56:19.866 --> 00:56:22.296 suggest that grading be allowed.

NOTE Confidence: 0.83735318

00:56:22.300 --> 00:56:22.880 So it's,

NOTE Confidence: 0.83735318

00:56:22.880 --> 00:56:24.620 it's not required but at local

NOTE Confidence: 0.83735318

00:56:24.620 --> 00:56:26.755 institutions like ours where some of the

NOTE Confidence: 0.83735318

00:56:26.755 --> 00:56:28.255 oncologists really want the grading.

NOTE Confidence: 0.83735318

00:56:28.260 --> 00:56:29.100 We still have the grading,

NOTE Confidence: 0.83735318

00:56:29.100 --> 00:56:29.744 but we just wanted,

NOTE Confidence: 0.83735318

00:56:29.744 --> 00:56:31.159 I think the idea was to make it

NOTE Confidence: 0.83735318

00:56:31.159 --> 00:56:32.174 clear that it wasn't required.

NOTE Confidence: 0.83735318

00:56:32.180 --> 00:56:35.330 And I think that sort of the

NOTE Confidence: 0.83735318

00:56:35.330 --> 00:56:36.860 balance that we left were left with.

NOTE Confidence: 0.8353682

00:56:40.300 --> 00:56:41.980 Yeah, right, right.

NOTE Confidence: 0.94427896

00:56:44.500 --> 00:56:45.420 Thank you for the question.

NOTE Confidence: 0.9402537

00:56:55.360 --> 00:56:57.320 Are you looking for the DA sequence?

NOTE Confidence: 0.9402537

00:56:57.320 --> 00:57:00.038 Are you looking for the most of PCM who

NOTE Confidence: 0.9402537

00:57:00.038 --> 00:57:02.584 might support the transportation but

NOTE Confidence: 0.9402537

00:57:02.584 --> 00:57:05.880 have you snapped any translocation that.

NOTE Confidence: 0.94780125

00:57:07.840 --> 00:57:09.840 No. So there's no, there's

NOTE Confidence: 0.94780125

00:57:09.840 --> 00:57:11.040 usually no rearrangement.

NOTE Confidence: 0.94780125

00:57:11.040 --> 00:57:13.000 Igh would be the common partner,

NOTE Confidence: 0.86512336

00:57:15.640 --> 00:57:18.200 yeah no I I don't know of any.

NOTE Confidence: 0.86512336

00:57:18.200 --> 00:57:19.532 I know that there's some new

NOTE Confidence: 0.86512336

00:57:19.532 --> 00:57:20.560 technologies that are that can

NOTE Confidence: 0.86512336

00:57:20.560 --> 00:57:22.940 that can pick up some uncommon.

NOTE Confidence: 0.86512336

00:57:22.940 --> 00:57:24.542 Types of transvocations and we've thought

NOTE Confidence: 0.86512336

00:57:24.542 --> 00:57:26.220 about submitting some of these to that,

NOTE Confidence: 0.86512336

00:57:26.220 --> 00:57:29.420 but there's no evidence to date of any

NOTE Confidence: 0.86512336

00:57:29.420 --> 00:57:33.140 rearrangements in these in these lesions.

NOTE Confidence: 0.86512336

00:57:33.140 --> 00:57:35.338 So the second question regarding more

NOTE Confidence: 0.83795913

00:57:35.580 --> 00:57:41.485 general for the P7 coma, so really P7

NOTE Confidence: 0.83795913

00:57:41.485 --> 00:57:43.340 coma that have ITG and location is.

NOTE Confidence: 0.83795913

00:57:43.340 --> 00:57:48.623 So what is driving by the ITG from overreach?

NOTE Confidence: 0.83795913

00:57:48.630 --> 00:57:50.835 Right. So because the right now the

NOTE Confidence: 0.83795913

00:57:50.835 --> 00:57:53.570 uncle gene always replaced by the ITG

NOTE Confidence: 0.83795913

00:57:53.570 --> 00:57:56.000 which so it's high and expressed.

NOTE Confidence: 0.83795913

00:57:56.000 --> 00:58:01.374 So my thought is that we if we instead

NOTE Confidence: 0.83795913

00:58:01.374 --> 00:58:04.150 of becoming even the uncle gene which

NOTE Confidence: 0.83795913

00:58:04.150 --> 00:58:06.494 is coming out the ITG transporting

NOTE Confidence: 0.83795913

00:58:06.494 --> 00:58:10.094 the level you keep the water

NOTE Confidence: 0.83795913

00:58:10.094 --> 00:58:12.094 transportation uncle gene fashion low.

NOTE Confidence: 0.83795913

00:58:12.094 --> 00:58:14.229 You see that will be high in your strategy.

NOTE Confidence: 0.942766971428571

00:58:15.230 --> 00:58:16.850 So targeting, targeting the

NOTE Confidence: 0.942766971428571

00:58:16.850 --> 00:58:18.065 rearrangement you're saying.

NOTE Confidence: 0.951435155555556

00:58:18.480 --> 00:58:20.965 No talking even though globally

NOTE Confidence: 0.951435155555556

00:58:20.965 --> 00:58:23.546 and trying to reliable because

NOTE Confidence: 0.951435155555556

00:58:23.546 --> 00:58:26.476 this this model actually friendly

NOTE Confidence: 0.951435155555556

00:58:26.480 --> 00:58:28.680 controlled by the ITG reliable.

NOTE Confidence: 0.949198844444445

00:58:29.760 --> 00:58:31.890 Yeah no, I've never really thought

NOTE Confidence: 0.949198844444445

00:58:31.890 --> 00:58:33.840 thought about that interesting idea.

NOTE Confidence: 0.9402536

00:58:38.360 --> 00:58:38.720 Thank you.