OK, so you know if you instant.

We will be starting.

So this is the server.

Seminar on the liver.

Tumor lecture we've launched in January.

And today we will have FaceTime to.

The medical treatment of HCC.

I remind you that this is part of our liver cancer program.

And it takes a village to treat.

You see, on the left all the different approaches that needs to be considered.

when we discuss the patient and
and on the right part of the people that takes part to our program. Between surgeons, interventional is the medical oncologist at geologies pathologist, and so on and so forth. And in the two prior seminars, we have the Doctor Billingslea from Service Surgical oncology Ann Dr. Model from interventional radiology today. We will have Stacy, which is a format of just so that to remind you very briefly how the program works. We have a a comment intake line and
00:01:26.424 --> 00:01:29.620 the patient is seeing in the liver
NOTE Confidence: 0.67705846
00:01:29.620 --> 00:01:32.480 cancer clinic and then discuss the
NOTE Confidence: 0.67705846
00:01:32.480 --> 00:01:35.505 tumor board where everybody participate.
NOTE Confidence: 0.67705846
00:01:35.510 --> 00:01:38.548 You see here on all the discipline
NOTE Confidence: 0.67705846
00:01:38.548 --> 00:01:41.340 that take part to our discussion
NOTE Confidence: 0.67705846
00:01:41.340 --> 00:01:43.665 and then a treatment is.
NOTE Confidence: 0.67705846
00:01:43.670 --> 00:01:45.752 Is discussed among us an and
NOTE Confidence: 0.67705846
00:01:45.752 --> 00:01:47.875 the patient is referred for the
NOTE Confidence: 0.67705846
00:01:47.875 --> 00:01:49.873 treatment and and the follow up.
NOTE Confidence: 0.67705846
00:01:49.880 --> 00:02:01.080 So today I am very happy to
NOTE Confidence: 0.67705846
00:02:01.080 --> 00:02:04.056 present Doctor Spacetime.
NOTE Confidence: 0.67705846
00:02:04.056 --> 00:02:06.951 Stacy is is a very valued member of our
NOTE Confidence: 0.67705846
00:02:06.951 --> 00:02:10.035 program. She had this battle studies.
NOTE Confidence: 0.67705846
00:02:10.040 --> 00:02:14.056 I looked gassed in New York she got
NOTE Confidence: 0.67705846
00:02:14.056 --> 00:02:18.056 the ND in the University University
NOTE Confidence: 0.67705846
00:02:18.056 --> 00:02:20.056 and then a master in science.
She did her residency in the Montefiore Medical Center in New York City and your college fellowship are and where you? She donyale in 2010. And she’s now associate professor of internal medicine ecology. She has leadership positions at the Center for Gas, intestinal cancer, and she’s a member of our steering committee of our Liver Cancer program, and she is one of the person that actually. Give us their guidelines through her activity in the effort. In addition, Stacy is one of the really
few medical oncologist who are expert
in the treatment of liver cancer,
which is a particularly difficult
condition to treat because of the
combined liver and an ecology diseases.
And in addition to that,
she has the time to be the.
Principal investigator or one of the Co.
Investigator in about 30 different clinical
trials and it’s really impressive.
And so without further ado,
let me share my screen Anne and
let Stacy begin his lecture.

OK great. Can you see it now?
Yep OK perfect.
Alright thanks Mario for the introduction,
so I’m really excited to be talking to you about combination therapy for HCC and you know,

I usually start talks by giving a lot of background information and really explaining why this is such a multidisciplinary disease to treat. But this group is well aware of that, and so I’m going to jump right into really thinking about the medical oncology piece of.

I like to start with looking at the BC else staging system because I think this really shows kind of where things were,
you know, and then thinking about where things are and then really thinking more broadly about where things are going in the feature. So we’ll come back to this slide later. But you know also, I feel like this reflects the time when I came to Yale 10 years ago and it was really a transplant conference at the time, not a liver tumor board. But I went to weekly and I kind of sat in the back of the room right out of fellowship. And when someone kind of came off the transplant list,
00:04:59.720 --> 00:05:01.646 you know someone would look back
00:05:01.646 --> 00:05:04.566 at me in the in the corner and say,
00:05:04.570 --> 00:05:06.656 do you want to see this patient
00:05:06.656 --> 00:05:08.439 and put them on Seraphim?
00:05:08.440 --> 00:05:10.807 And so I feel like the story that I
00:05:10.807 --> 00:05:13.211 could present today is kind of all
00:05:13.211 --> 00:05:15.357 the new treatment options really come
00:05:15.357 --> 00:05:17.433 in parallel with my experience and
00:05:17.433 --> 00:05:20.080 kind of growth here in this field.
00:05:20.080 --> 00:05:21.073 So you know,
00:05:21.073 --> 00:05:23.059 really seraphim’s been the one drug
00:05:23.059 --> 00:05:25.201 that’s been around for awhile and
00:05:25.201 --> 00:05:26.946 now we have different treatment
00:05:27.013 --> 00:05:29.194 options and we’re kind of, you know,
00:05:29.194 --> 00:05:30.729 sandwich done after the cure
00:04:59.720 --> 00:05:01.646 you know someone would look back
00:05:01.646 --> 00:05:04.566 at me in the in the corner and say,
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00:05:27.013 --> 00:05:29.194 options and we’re kind of, you know,
00:05:29.194 --> 00:05:30.729 sandwich done after the cure
it if intent therapies,
NOTE Confidence: 0.92804784
00:05:32.672 --> 00:05:35.488 And then the local regional therapies for the Child Pugh for the BCLCB patients.
NOTE Confidence: 0.92804784
00:05:39.460 --> 00:05:42.520 although this staging system isn’t perfect,
NOTE Confidence: 0.92804784
00:05:43.788 --> 00:05:46.466 The you know the importance of thinking of the underlying liver function of the patient,
NOTE Confidence: 0.92804784
00:05:50.424 --> 00:05:52.590 The tumor characteristics and so starting at the beginning here with the sharp study,
NOTE Confidence: 0.92804784
00:05:54.840 --> 00:05:56.415 which I’m sure everyone is familiar with rates,
so this goes back to 2008 and this was the first study to show a survival benefit of a systemic therapy in HCC. So other drugs like doxorubicin had been used in the past, but they had ever never actually been shown in a randomized child to show a survival benefit. So in this study you could see that Seraphim was actually randomized to placebo, right? Which is unusual for a first line systemic therapy option. An in this study we saw an overall survival benefit going from 7.9
months with placebo to 10.7

and so based on this data,

this became the new standard of care option and you could see also that there was a time to radiologic progression on this on this drug and just remember, you know Seraphim, right? It’s not chemotherapy in the exact strict sense of the term rate, but it’s a TKI and multi tyrosine kinase inhibitor, and because of that you know it’s really targeting multiple pathways. It’s kind of a dirty drug and you know they’re not.
Although their oral and they’re taken daily, and they may not have some of the more serious side effects that some chemotherapy drugs have.

They do have a lot of great toxicities that often affect our patients like fatigue. Sometimes decreased appetite, hand foot, skin reaction, diarrhea, right? Which are definitely important in the management of these patients still. Stay on therapy and I’m just going to focus now on first line therapy and then we could talk more about. The second line therapy option so Lynn.
van if another tyrosine kinase inhibitor, was the next drug that had a positive result in a first line study, and so this study is actually powered to look for either superiority or non inferiority to Seraphim. And this is the reflect study and I'm just going to manage mention for this study. Some of the criteria and then you could see that really all of the systemic therapy studies in HTC kind of follow. Pretty closely this standard criteria so you know patients have to have measurable lesions. BBC else stage B or C. Usually child Pugh a disease.
Some studies may have included some patients with B7 disease, but most are primarily Child Pugh. A good performance status of zero or one, and then you know usual parameters for adequate organ function. They excluded patients that had more advanced disease like Portal vein invasion and then they were stratified by region, whether they had Macrovascular invasion or extrahepatic spread and E COGS status and they were randomized one to one to live at nib.
which you know most patients received the 12 milligram dose to start, or saraf nib and the primary endpoint was overall survival with multiple secondary endpoints. And you could see that basically they didn’t show that it was superior and the lines cross a few times but it was non inferior so the median overall survival is very similar between the two. But the reason why many people would consider this a better option for first line therapy for patients who are going to start therapy on a TKI is that even though the survival was similar,
00:09:26.740 --> 00:09:28.756 the progression free survival was better.

00:09:28.760 --> 00:09:30.788 Although the study was not powered.

00:09:30.790 --> 00:09:32.980 You know to have this as

00:09:32.980 --> 00:09:34.075 the primary endpoint.

00:09:34.080 --> 00:09:36.446 And if you look at the bottom,

00:09:36.450 --> 00:09:37.810 the overall response rate,

00:09:37.810 --> 00:09:40.518 which 9% to me is high for seraphon.

00:09:42.898 --> 00:09:44.250 the Lynn Vatanen arm.

00:09:44.250 --> 00:09:46.746 And so you know you could argue without

00:09:46.746 --> 00:09:48.659 the benefit of overall survival.

00:09:48.660 --> 00:09:50.355 Whether there really is a

00:09:50.355 --> 00:09:52.050 benefit of having a response.

00:09:52.050 --> 00:09:54.288 But I think most most people

00:09:54.288 --> 00:09:55.780 that take care of
these patients would think that. Potentially having a response. May help with better symptom management. And this just showed a subset analysis looking at multiple different groups that in all the groups in the subset they favored linv at NAB. And so now moving to immune therapy. So obviously this is an exciting area for HCC and there’s multiple ways rate that we could think about. You know using immune therapy for different targets. Immune therapy was a little bit late in the game to HCC,
I think largely because before there were drug approvals, it seemed like a risky choice to give to patients who had either hepatitis B or C or were at higher risk, potentially for D compensation. If they had autoimmune. Effects to the liver, and so these studies weren’t really started until they already had FDA approval for other indications and out of the concern for potential viral reactivation. These initial studies in the Phase one setting separated the
patients out into a hepatitis C
Group A hepatitis B group, and then you see they had some patients
who have progressed on sorafenib. But then there’s also this fourth group
of some patients who actually we’re getting this as first line therapy.
And what you could see? You know on these patient bars is that the four groups are pretty
much superimposable on each other, and so you know there were many patients that were on treatment
for at least a year and they were pretty similar across the groups. And this just shows on the left
the spider plots, so anything that goes below the 30% response there on the bottom was at least a partial response and you could see that those are pretty similar across the groups and then on the right is just another form of looking at the data in a waterfall plot and you could see from the red dotted line going across the bottom. All the patients that went below that had had at least a partial response to the drug and basically the four graphs are. Very similar and so. Based on this data,
the FDA approved Nuvola MAB with conditional approval that there would be randomized data in the future, but this allowed patients to have access to immune therapy for HCC, in a similar study. The keynote 224 study very similar design. This looked at pembrolizumab and they separated the patients out in a similar fashion with hepatitis B, a similar fashion with hepatitis B, hepatitis C, and uninfected group. And you could see again that in in there were responses in all of the groups and that they were pretty similar in distribution.
And so again they got a very similar FDA approval that was conditional on having future randomized data and so now we get to more exciting data rate of thinking of combination therapy in the first line. And so this study looked at a combination of atisa Les Mab. With bevacizumab of veg F inhibitor and what’s interesting is that bevacizumab had been looked at in HCC before in a small couple small phase two studies, and there was a response rate. They weren’t randomized to show a clear,
you know, survival benefit, but there was a signal that there was clearly benefit of giving anti VEGF therapy, but there was never approval for or an application for approval. So before this berbasis map was not an approved drug for each CC and you know, it’s interesting to think about why there is potentially synergy between these two drugs as opposed to an additive benefit, but it seems like Bevis is. Mab does normalize the tumor vasculature? An actually allows for more T cell infiltration, and so this is the phase one study.
This is the Geo 30140 study that looked at several arms of which. HTC was one of the arms on the study, and so these were the other arms that we also had open here are may was for unresectable advanced HCC. They did include some B7 patients on the study. To have measurable disease rate very similar eligibility criteria and. The primary endpoint here, because it was a phase one study with safety and tolerability, safety and tolerability and then looking at the overall response.
rate by resist 1.1 there’s also. Duration of response progression. Free response time to radio graphic

F ree response time to radio graphic

progression and then they also looked at modified resist criteria and overall survival so this looks at the baseline demographics of this study. So in total there were 103 patients on the Phase one study, predominantly male, which is the HTC population that we see about half the patients were in Asia and the other 40% were in Japan or the US patients were split between E kog performance, status of zero and one and the majority
00:15:41.280 --> 00:15:44.261 of the patients had child Pugh A5

00:15:44.261 --> 00:15:47.160 disease with 20% ASICS and you could

00:15:47.160 --> 00:15:50.030 see there were only six patients that

00:15:50.030 --> 00:15:52.788 wound up in rolling with B7 disease.

00:15:52.790 --> 00:15:55.604 About half the patients had hepatitis B,

00:15:55.610 --> 00:15:58.106 reflecting the you know mostly the

00:15:58.106 --> 00:16:00.431 Asian population that enrolled 30% with

00:16:00.431 --> 00:16:03.244 hepatitis C and another 20% more nonviral.

00:16:03.244 --> 00:16:05.254 The majority of the patients

00:16:05.254 --> 00:16:06.460 had extrahepatic spread.

00:16:06.460 --> 00:16:08.570 About half had Macrovascular invasion.

00:16:08.570 --> 00:16:11.333 And so when you think of those two as

00:16:11.333 --> 00:16:14.148 being kind of high risk characteristics,

00:16:14.150 --> 00:16:14.522 right,

00:16:14.522 --> 00:16:17.870 about 90% of the patients had one or both,
and then they also looked at AFP to see if that was potentially a.

You know show different responses and that was about half with less than 400 AFP. About half the patients had prior taste and about a third had prior radiotherapy, and this Spider plot shows the responses to treatment and you could see that the green lines or the patients who had either a partial or complete response to treatment. The red bars show progressive disease, it’s stable disease than the red. The red bars show progressive disease,

Then there were many patients in blue, so you could see that for the patients you know,
they often had a good response.

Kind of starting pretty early into treatment and many of the patients had a quite sustained response. So if you look at the Disease Control rate, there were. There were many responders and there were many that lasted a significant amount of time with the progression free survival of 15 months and the median overall survival had been reached at the time. When you know this was considered a positive study. So based on this Phase,
one data that I am brave 150
study was designed and this is a randomized study then to look
Then because was given in the Phase one study randomized to Seraphim.
Which at the time when this was started, it was still the standard of care and it was randomized 2 to one and again with the same stratifications.
And so the I am brave 150 study was published back in June and based on that data, there was FDA approval. I’m actually showing you here. The updated overall survival and progression free survival data
that was presented at the GI

So this is newer, newer data and you know you could see here that the overall survival. The median overall survival for Seraphim was 13.4 months, so as these studies go on in time, the median overall survival for this combination was an impressive 19.2 months.
so this is really the best data that we have so far for first line therapy for HCC and you could see the progression free. The PFS data for Steven it was 4.3 months, and for that is above arms 6.9 and you could see that there’s a nice separation of the curves at six months, 12 months going out to 18 months and on for both the OS and PFS. And looking at responses to, they looked at resist 1.1 and modified resist and the confirmed overall response rate for Seraphim is now 11%, which seems to also keep going.
00:19:27.500 --> 00:19:29.160 up for Seraphim data,
00:19:29.160 --> 00:19:31.056 which I find interesting,
00:19:31.056 --> 00:19:34.532 but I'm not sure how to explain
00:19:34.532 --> 00:19:36.128 that and then.
00:19:36.130 --> 00:19:37.905 The response rate was an
00:19:37.905 --> 00:19:39.904 impressive 30% for the A tease.
00:19:39.904 --> 00:19:42.263 Oh Bev combination and you know the
00:19:42.263 --> 00:19:44.790 response rates are always a little bit
00:19:44.790 --> 00:19:47.426 higher when their looked at by modified
00:19:47.426 --> 00:19:50.380 resist as opposed to resist 1.1 and
00:19:50.380 --> 00:19:53.710 so we saw some complete responses.
00:19:53.710 --> 00:19:54.775 Several partial responses.
00:19:54.775 --> 00:19:56.550 Many patients with stable disease,
00:19:56.550 --> 00:19:59.091 and so when you look at the
00:19:59.091 --> 00:20:00.180 overall Disease Control.
Rates it’s an impressive. It’s an impressive 74% and so the median duration of response for Seraphim was 14.9 and four that is above combination 18.1 and, importantly, looking at the adverse events. So there was some decreased appetite fatigue, pyrexia rash. Hypertension, which is mostly from the bevacizumab which we know from you know, veg F inhibition. We see this and it’s easily treatable with blood pressure medication, you know. Importantly, there is a lot of interest in
looking at bleeding events in these patients because we are giving bevacizumab and the variceal hemorrhage rate was very low. Upper GI hemorrhage rate also low, and so now comparing the safety data between Saraf and amenities. Of course we see more. More grade one into diarrhea. It’s Arafa nib and less with a tease. Oh Bev hand foot skin reaction, really exclusively with Saraf nib decreased appetite in both groups hypertension and we see that in Seraphim also. Of course, because there’s
partial veg F inhibition there.

Some infusion related reactions,

Some proteinuria which we see also

with veg F inhibition and are used

to checking blood pressure at every

visit and checking your Infor for

protein as we do with bevacizumab.

Another disease groups.

And importantly,

you know for the phase one and phase three

study all patients had to have an EGD

within six months of initiating therapy,

so you know.

Now we think of really doing that

exclusively for the patients

who have underlying cirrhosis.
But for the studies they didn’t.

Distinguish between patients who did or did not have cirrhosis,

so all patients had an EGD within six months of starting therapy and they had to have verisys treated according to local standard of care, and so importantly, looking at the upper GI bleeding rate in the combination versus Seraphim. EBIT increased from 4.5% in Strafford, up to 7% with a tease. Oh bed, which is considered safe and also importantly thinking about quality of life.
00:22:31.750 --> 00:22:33.454 All patients filled out.
NOTE Confidence: 0.766574374
00:22:33.454 --> 00:22:35.584 Patient reported outcomes on this
NOTE Confidence: 0.766574374
00:22:35.584 --> 00:22:37.814 study and patients reported a
NOTE Confidence: 0.766574374
00:22:37.814 --> 00:22:39.979 significantly better quality of life
NOTE Confidence: 0.766574374
00:22:39.979 --> 00:22:42.676 with a time to clinical deterioration.
NOTE Confidence: 0.766574374
00:22:42.680 --> 00:22:45.488 Much improved from 3.6 months on
NOTE Confidence: 0.766574374
00:22:45.488 --> 00:22:48.368 Seraphim to 11.2 months on a tease.
NOTE Confidence: 0.766574374
00:22:48.370 --> 00:22:49.072 Oh Bev,
NOTE Confidence: 0.766574374
00:22:49.072 --> 00:22:51.880 so not only are we seeing increases in
NOTE Confidence: 0.766574374
00:22:51.961 --> 00:22:54.936 survival and progression free survival,
NOTE Confidence: 0.766574374
00:22:54.940 --> 00:23:00.556 but we're actually seeing patients
NOTE Confidence: 0.766574374
00:23:00.556 --> 00:23:03.720 reporting that they feel like they
NOTE Confidence: 0.766574374
00:23:03.720 --> 00:23:06.537 have a better quality of life for
NOTE Confidence: 0.766574374
00:23:06.540 --> 00:23:09.256 significantly more months on this regimen.
NOTE Confidence: 0.766574374
00:23:09.260 --> 00:23:10.022 So you know, based on this data,
So it is so Bev is the first line.

Preferred option for patients who are considered good countenance for the regiment.

And this was really a game changer in the field.

So thinking about combination therapy, this is really the gold standard now, but will go through some emerging data.

So I wanted to go back first and think about now the second line. You know the second line data that we have, so again, you know the initial studies were.
with tyrosine kinase inhibitors.

So these studies were designed when Saraf and it was the only drug approved and. They were randomized to placebo and so in this study the celestial study patients were randomized 2 to one to khabbaz antonym or to placebo with similar stratifications. And based on this study, the progression free survival increased from about two months to 5.2. There was a very low response rate with cabozantinib that we often see with tyrosine kinase inhibitors, you know. And so very few partial responses. It was mostly stable disease that was seen,
but there was an overall survival benefit of another two months. You know which is interesting. So is there something really different? About the pathways targeted with cabins, antonym or would just staying on any TKI kind of post progression still give you some. You know some survival benefit, but this was positive data. There were also mentioned some patients who received this in the third line on the study and then a similar design. The resource study looked at red graph nib versus placebo and very similar design. of primary endpoint of overall survival.
And you can see here that there was a survival benefit of again about a two month benefit here. This is the progression free survival curves and the probability of progression here. And if you look at all the subgroups that favored by graphene, if also so cab is answered have been red graph, and if we’re both approved in the second line, you know for those who have experience with using these drugs, I would say I think that overall cabins antonym. Is probably better tolerated
than than Reg Raffa nib.

But a similar kind of TKI side effects,

and then to mention you know other other data in the veg F area,

so ramucirumab,

another veg F inhibitor,

was looked at in the REACH study where they looked at this in the second line versus placebo,

was a negative study.

But in subset analysis there seemed to be a benefit in the patients who had an AFP level of greater than 400.

So they went back and design the reach two study and so using similar criteria.
But for this study they only included patients who had a baseline AFP level of greater than 400 and they were randomized 2 to one to ramucirumab or placebo and that study did show a survival benefit and then if you pull the data from this study plus the patients who had an AFP of over 400 from the first reach study, you see that there was. Clearly, uh, you know positive benefit again in the same range of a couple of months. So for patients with an AFP level of over 400 for second line therapy, this is another potential option.
00:26:57.650 --> 00:27:00.326 So now thinking of you know.

00:27:00.330 --> 00:27:02.694 So I mentioned before that nivolumab and pembrolizumab were both approved as conditional approvals pending randomized data.

00:27:02.694 --> 00:27:04.846 and pembrolizumab were both approved as conditional approvals pending randomized data.

00:27:04.846 --> 00:27:06.886 as conditional approvals pending randomized data.

00:27:06.886 --> 00:27:07.906 randomized data.

00:27:07.910 --> 00:27:10.514 So the two companies took different approaches in thinking about randomized.

00:27:10.514 --> 00:27:13.070 Studies this Checkmate 459 study looks at nivolumab versus rap native sorafenib as first line treatment and so again looks at similar patient population.

00:27:13.070 --> 00:27:15.130 Studies this Checkmate 459 study looks at nivolumab versus rap native sorafenib as first line treatment and so again looks at similar patient population.

00:27:15.130 --> 00:27:17.654 looks at nivolumab versus rap native sorafenib as first line treatment and

00:27:17.654 --> 00:27:20.006 so again looks at similar patient population.

00:27:20.006 --> 00:27:23.250 They looked at primary endpoints

00:27:23.250 --> 00:27:25.105 They looked at primary endpoints

00:27:25.105 --> 00:27:26.960 of time to progression and

00:27:26.960 --> 00:27:28.864 overall survival and secondary endpoints of response rate

00:27:28.864 --> 00:27:30.700 overall survival and secondary endpoints of response rate

NOTE Confidence: 0.80620193
and progression free survival. An you know the study did not meet its primary endpoint so you could see that the lines really cross. There’s a little bit of separation at the end. You know, it’s interesting because we know that there is a percent of patients right in about the 18% range that responds to pembrolizumab and nivolumab, and so you know you could argue the subtleties of the statistical analysis of the study of how it maybe could have met the primary endpoint if it had been designed differently.
but it was a negative study, and similarly, you know the Pember Lizum app study. They actually went for the second line indication. And randomized to best supportive care, which seems to be a very low bar. Knowing again that we see, you know, usually about an 18% response rate. With pembrolizumab they randomized over 400 patients to Pembroke Plus over 400 patients to Pembroke Plus best supportive care versus placebo. best supportive care versus placebo. Plus best supportive care, but they split the primary endpoint and so even though these P values are very low,
they actually did not meet the threshold for the study, and so I think one could argue that if the study had been designed a little bit differently with maybe just one primary endpoint and the other. As a secondary endpoint, it may have been positive, but basically both of these studies turned out to be negative, and it remains to be determined what the FDA will do with this data, so they may or may not continue to have an indication as as a single agent therapy in HCC so will probably know more later this year about that,
but I think you know really. Excitingly though, you know there’s a lot more combination therapy that’s being looked at. And so you know, there’s several studies, so one is the LEAP 02 study looking at lens at an IM plus Pember lizum app versus Limbaugh and their balloon. And so this is looking at a combination of right so so PD one inhibition plus a TKI. So this is the Keynote 524 study was the Phase 1B study and that data is already been presented. There was an overall response rate of.
but I just caution you that when the Phase one data was initially presented, the response rate.

You know from the beginning was very high, even higher than this, and so you know as you get randomized data, the response rate often comes down so you know the final data for this may not be as high as this, ’cause often the patient selection for the Phase one study is very selective. An in the Phase one study they had a median overall survival of 2022 months and that was about 100 patients. And so I think it will be really interesting to see the combination
NOTE Confidence: 0.80620193
00:30:31.976 --> 00:30:33.170 data for this.
NOTE Confidence: 0.80620193
00:30:33.170 --> 00:30:33.900 You know,
NOTE Confidence: 0.80620193
00:30:33.900 --> 00:30:36.090 and then you could really kind
NOTE Confidence: 0.80620193
00:30:36.090 --> 00:30:37.790 of think about right?
NOTE Confidence: 0.82374823
00:30:37.790 --> 00:30:40.100 Which patient might be best suited
NOTE Confidence: 0.82374823
00:30:40.100 --> 00:30:41.640 for which combination therapy,
NOTE Confidence: 0.82374823
00:30:41.640 --> 00:30:43.602 and similarly the Cosmic 312 study
NOTE Confidence: 0.82374823
00:30:43.602 --> 00:30:45.953 is looking at cabins antonym plus
NOTE Confidence: 0.82374823
00:30:45.953 --> 00:30:48.282 atezolizumab versus rafanan, so again,
NOTE Confidence: 0.82374823
00:30:48.282 --> 00:30:50.437 you know another tyrosine kinase
NOTE Confidence: 0.82374823
00:30:50.437 --> 00:30:53.106 inhibitor plus plus PD one inhibitor and
NOTE Confidence: 0.82374823
00:30:53.106 --> 00:30:55.904 you know we know right cab is antonym
NOTE Confidence: 0.82374823
00:30:55.904 --> 00:30:58.196 is active in second line therapy.
NOTE Confidence: 0.82374823
00:30:58.200 --> 00:31:00.881 And as I mentioned there were some
NOTE Confidence: 0.82374823
00:31:00.881 --> 00:31:03.289 patients that had been treated as.
NOTE Confidence: 0.82374823
Third line therapy.

So this I think this is a promising combination also and then the other two studies.

Look at the combination of with a CTL A4 antibody right and so we know from other diseases you know, adding a CTL A4 antibody often increases response rate in immune therapy, but also increases the immune related adverse events, and so the check mate and I have some slides to show you from this, But the check Mate 040 study, which was the 1B study that I showed you the single agent data for.
Also had a small arm that looked at the combination of it Bluma, Mebane, nivolumab and so their response rate was up to 32% there with an impressive median overall survival of over 20 months. And so this study is looking at the combination of niveau nippy versus Seraphim, Berlin, Baton IB in the first line, and then another combination again of PD. One inhibition with a CTL A4 antibody is the durvalumab and tremelimumab study. And so this is the Himalayas study that I'll show you the study design for.
As you know so far has showed a response rate of 24% and the median overall survival of 19 months with the one of the arms of this study. So you know. There will be a lot of data coming which will be exciting to see the final data and then I think there’s a lot to debate about which patients are best suited. really kind of peacing out who responded, what the adverse events were. You know? What were the difference in side effects of who might be a better
00:32:56.872 --> 00:32:58.542 candidate for addition with the

00:32:58.614 --> 00:33:00.854 CTA for antibody versus bevacizumab

00:33:00.854 --> 00:33:03.094 versus a tyrosine kinase inhibitor?

00:33:03.100 --> 00:33:05.100 And those will be exciting.

00:33:05.100 --> 00:33:07.284 Discussions to have just to show

00:33:07.284 --> 00:33:10.040 you this is the Himalaya design,

00:33:10.040 --> 00:33:12.215 so the development plus Tremelimumab

00:33:12.215 --> 00:33:14.878 as first line therapy and they

00:33:14.878 --> 00:33:17.362 used a couple of different arms

00:33:17.362 --> 00:33:19.794 of tremelimumab dosing so you know

00:33:19.794 --> 00:33:22.026 in the other disease groups where

00:33:22.026 --> 00:33:24.048 there’s been approval for CTA

00:33:24.048 --> 00:33:26.108 for combination like in Melanoma.

00:33:26.110 --> 00:33:28.540 Typically the patients get four

00:33:28.540 --> 00:33:30.970 cycles with the combination and

NOTE Confidence: 0.82374823
then go on to the single agent drug of Nuvola MAB by itself.

So in this study they did a couple of different regimens. One where there were four doses of tremelimumab and also looking at different doses. Then there was also a small cohort that looked at just one dose of tremelimumab to start, and that one actually seemed to have more responses, but less toxicity, and so it’ll be interesting to see in the end if that’s the arm that really is the best one to move forward to within HCC,
and this is to show you the group I mentioned from the Phase one study.

from the Checkmate 040 study of the combination of Nivolumab and IP,

aluminum AB and so they used again. You know a few different dosing schemes for the patients,

for HCC the winner was really. Than evil one it be 3 arm that had the best overall survival and so that’s sort of these colors came out different on this one, but basically it’s this dosing here of the four doses and then they
00:34:40.526 --> 00:34:43.172 continue with just nuvola MAB alone.
NOTE Confidence: 0.8228799
00:34:43.180 --> 00:34:46.190 And you know, so lots of so.
NOTE Confidence: 0.8228799
00:34:46.190 --> 00:34:47.910 Lots of good questions.
NOTE Confidence: 0.8228799
00:34:47.910 --> 00:34:49.630 Kind of thinking about,
NOTE Confidence: 0.8228799
00:34:49.630 --> 00:35:00.488 you know the combination data and.
NOTE Confidence: 0.8559677
00:35:00.488 --> 00:35:02.800 T wo of the biggest questions to really
NOTE Confidence: 0.8559677
00:35:02.800 --> 00:35:05.201 think about our how do we sequence
NOTE Confidence: 0.8559677
00:35:05.201 --> 00:35:07.697 after tease Alisme Heaven Bevis is mad,
NOTE Confidence: 0.8559677
00:35:07.700 --> 00:35:10.122 so if that’s the first line option
NOTE Confidence: 0.8559677
00:35:10.122 --> 00:35:12.779 then what do we do in second line?
NOTE Confidence: 0.8559677
00:35:12.780 --> 00:35:15.545 Do we restart with a tyrosine kinase
NOTE Confidence: 0.8559677
00:35:15.545 --> 00:35:17.568 inhibitor like Lynn Fat and if
NOTE Confidence: 0.8559677
00:35:17.568 --> 00:35:20.125 so go to a first line and kind of
NOTE Confidence: 0.8559677
00:35:20.125 --> 00:35:22.596 start through the you know the first
slide into the second line again.

Or do we think about going into combination immunotherapy?

You know we have. It be anevo, now approved as a second line regimen,

and then do we use another TKI and the third line?

You know, I think about and I mean, obviously you know this is relatively new,

'cause we've only had approval of the regimen since June,

and so depending on how long someone’s on the regimen,

I think that could potentially help guide
you know what you would want to do next.
So if someone really, I think progressives quickly through a tease. Oh, Bev.
I don’t know that going to a combination immune therapy you know regimen would be the best, but perhaps if someone responds and then eventually progresses, you may want to think about combination immune therapy.
For the patients that tolerate a tyrosine kinase inhibitor and maybe have good control or decrease in AFP initially,
I think it’s very reasonable to go to another tyrosine kinase inhibitor. You know, maybe for patients that really did not tolerate a TKI well, even at reduced dose, and they have a high AFP that maybe a group that I would think more about ramucirumab in. I think another big question to think about, you know, for treating these patients, is that all of the clinical child data that you know that I presented here really only reflects the child Pugh, a population and maybe a couple of B7’s.
And you know,

as we know,

the majority of the patients that were actually treating in our practice have child Pugh B disease and so the question then is what is safe to give those patients?

And as the data that we are seeing. From the trial really, is it really applicable to these patients?

So as a tease?

Oh, and Bev safe in the child Pugh B patients.

I think we’re going to have a lot of data from that soon.
You know, as patients are being treated out in the community, you know patients with child PB disease or being treated regularly. My hope is that at least everyone's getting endoscopies so that we're not seeing higher incidence of GI bleeding. But that's certainly a concern that I have. An you know which tyrosine kinase inhibitors you know. We're better to give. We have a lot of data for Saraf.
and if in Child Pugh B disease, so there was a Gideon registry that included a lot of data for patients with Child PB and even somewhat see disease which basically showed that patients would see disease barely or on the drug for any length of time and don’t seem to be on it long enough. Overall I would say it seems to me that these patients really
NOTE Confidence: 0.8055654
00:38:30.400 --> 00:38:32.776 wind up with more dose reductions,
NOTE Confidence: 0.8055654
00:38:32.780 --> 00:38:35.139 which is what the data suggests below.
NOTE Confidence: 0.8055654
00:38:35.140 --> 00:38:37.506 None of these were randomized studies right,
NOTE Confidence: 0.8055654
00:38:37.510 --> 00:38:39.538 but just you know more observation.
NOTE Confidence: 0.8055654
00:38:39.540 --> 00:38:41.948 ULL and I think the really when we
NOTE Confidence: 0.8055654
00:38:41.948 --> 00:38:43.738 think about the combination data
NOTE Confidence: 0.8055654
00:38:43.738 --> 00:38:45.976 from the slide I showed before
NOTE Confidence: 0.8055654
00:38:45.976 --> 00:38:47.988 right of thinking of you know,
NOTE Confidence: 0.8055654
00:38:47.990 --> 00:38:50.686 are we adding a see TL A4 antibody,
NOTE Confidence: 0.8055654
00:38:50.690 --> 00:38:53.168 a tyrosine kinase or Beves ISM AB?
NOTE Confidence: 0.8055654
00:38:53.170 --> 00:38:56.106 I think it’s going to be really important
NOTE Confidence: 0.8055654
00:38:56.106 --> 00:38:58.900 to have data in those groups later
NOTE Confidence: 0.8055654
00:38:58.900 --> 00:39:01.372 with Child Pugh B patients because
NOTE Confidence: 0.8055654
00:39:01.372 --> 00:39:04.256 it may turn out that one combination
NOTE Confidence: 0.8055654
00:39:04.256 --> 00:39:06.668 is clearly better in that group,
or at least you know safer.

And so I think having that data after we have the initial trial data is going to be really important. So you know one thing that I haven’t mentioned at all, which we usually spend a lot of time in other oncology talks. Thinking about right is molecular directed therapy. And so I just wanted to mention, you know, I think that this is a big issue, right? So we’re only talking about mostly tyrosine kinase inhibitors and then immune therapy.
So we really have no biomarker. You know we have ramucirumab with a higher AFP, although I wouldn’t necessarily call that a. No marker, you know, and even for the immune therapy responses in many diseases, you see that there is clear correlation with PDL one status and. There does not seem to be any correlation for HTC, which makes it harder for us to know.
which patients are more likely to respond.

You know, there have been studies with met amplification. There's some studies looking at chromosome remodeling, which will be interesting to see right, but so far we have. No molecular directed therapy we are aware of course of the mutational landscape of HCC, you know, but unfortunately right the ones on the top there, on the top there, we don’t have any drugs for and the drugs that we do have for the
00:40:46.242 --> 00:40:48.819 targets at the bottom of the slide,
00:40:48.820 --> 00:40:52.168 right or very uncommon in HCC.
00:40:54.960 --> 00:41:04.838 a couple of Baraka carriers which
00:41:02.370 --> 00:41:04.838 especially ones that had no underlying
00:41:07.298 --> 00:41:09.288 cirrhosis and this kind of confusing
00:41:04.838 --> 00:41:07.298 why they developed HCC and we found
00:41:09.288 --> 00:41:10.880 have not been well described in
00:41:02.370 --> 00:41:04.838 the literature as thinking about
00:41:10.880 --> 00:41:12.825 and we’ve seen some back one mutations,
00:41:07.298 --> 00:41:09.288 HCC’s abrao related disease.
00:41:10.880 --> 00:41:13.659 And we’ve seen some back one mutations,
00:41:09.288 --> 00:41:10.880 so I think it’s you know it’s interesting
00:41:13.660 --> 00:41:16.476 to find these select patients,
00:41:16.476 --> 00:41:18.838 although it’s not clear that they
00:41:18.840 --> 00:41:21.222 necessarily, you know, respond better to.
PARP inhibitors or that there’s really necessarily other targeted therapy for them, but I think you know the more patients we sequence and do testing on. We may. You know, we may find more. And of course you know a lot of the patients with HCC get treated in the absence of biopsy, which is really unique to this to this disease. And so going back to the BC else staging system. So I think this is an important slide to kind of circle circle back to right so? You know, thinking of the narrow role where oncology could fall kind of
just in this advanced stage C group, you know we’ve now accumulated rates of several different drugs in this category, so adding into seref and if now we have a tease.

Oh, and Bev approved in the first line. Also Lynn VAT and approved in the first line cabins, antonym burgraaff and IMMA ramucirumab approved in the second line. Also it be niveau right and then we have pen Bruen Niveau still kind of conditionally approved a single agent drugs. But I think those will be largely replaced soon by the multiple combination
studies of data that’s going to come out, and so we’ve really added a lot in this category here, but I think that even more importantly, right now we need to kind of think of the whole, you know, the whole staging system he ran. Really say now that we finally have more effective therapies. You know, in my mind, combination doesn’t just mean combination of two systemic therapies, but it’s really combination of all the modalities that we use in this disease, with potentially systemic therapy,
and so you know, there’s a lot of interest now. I’m thinking of Advent therapy, thinking of combination therapy with local therapy. This study is that it weren’t done in the past. You know, looked at Saraf, and it’s so there was an adjutant fit study that looked at Seraphim after reception. That study was negative, but as far as I know, I don’t think there’s a tyrosine kinase inhibitor approved in any.
diseases adjutant therapy because,

you know,

when you think of the mechanism of action.

I don’t think it’s actually really illuminating microscopic disease,

and so it’s not surprising.

I guess in retrospect that it wasn’t a positive study.

There was also the first study that I opened when I came here was the E Card 1208 study which was looking at the role of adding saraf number placebo to sequential tastes.

And you know,

I think it’s interesting ’cause going back.

You know,
to almost 10 years ago now. You know doing this study. It accrued really poorly across the country, and so the study never finished. Accrual and it, kind of. Ended halfway through the data somehow is still not published from it. There was another study in the UK that looked at a similar question in a smaller way, but you know, I think partially why it didn’t accrue well was because there wasn’t the kind of multidisciplinary groups that were able to do studies together.
Because this study really required a relationship with interventional radiology that allowed everyone to work together, and really approach the patients. Before they moved on to systemic therapy to get them interested in the study and work together. Which is why I think we're in such a different place now in 2021 that I think we have the ability at Yale, as do other centers to really do multidisciplinary studies like the AGEMENT study, and like the combination with local therapy study. And so I'm excited to really think
about what the role is for combination therapy in this intermediate stage. You know group and so I just wanted to mention a couple of studies that we have open now at Yale. So one of them is the Keynote 937 study. So this study is looking at Agilent Pember Lizum app versus placebo. So for patients that have had a complete radiologic response after surgical resection or local ablation of HCC, they're planning to enroll close to 1000 patients. In one to one randomization September, Liz, member,
placebo,
which would be for one year and then they’ll be followed for survival with primary objectives of recurrence free survival in overall survival and also safety and patient reported outcomes will be collected, so I think this is an interesting study. This is not the only adjuvant study, you know. There’s other companies that are doing kind of similar design. Similar design studies, so I think this will be interesting. And then I wanted to mention that we also have a study open of the
safety and efficacy of live at
and it was Pember Lizum app.
So one of the.
Doublet regimens that’s being looked at in the advanced setting.
That’s a typo there versus placebo in combination with tastes
and David Mann office.
The Pi of this study here at Yale, and we have the primary outcomes of progression,
free survival and overall survival,
and then multiple secondary outcomes that will be looked at by resist
and by the modified resist.
And so I think you know, and again, there's other studies in combination with tastes and why 90. That are in development or, you know, recently started in the country. And I think this will give us really interesting information to see you know, are these patients kind of better off by getting systemic therapy earlier in the algorithm and.

We also are planning to open the Morpheus HCC study so this is, Morpheus where it allows them to do a bunch of small protocols. Kind of that can cycle into the
00:47:37.733 --> 00:47:39.820 trial as there’s new combinations

00:47:39.820 --> 00:47:42.008 that look potentially interesting.

00:47:42.010 --> 00:47:44.768 So the competitor the comparator arm in

00:47:44.768 --> 00:47:48.040 this study is the combination of a tease.

00:47:48.040 --> 00:47:49.177 Oh and Bev.

00:47:49.177 --> 00:47:51.830 So all patients get that and then

00:47:51.920 --> 00:47:55.040 right now the experimental stage one.

00:47:55.040 --> 00:48:00.329 Looks at a drug added called to

00:48:00.329 --> 00:48:02.789 Raghuram AB and then the other one

00:48:02.871 --> 00:48:05.479 going to be 2 new arms opening soon

00:48:05.479 --> 00:48:07.990 which I can tell you more about.

00:48:07.990 --> 00:48:10.552 Once once we have those open this

00:48:12.800 --> 00:48:15.131 but once the two new arms open
00:48:15.131 --> 00:48:17.609 will will be opening the study.
NOTE Confidence: 0.831055
00:48:17.610 --> 00:48:20.200 Hopefully in the next couple of months.
NOTE Confidence: 0.831055
00:48:20.200 --> 00:48:23.644 So this will be a good first
NOTE Confidence: 0.831055
00:48:23.644 --> 00:48:25.120 line systemic therapy.
NOTE Confidence: 0.831055
00:48:25.120 --> 00:48:29.240 Option for our patients.
NOTE Confidence: 0.831055
00:48:29.240 --> 00:48:30.780 And so you know,
NOTE Confidence: 0.831055
00:48:30.780 --> 00:48:32.705 I just wanted to mention,
NOTE Confidence: 0.831055
00:48:32.710 --> 00:48:33.360 as Mario,
NOTE Confidence: 0.831055
00:48:33.360 --> 00:48:35.635 was discussing in the introduction.
NOTE Confidence: 0.831055
00:48:35.635 --> 00:48:37.933 that this disease really requires
NOTE Confidence: 0.831055
00:48:37.933 --> 00:48:38.889 multidisciplinary care.
NOTE Confidence: 0.831055
00:48:38.890 --> 00:48:41.344 I really enjoy meeting with my
NOTE Confidence: 0.831055
00:48:41.344 --> 00:48:42.980 colleagues every Thursday at
NOTE Confidence: 0.831055
00:48:42.980 --> 00:48:45.066 our at our liver tumor board.
NOTE Confidence: 0.831055
00:48:45.070 --> 00:48:46.069 And, you know,
I think we have great discussions on the patients because even though there are guidelines, they really are just guidelines and there never a replacement for the real discussion that happens, you know, centered. For each patient, and so you know, I think as we have more systemic therapy options, we have to think about, you know the role for that and how that affects the other modalities of treatment that we’re giving and how best to sequence things.
over the last 10 years to have such a great team to work with, and also to see so much growth and new treatment options. For our patients, so with that I’ll end in leave some room for questions. Thank you.

Fuller’s courses then at Andrew. Very successful 10 years in which we saw everything changing so we have already a few questions one. Is a question is would you stop at ease or Bev completely if they do have very cell bleed on treatment?
00:50:14.830 --> 00:50:17.310 Yeah, you know that’s that’s a good question.
00:50:17.310 --> 00:50:19.782 I mean, so I guess the question then
00:50:19.782 --> 00:50:22.267 is you know if they could be so.
00:50:22.270 --> 00:50:24.750 I mean, hopefully the risk is very low.
00:50:24.750 --> 00:50:26.920 ’cause if we’re selecting the right patients,
00:50:26.920 --> 00:50:29.090 then hopefully they shouldn’t have a bleed.
00:50:29.090 --> 00:50:31.146 And so I guess the question then you
00:50:31.146 --> 00:50:33.477 know if someone bleeds where they on
00:50:33.477 --> 00:50:35.910 anticoagulation do they need to be on
00:50:35.910 --> 00:50:37.770 an anticoagulation and could they be
00:50:37.770 --> 00:50:39.494 banded and then be considered back?
00:50:39.494 --> 00:50:42.420 Kind of in a low risk population you know.
00:50:42.420 --> 00:50:44.948 I will mention that there was another arm
00:50:44.948 --> 00:50:47.895 on the study from the Phase one study so.
00:50:47.900 --> 00:50:49.868 After the arm A was positive,
the combination the FDA asked for data
for single agent at Easel is a map,
so there was another arm on the Phase
one study that looked at the combination
versus a tease oh alone and you really
do not get the same responses with a tease.
So I think if you could you would
try to continue the you know the
combination if if you were able to,
you know bans them or you know put
them back in a lower risk category.
I haven’t had that.
I haven’t been in that situation yet,
but I think I think it’s something
that you know. If we could, we would.
We would try to get them back on systemic therapy if they were responding.

So let me ask you a question in this regard, but so outside of a try, we're probably you will have to have a certain month of leeway. You know you probably need to have a recent endoscopy, but we do have a very well detailed guidelines, so you know what, how many times the patient should undergo, but it’s still in the Earth in the Oscar people, very sick screening, you know where they are in.
A beta blocker there.
Nothing but the blocker, so it’s it’s a pretty well a detailed protocol.
In order for you to put the patient in one of such a treatment.
What do you need?
I mean, do you need somebody who has already done at an endoscopy?
Or do you need to have something?
A more recent and what are the mechanism of breathing in that case?
Yeah, so I mean you know the truth is right.
So we treat a lot of other cancers like colon cancer.
Bevacizumab is a staple of therapy, you know.
Unfortunately we just see bleeding sometimes. You know we see bleeding from the tumor or we just see you know we see other causes of bleeding. So it’s not only variceal bleed, you know there was a patient on the study that just had like an abdominal hemorrhage. So you know. So there’s always a risk with Bevis ISM AB and let you know when patients are on anticoagulation, right? You have to think about that too if you think they might be having a surgical procedure, right? So? You know there’s more thought around that,
but overall you know if they’ve had an endoscopy. Even if it was a little bit out of six months, but I, but they have a hepatologist following them, who thinks that their risk is low. You know, I think right whenever patients are not on a trial, I think there’s always a little bit more leeway kind of discussion, you know, and thinking about each patient, I just think that you know it would be a mistake. I think for an oncologist to treat a patient like this without any hepatology input.
You know, and so I think if you at least have the hepatology input of someone familiar with this data to really say, I think this patient is low risk even if you didn’t do it exactly in the timeframe that was required on the child. I think that’s fine.

Another question, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer. Another question, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer. Another question, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer, thank you for your answer. Another question. I think that’s fine, there’s another question.

from Leshan why Japan is excluded and food Japan and US together. Any specific missing?

90
Yeah, I don’t know.

You know I have a feeling that was more based on how the company was opening the study. Because you’re right, I don’t have a good answer for that, but I think it probably has to do with where the company is located and how they set up the child because I don’t think that there really is a separate signature.

OK, more questions so.