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
the patient is seeing in the liver cancer clinic and then discuss the tumor board where everybody participate. You see here on all the discipline that take part to our discussion and then a treatment is. The patient is referred for the treatment and the follow up. So today I am very happy to present Doctor Spacetime. Stacy is a very valued member of our program. She had this battle studies. I looked gassed in New York she got the ND in the University and then a master in science.
She did her residency in the Montefiore Medical Center in New York City 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 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.
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,
you know someone would look back
at me in the corner and say, do you want to see this patient
and put them on Seraphim?
And so I feel like the story that I
could present today is kind of all
the new treatment options really come
in parallel with my experience and
kind of growth here in this field.
So you know,
really seraphim’s been the one drug
that’s been around for awhile and
now we have different treatment
options and we’re kind of, you know,
if intent therapies, right? And then the local regional therapies for the Child Pugh for the BCLCB patients. And so you know, I think. Also, although this staging system isn’t perfect, it really reflects the importance of thinking of the underlying liver function of the patient, their performance status and. The tumor characteristics and so starting at the beginning here with the sharp study, which I’m sure everyone is familiar with.
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. And in this study we saw an overall survival benefit going from 7.9
00:06:26.219 --> 00:06:27.979 months with placebo to 10.7
NOTE Confidence: 0.92804784
00:06:27.979 --> 00:06:30.209 months and so based on this data,
NOTE Confidence: 0.92804784
00:06:30.210 --> 00:06:32.166 this became the new standard of
NOTE Confidence: 0.92804784
00:06:32.166 --> 00:06:34.499 care option and you could see also
NOTE Confidence: 0.92804784
00:06:34.499 --> 00:06:36.739 that there was a time to radiologic
NOTE Confidence: 0.92804784
00:06:36.805 --> 00:06:38.977 progression on this on this drug
NOTE Confidence: 0.92804784
00:06:38.977 --> 00:06:40.063 and just remember,
NOTE Confidence: 0.82814777
00:06:40.070 --> 00:06:41.502 you know Seraphim, right?
NOTE Confidence: 0.82814777
00:06:41.502 --> 00:06:43.650 It’s not chemotherapy in the exact
NOTE Confidence: 0.82814777
00:06:43.717 --> 00:06:45.505 strict sense of the term rate,
NOTE Confidence: 0.82814777
00:06:45.510 --> 00:06:47.934 but it’s a it’s a TKI and multi
NOTE Confidence: 0.82814777
00:06:47.934 --> 00:06:49.250 tyrosine kinase inhibitor,
NOTE Confidence: 0.82814777
00:06:49.250 --> 00:06:51.483 and because of that you know it’s
NOTE Confidence: 0.82814777
00:06:51.483 --> 00:06:52.990 really targeting multiple pathways.
NOTE Confidence: 0.82814777
00:06:52.990 --> 00:06:55.280 It’s kind of a dirty.
NOTE Confidence: 0.82814777
00:06:55.280 --> 00:06:57.938 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, you know more 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 you know 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,
the progression free survival was better. Although the study was not powered. You know to have this as the primary endpoint. And if you look at the bottom, the overall response rate, which 9% to me is high for seraphon. But it was up to 24% with the Lynn Vatanen arm. And so you know you could argue without the benefit of overall survival. Whether there really is a benefit of having a response. But I think most most people 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
going this as first line therapy.
And what you could see?
You know on these 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, an 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, 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,
00:13:39.760 --> 00:13:41.396 you know, survival benefit,
NOTE Confidence: 0.8179294
00:13:41.396 --> 00:13:44.821 but there was a signal that there was
NOTE Confidence: 0.8179294
00:13:44.821 --> 00:13:47.943 clearly benefit of giving anti VEGF therapy,
NOTE Confidence: 0.8179294
00:13:47.950 --> 00:13:50.386 but there was never approval for
NOTE Confidence: 0.8179294
00:13:50.386 --> 00:13:52.770 or an application for approval.
NOTE Confidence: 0.8179294
00:13:52.770 --> 00:13:54.710 You know for the drug.
NOTE Confidence: 0.8179294
00:13:54.710 --> 00:14:00.916 So before this berbasis map was not an
NOTE Confidence: 0.8179294
00:14:00.920 --> 00:14:03.741 approved drug for each CC and you know,
NOTE Confidence: 0.8179294
00:14:03.741 --> 00:14:06.116 it’s interesting to think about why there
NOTE Confidence: 0.8179294
00:14:06.116 --> 00:14:08.671 is potentially synergy between these two
NOTE Confidence: 0.8179294
00:14:08.680 --> 00:14:11.008 drugs as opposed to an additive benefit,
NOTE Confidence: 0.8179294
00:14:11.010 --> 00:14:13.326 Mab does normalize the tumor vasculature?
NOTE Confidence: 0.8179294
00:14:13.330 --> 00:14:14.882 An actually allows for
NOTE Confidence: 0.8179294
00:14:14.882 --> 00:14:16.434 more T cell infiltration,
NOTE Confidence: 0.8179294
00:14:16.440 --> 00:14:19.536 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. 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
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 was split between East performance status of zero and one and the majority in Asia and the other 40% were in Japan or the US patients were split between East kog performance status, and the other 40% were in Asia.
00:15:41.280 --> 00:15:44.261 of the patients had Child Pugh A5 disease with 20% ASICS and you could see there were only six patients that wound up in rolling with B7 disease. About half the patients had hepatitis B, reflecting the mostly Asian population that enrolled 30% with hepatitis C and another 20% more nonviral. The majority of the patients had extrahepatic spread. About half had Macrovascular invasion. And so when you think of those two as being kind of high risk characteristics, 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 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. Then there were many patients in blue, it’s stable disease than the red. The red bars show progressive disease, 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.
one data that I am brave 150

study was designed and this is

a randomized study then to look

Oh Bevaus 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 ASCO meeting in January. So this is newer, newer data and you know you could see here that the overall survival for Seraphim was 13.4 months, so as these studies go on in time, the median overall survival for this rafina Barb keeps getting better, reflecting that most patients are going on to at least second line therapy and the median overall survival for the 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. So not surprisingly, 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
00:21:27.856 --> 00:21:30.826 partial veg F inhibition there.
NOTE Confidence: 0.766574374
00:21:30.830 --> 00:21:32.494 Some infusion related reactions,
NOTE Confidence: 0.766574374
00:21:32.494 --> 00:21:34.990 some proteinuria which we see also
NOTE Confidence: 0.766574374
00:21:35.058 --> 00:21:37.277 with veg F inhibition an are used
NOTE Confidence: 0.766574374
00:21:37.277 --> 00:21:39.389 to checking blood pressure at every
NOTE Confidence: 0.766574374
00:21:39.389 --> 00:21:41.585 visit and checking your Infor for
NOTE Confidence: 0.766574374
00:21:41.585 --> 00:21:43.820 protein as we do with bevacizumab.
NOTE Confidence: 0.766574374
00:21:43.820 --> 00:21:44.930 Another disease groups.
NOTE Confidence: 0.766574374
00:21:44.930 --> 00:21:45.670 And importantly,
NOTE Confidence: 0.766574374
00:21:45.670 --> 00:21:48.712 you know for the phase one and phase three
NOTE Confidence: 0.766574374
00:21:48.712 --> 00:21:51.539 study all patients had to have an EGD
NOTE Confidence: 0.766574374
00:21:51.539 --> 00:21:54.200 within six months of initiating therapy,
NOTE Confidence: 0.766574374
00:21:54.200 --> 00:21:55.067 so you know.
NOTE Confidence: 0.766574374
00:21:55.067 --> 00:21:57.090 Now we think of really doing that
NOTE Confidence: 0.766574374
00:21:57.162 --> 00:21:59.018 exclusively for the patients
NOTE Confidence: 0.766574374
00:21:59.018 --> 00:22:00.874 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.
All patients filled out.

Patient reported outcomes on this study and patients reported a significantly better quality of life with a time to clinical deterioration.

Much improved from 3.6 months on Seraphim to 11.2 months on a tease.

Oh Bev, so not only are we seeing increases in survival and progression free survival, but we’re actually seeing patients reporting that they feel like they have a better quality of life for significantly more months on this regimen.

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, and the study 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 over 400 for second line therapy, this is another potential option.
So now thinking of you know. So I mentioned before that nivolumab and pembrolizumab were both approved as conditional approvals pending randomized data. So the two companies took different approaches in thinking about randomized. Studies this Checkmate 459 study looks at nivolumab versus rap native sorafenib as first line treatment and so again looks at similar patient population. They looked at primary endpoints of time to progression and overall survival and secondary endpoints of response rate.
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 best supportive care versus placebo. 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 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 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 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
candidate for addition with the CT A for antibody versus bevacizumab versus a tyrosine kinase inhibitor? And those will be exciting. Discussions to have just to show you this is the Himalaya design, so the development plus Tremelimumab as first line therapy and they used a couple of different arms of tremelimumab dosing so you know in the other disease groups where there’s been approval for CT A for combination like in Melanoma. Typically the patients get four cycles with the combination and
then go on to the single agent 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, and it looks like you know 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
continue with just nuvola MAB alone.

And you know, so lots of so.

Lots of good questions.

Kind of thinking about,

I think the biggest ones you know right now, right eye for me.

Two of the biggest questions to really think about our how do we sequence after tease Alisme Heaven Bevis is mad, so if that’s the first line option so if that’s the first line option then what do we do in second line?

Do we restart with a tyrosine kinase inhibitor like Lynn Fat and if so go to a first line and kind of start through the you know the first
NOTE Confidence: 0.8559677
00:35:22.596 --> 00:35:24.650 slide into the second line again.
NOTE Confidence: 0.8559677
00:35:24.650 --> 00:35:26.678 Or do we think about going
NOTE Confidence: 0.8559677
00:35:26.678 --> 00:35:27.692 into combination immunotherapy?
NOTE Confidence: 0.8559677
00:35:27.700 --> 00:35:29.156 You know we have.
NOTE Confidence: 0.8559677
00:35:29.156 --> 00:35:30.248 It be anevo,
NOTE Confidence: 0.8559677
00:35:30.250 --> 00:35:32.798 now approved as a second line regimen,
NOTE Confidence: 0.8559677
00:35:32.800 --> 00:35:35.624 and then do we use another TKI and
NOTE Confidence: 0.8559677
00:35:35.624 --> 00:35:36.820 the third line?
NOTE Confidence: 0.8559677
00:35:36.820 --> 00:35:39.740 You know, I think about and I mean,
NOTE Confidence: 0.8559677
00:35:39.740 --> 00:35:42.288 obviously you know this is relatively new,
NOTE Confidence: 0.8559677
00:35:42.290 --> 00:35:44.480 'cause we've only had approval of
NOTE Confidence: 0.8559677
00:35:44.480 --> 00:35:45.940 the regimen since June,
NOTE Confidence: 0.8559677
00:35:45.940 --> 00:35:48.130 and so depending on how long
NOTE Confidence: 0.8559677
00:35:48.130 --> 00:35:49.590 someone's on the regimen,
NOTE Confidence: 0.8559677
00:35:49.590 --> 00:35:52.334 I think that could potentially help guide
NOTE Confidence: 0.8559677
you know what you would want to do next. 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. And. 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? 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 with approval now and 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
00:37:57.765 --> 00:38:00.033 and if in Child Pugh B disease,
NOTE Confidence: 0.8559677
00:38:00.040 --> 00:38:01.726 so there was a Gideon registry
NOTE Confidence: 0.8559677
00:38:01.726 --> 00:38:02.850 that included a lot
NOTE Confidence: 0.8055654
00:38:02.911 --> 00:38:04.663 of data for patients with child
NOTE Confidence: 0.8055654
00:38:04.663 --> 00:38:06.637 PB and even somewhat see disease
NOTE Confidence: 0.8055654
00:38:06.637 --> 00:38:08.492 which basically showed that patients
NOTE Confidence: 0.8055654
00:38:08.492 --> 00:38:10.846 would see disease barely or on the
NOTE Confidence: 0.8055654
00:38:10.846 --> 00:38:13.063 drug for any length of time and
NOTE Confidence: 0.8055654
00:38:13.063 --> 00:38:15.367 don’t seem to be on it long enough
NOTE Confidence: 0.8055654
00:38:15.367 --> 00:38:17.907 to really get any benefit from it.
NOTE Confidence: 0.8055654
00:38:17.910 --> 00:38:20.213 We do have some child Pugh B
NOTE Confidence: 0.8055654
00:38:20.213 --> 00:38:22.298 data now with Lynn VAT nib.
NOTE Confidence: 0.8055654
00:38:22.300 --> 00:38:24.804 Um, and we do have some data with
NOTE Confidence: 0.8055654
00:38:24.804 --> 00:38:26.690 with cabins antonym you know.
NOTE Confidence: 0.8055654
00:38:26.690 --> 00:38:28.685 Overall I would say it seems to
NOTE Confidence: 0.8055654
00:38:28.685 --> 00:38:30.400 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,
NOTE Confidence: 0.8055654

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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. So a lot of drug approvals are based on the CPS scores that we get from our pathologist and those multiple studies do not. 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, 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.

00:40:52.170 --> 00:40:54.956 I have sequence in patients this year,

00:40:54.960 --> 00:40:57.510 especially ones that had no underlying

00:40:57.510 --> 00:40:59.969 cirrhosis and this kind of confusing

00:40:59.969 --> 00:41:02.370 why they developed HCC and we found

00:41:02.370 --> 00:41:04.838 a couple of Baraka carriers which

00:41:04.838 --> 00:41:07.298 have not been well described in

00:41:07.298 --> 00:41:09.288 the literature as thinking about

00:41:09.288 --> 00:41:10.880 HCC’s abraco related disease.

00:41:10.880 --> 00:41:13.659 And we’ve seen some back one mutations,

00:41:13.660 --> 00:41:16.476 so I think it’s you know it’s interesting

00:41:16.476 --> 00:41:18.838 to find these select patients,

00:41:18.840 --> 00:41:21.222 although it’s not clear that they

00:41:21.222 --> 00:41:23.880 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 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
00:43:32.350 --> 00:43:34.110 diseases adjutant therapy because,
NOTE Confidence: 0.85235196
00:43:34.110 --> 00:43:34.882 you know,
NOTE Confidence: 0.85235196
00:43:34.882 --> 00:43:37.970 when you think of the mechanism of action.
NOTE Confidence: 0.85235196
00:43:37.970 --> 00:43:40.280 I don't think it’s actually really
NOTE Confidence: 0.85235196
00:43:40.280 --> 00:43:41.435 illuminating microscopic disease,
NOTE Confidence: 0.85235196
00:43:41.440 --> 00:43:43.550 and so it’s not surprising.
NOTE Confidence: 0.85235196
00:43:43.550 --> 00:43:45.345 I guess in retrospect that
NOTE Confidence: 0.85235196
00:43:45.345 --> 00:43:47.140 it wasn’t a positive study.
NOTE Confidence: 0.85235196
00:43:47.140 --> 00:43:49.506 There was also the first study that
NOTE Confidence: 0.85235196
00:43:49.506 --> 00:43:52.252 I that I opened when I came here
NOTE Confidence: 0.85235196
00:43:52.252 --> 00:43:55.163 was the E Card 1208 study which was
NOTE Confidence: 0.85235196
00:43:55.163 --> 00:43:57.910 looking at the role of adding saraf
NOTE Confidence: 0.85235196
00:43:57.910 --> 00:43:59.710 number placebo to sequential tastes.
NOTE Confidence: 0.85235196
00:43:59.710 --> 00:44:00.787 And you know,
NOTE Confidence: 0.85235196
00:44:00.787 --> 00:44:03.300 I think it’s interesting ’cause going back.
NOTE Confidence: 0.85235196
00:44:03.300 --> 00:44:03.964 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, an 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
NOTE Confidence: 0.88146096
00:46:22.138 --> 00:46:24.339 safety and efficacy of live at
NOTE Confidence: 0.88146096
00:46:24.339 --> 00:46:26.355 and it was Pember Lizum app.
NOTE Confidence: 0.88146096
00:46:26.360 --> 00:46:27.828 So one of the.
NOTE Confidence: 0.88146096
00:46:27.828 --> 00:46:29.296 Doublet regimens that’s being
NOTE Confidence: 0.88146096
00:46:29.296 --> 00:46:31.738 looked at in the advanced setting.
NOTE Confidence: 0.88146096
00:46:31.740 --> 00:46:34.068 That’s a typo there versus placebo
NOTE Confidence: 0.88146096
00:46:34.068 --> 00:46:35.620 in combination with tastes
NOTE Confidence: 0.88146096
00:46:35.689 --> 00:46:37.089 and David Mann office.
NOTE Confidence: 0.88146096
00:46:37.090 --> 00:46:40.138 The Pi of this study here at Yale,
NOTE Confidence: 0.88146096
00:46:40.140 --> 00:46:42.050 and we have the primary
NOTE Confidence: 0.88146096
00:46:42.050 --> 00:46:43.196 outcomes of progression,
NOTE Confidence: 0.88146096
00:46:43.200 --> 00:46:45.110 free survival and overall survival,
NOTE Confidence: 0.88146096
00:46:45.110 --> 00:46:47.115 and then multiple secondary outcomes
NOTE Confidence: 0.88146096
00:46:47.115 --> 00:46:49.895 that will be looked at by resist
NOTE Confidence: 0.88146096
00:46:49.895 --> 00:46:51.989 1.1 and by the modified resist.
NOTE Confidence: 0.88146096
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 HCC study so this is, uh, so Genentech has this platform called Morpheus where it allows them to do a bunch of small protocols. Kind of that can cycle into the
NOTE Confidence: 0.831055
00:47:37.733 --> 00:47:39.820 trial as there’s new combinations
NOTE Confidence: 0.831055
00:47:39.820 --> 00:47:42.008 that look potentially interesting.
NOTE Confidence: 0.831055
00:47:42.010 --> 00:47:44.768 So the competitor the comparator arm in
NOTE Confidence: 0.831055
00:47:44.768 --> 00:47:48.040 this study is the combination of a tease.
NOTE Confidence: 0.831055
00:47:48.040 --> 00:47:49.177 Oh and Bev.
NOTE Confidence: 0.831055
00:47:49.177 --> 00:47:51.830 So all patients get that and then
NOTE Confidence: 0.831055
00:47:51.920 --> 00:47:55.040 right now the experimental stage one.
NOTE Confidence: 0.831055
00:47:55.040 --> 00:48:00.329 Looks at a drug added called to
NOTE Confidence: 0.831055
00:48:00.329 --> 00:48:02.789 Raghuram AB and then the other one
NOTE Confidence: 0.831055
00:48:02.871 --> 00:48:05.479 is totalism AB and there’s actually
NOTE Confidence: 0.831055
00:48:05.479 --> 00:48:07.990 going to be 2 new arms opening soon
NOTE Confidence: 0.831055
00:48:07.990 --> 00:48:10.552 which I can tell you more about.
NOTE Confidence: 0.831055
00:48:07.990 --> 00:48:10.552 Once once we have those open this
NOTE Confidence: 0.831055
00:48:10.552 --> 00:48:12.799 study we don’t have open yet,
NOTE Confidence: 0.831055
00:48:12.800 --> 00:48:15.131 but once the two new arms open
NOTE Confidence: 0.831055

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will be opening the study.

Hopefully in the next couple of months.

So this will be a good first line systemic therapy.

Option for our patients.

And so you know,

I just wanted to mention,

as Mario,

And you know,

was discussing in the introduction that this disease really requires multidisciplinary care.

I really enjoy meeting with my colleagues every Thursday at our liver tumor board.

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 that we’re giving and how best to sequence things. And it’s been really great for me.
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. have very cell bleed on treatment?
Yeah, you know that’s that’s a good question. I mean, so I guess the question then is you know if they could be so. I mean, hopefully the risk is very low. ’cause if we’re selecting the right patients, then hopefully they shouldn’t have a bleed. And so I guess the question then you know if someone bleeds where they on anticoagulation do they need to be on an anticoagulation and could they be banded and then be considered back? Kind of in a low risk population you know. I will mention that there was another arm on the study from the Phase one study so. 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 n’t 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 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 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, 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, you know.

Another question, thank you for your answer, there’s another question from Leshan why Japan is excluded and food Japan and US together. Any specific missing?
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 it up because I don’t think that there really is a separate signature.

OK, more questions so.