OK, so you know if you instant. We will be starting. So this is the server. Seminar on the liver. 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 the patient with liver cancer. 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 and the follow up.

So today I am very happy to present Doctor Spacetime. Stacy is 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 University and then a master in science.
She did her residency in the Montefiore Medical Center in New York City and her 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 oncologists 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. Principal 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. Of treatment and so you know, 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, sandwich done after the cure.
it 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 right? The you know 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 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.
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 two 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 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 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

Whether there really is a benefit of having a response. But I think most most people that take care of
00:09:55.869 --> 00:09:58.469 these patients would think that.
NOTE Confidence: 0.8380414
00:09:58.470 --> 00:10:00.770 Potentially having a response.
NOTE Confidence: 0.8380414
00:10:00.770 --> 00:10:03.645 May help with better symptom
NOTE Confidence: 0.8380414
00:10:03.645 --> 00:10:06.510 you know symptom management.
NOTE Confidence: 0.8380414
00:10:06.510 --> 00:10:09.464 And this just showed a subset analysis
NOTE Confidence: 0.8380414
00:10:09.464 --> 00:10:11.579 looking at multiple different groups
NOTE Confidence: 0.8380414
00:10:11.579 --> 00:10:14.281 that in all the groups in the
NOTE Confidence: 0.8380414
00:10:14.281 --> 00:10:16.559 subset they favored linv at NAB.
NOTE Confidence: 0.8380414
00:10:16.560 --> 00:10:22.560 And so so now moving to immune therapy.
NOTE Confidence: 0.8380414
00:10:22.560 --> 00:10:24.822 So obviously this is an exciting
NOTE Confidence: 0.8380414
00:10:24.822 --> 00:10:27.322 area for HCC and there’s multiple
NOTE Confidence: 0.8380414
00:10:27.322 --> 00:10:30.500 ways rate that we could think about.
NOTE Confidence: 0.8380414
00:10:30.500 --> 00:10:32.590 You know using immune therapy
NOTE Confidence: 0.8380414
00:10:32.590 --> 00:10:33.844 for different targets.
NOTE Confidence: 0.8380414
00:10:33.850 --> 00:10:35.995 Immune therapy was a little
NOTE Confidence: 0.8380414
00:10:35.995 --> 00:10:38.860 bit late in the game to HCC,
00:10:38.860 --> 00:10:40.945 I think largely because before
00:10:40.945 --> 00:10:42.613 there were drug approvals,
00:10:42.620 --> 00:10:46.052 it seemed like a risky choice to give
00:10:46.052 --> 00:10:48.473 to patients who had either hepatitis
00:10:48.473 --> 00:10:51.819 B or C or were at higher risk,
00:10:51.820 --> 00:10:53.540 potentially for D compensation.
00:10:53.540 --> 00:10:55.260 If they had autoimmune.
00:10:55.260 --> 00:10:56.700 Effects to the liver,
00:10:56.700 --> 00:10:58.860 and so these studies weren’t really
00:10:58.924 --> 00:11:01.384 started until they already had FDA
00:11:01.384 --> 00:11:03.486 approval for other indications and
00:11:03.486 --> 00:11:05.844 out of the concern for potential
00:11:05.844 --> 00:11:06.630 viral reactivation.
00:11:06.630 --> 00:11:08.705 These initial studies in the
00:11:08.705 --> 00:11:10.780 Phase one setting separated the
00:11:10.849 --> 00:11:12.961 patients out into a hepatitis C
NOTE Confidence: 0.8380414
00:11:12.961 --> 00:11:14.860 Group A hepatitis B group,
NOTE Confidence: 0.8380414
00:11:14.860 --> 00:11:17.540 and then you see they had some patients
NOTE Confidence: 0.8380414
00:11:17.540 --> 00:11:19.960 who have progressed on sorafenib.
NOTE Confidence: 0.8380414
00:11:19.960 --> 00:11:22.620 But then there’s also this fourth group
NOTE Confidence: 0.8380414
00:11:22.620 --> 00:11:25.061 of some patients who actually we’re
NOTE Confidence: 0.8380414
00:11:25.061 --> 00:11:27.509 getting this as first line therapy.
NOTE Confidence: 0.8380414
00:11:27.510 --> 00:11:30.310 And what you could see?
NOTE Confidence: 0.8380414
00:11:30.310 --> 00:11:32.718 You know on these on these patient bars
NOTE Confidence: 0.8380414
00:11:32.718 --> 00:11:35.334 is that the four groups are pretty
NOTE Confidence: 0.8380414
00:11:35.334 --> 00:11:37.284 much superimposable on each other,
NOTE Confidence: 0.8380414
00:11:37.290 --> 00:11:39.999 and so you know there were many
NOTE Confidence: 0.8380414
00:11:39.999 --> 00:11:41.950 patients that were on treatment
NOTE Confidence: 0.8380414
00:11:41.950 --> 00:11:44.798 for at least a year and they were
NOTE Confidence: 0.8380414
00:11:44.876 --> 00:11:47.426 pretty similar across the groups.
NOTE Confidence: 0.8380414
00:11:47.430 --> 00:11:49.642 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 the 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 the waterfall plot that 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 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
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 --> 00:16:00.431 reflecting the you know mostly the
00:16:00.431 --> 00:16:03.244 Asian population that enrolled 30% with
00:16:03.244 --> 00:16:05.254 hepatitis C and another 20% more nonviral.
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,
00:16:17.870 --> 00:16:20.985 and then they also looked at AFP
NOTE Confidence: 0.8179294
00:16:20.985 --> 00:16:24.867 to see if that was potentially a.
NOTE Confidence: 0.8179294
00:16:24.870 --> 00:16:27.636 You know show different responses and
NOTE Confidence: 0.8179294
00:16:27.636 --> 00:16:31.427 that was about half with less than 400 AFP.
NOTE Confidence: 0.8179294
00:16:31.430 --> 00:16:34.118 About half the patients had prior taste
NOTE Confidence: 0.8179294
00:16:34.118 --> 00:16:37.540 and about a third had prior radiotherapy,
NOTE Confidence: 0.8179294
00:16:37.540 --> 00:16:40.204 and this Spider plot shows the
NOTE Confidence: 0.8179294
00:16:40.204 --> 00:16:42.846 responses to treatment and you could
NOTE Confidence: 0.8179294
00:16:42.846 --> 00:16:45.576 see that the green lines or the
NOTE Confidence: 0.8179294
00:16:45.576 --> 00:16:48.346 patients who had either a partial
NOTE Confidence: 0.8179294
00:16:48.346 --> 00:16:50.646 or complete response to treatment.
NOTE Confidence: 0.8179294
00:16:50.650 --> 00:16:53.709 Then there were many patients in blue,
NOTE Confidence: 0.8179294
00:16:53.710 --> 00:16:56.566 it’s stable disease than the red.
NOTE Confidence: 0.8179294
00:16:56.570 --> 00:16:58.646 The red bars show progressive disease,
NOTE Confidence: 0.85702395
00:16:58.650 --> 00:17:00.732 so you could see that for
NOTE Confidence: 0.85702395
00:17:00.732 --> 00:17:02.120 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

Oh Bevause 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
00:18:12.322 --> 00:18:14.642 that was presented at the GI ASCO meeting in January.

00:18:14.642 --> 00:18:16.078 So this is newer,

00:18:16.080 --> 00:18:17.868 newer data and you know you could see here that the overall survival.

00:18:17.868 --> 00:18:21.242 The median overall survival for Seraphim was 13.4 months,

00:18:21.242 --> 00:18:24.740 so as these studies go on in time,

00:18:24.740 --> 00:18:26.348 the median overall survival for this rafina Barb keeps getting better,

00:18:26.348 --> 00:18:28.358 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.
up for Seraphim data,
which I find interesting,
but I’m not sure how to explain
The response rate was an
The response rate was an impressive 30% for the A tease.
Oh Bev combination and you know the
response rates are always a little bit higher when their looked at by modified
resist as opposed to resist 1.1 and
so we saw some complete responses.
Several partial responses.
Many patients with stable disease,
and so when you look at the
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. Oh Bev. So not surprisingly, 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 an are used

checking blood pressure at every

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.
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, this now is.
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, 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 of 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. 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 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 and so PD one inhibition plus a TKI. So this is the Keynote 524 study and that 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.
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
NOTE Confidence: 0.82374823
00:32:56.872 --> 00:32:58.542 candidate for addition with the
NOTE Confidence: 0.82374823
00:32:58.614 --> 00:33:00.854 CTA for antibody versus bevacizumab
NOTE Confidence: 0.82374823
00:33:00.854 --> 00:33:03.094 versus a tyrosine kinase inhibitor?
NOTE Confidence: 0.82374823
00:33:03.100 --> 00:33:05.100 And those will be exciting.
NOTE Confidence: 0.82374823
00:33:05.100 --> 00:33:07.284 Discussions to have just to show
NOTE Confidence: 0.82374823
00:33:07.284 --> 00:33:10.040 you this is the Himalaya design,
NOTE Confidence: 0.82374823
00:33:10.040 --> 00:33:12.215 so the development plus Tremelimumab
NOTE Confidence: 0.82374823
00:33:12.215 --> 00:33:14.878 as first line therapy and they
NOTE Confidence: 0.82374823
00:33:14.878 --> 00:33:17.362 used a couple of different arms
NOTE Confidence: 0.82374823
00:33:17.362 --> 00:33:19.794 of tremelimumab dosing so you know
NOTE Confidence: 0.82374823
00:33:19.794 --> 00:33:22.026 in the other disease groups where
NOTE Confidence: 0.82374823
00:33:22.026 --> 00:33:24.048 there’s been approval for CTA
NOTE Confidence: 0.82374823
00:33:24.048 --> 00:33:26.108 for combination like in Melanoma.
NOTE Confidence: 0.82374823
00:33:26.110 --> 00:33:28.540 Typically the patients get four
NOTE Confidence: 0.82374823
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, 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,

you know the combination data and.

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
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

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, 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
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 to really get any benefit from it. We do have some child Pugh B data now with Lynn VAT nib. Um, and we do have some data with cabins antonym you know. Overall I would say it seems to me that these patients really
wind up with more dose reductions, which is what the data suggests below.

None of these were randomized studies right, but just you know more observation. ULL and I think the really when we think about the combination data from the slide I showed before right of thinking of you know, are we adding a see TL A4 antibody, a tyrosine kinase or Beves ISM AB? I think it’s going to be really important to have data in those groups later with Child Pugh B patients because it may turn out that one combination 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. 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, 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 cirrhosis and this kind of confusing
00:40:57.510 --> 00:41:02.370 why they developed HCC and we found a couple of Baraka carriers which have not been well described in the literature as thinking about HCC’s abraço related disease.
00:41:02.370 --> 00:41:04.838 and we’ve seen some back one mutations, so I think it’s you know it’s interesting to find these select patients,
00:41:04.838 --> 00:41:07.298 although it’s not clear that they necessarily, you know, respond better to.
PARP inhibitors or that there’s really necessary 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 disease. And so going back to the BC else staging system. So I think this is an important slide to kind of 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
00:42:30.446 --> 00:42:33.460 studies of data that’s going to come out,
NOTE Confidence: 0.85235196
00:42:33.460 --> 00:42:35.524 and so we’ve really added a
NOTE Confidence: 0.85235196
00:42:35.524 --> 00:42:37.330 lot in this category here,
NOTE Confidence: 0.85235196
00:42:37.330 --> 00:42:39.794 but I think that even more importantly,
NOTE Confidence: 0.85235196
00:42:39.800 --> 00:42:42.110 right now we need to kind of
NOTE Confidence: 0.85235196
00:42:42.110 --> 00:42:44.374 think of the whole, you know,
NOTE Confidence: 0.85235196
00:42:44.374 --> 00:42:46.486 the whole staging system he ran.
NOTE Confidence: 0.85235196
00:42:46.490 --> 00:42:48.602 Really say now that we finally
NOTE Confidence: 0.85235196
00:42:48.602 --> 00:42:50.010 have more effective therapies.
NOTE Confidence: 0.85235196
00:42:50.010 --> 00:42:51.770 You know, in my mind,
NOTE Confidence: 0.85235196
00:42:51.770 --> 00:42:53.174 combination doesn’t just mean
NOTE Confidence: 0.85235196
00:42:53.174 --> 00:42:54.929 combination of two systemic therapies,
NOTE Confidence: 0.85235196
00:42:54.930 --> 00:42:56.840 but it’s really combination of.
NOTE Confidence: 0.85235196
00:42:56.840 --> 00:42:58.940 All the modalities that we
NOTE Confidence: 0.85235196
00:42:58.940 --> 00:43:00.620 use in this disease,
NOTE Confidence: 0.85235196
00:43:00.620 --> 00:43:02.300 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,
NOTE Confidence: 0.85235196
you know,
NOTE Confidence: 0.85235196
when you think of the mechanism of action.
NOTE Confidence: 0.85235196
I don’t think it’s actually really
illuminating microscopic disease,
NOTE Confidence: 0.85235196
and so it’s not surprising.
NOTE Confidence: 0.85235196
I guess in retrospect that
it wasn’t a positive study.
NOTE Confidence: 0.85235196
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.
NOTE Confidence: 0.85235196
And you know,
NOTE Confidence: 0.85235196
I think it’s interesting ’cause going back.
NOTE Confidence: 0.85235196
You know,
00:44:03.964 --> 00:44:05.956 to almost 10 years ago now
00:44:05.956 --> 00:44:07.960 you know doing this study.
00:44:07.960 --> 00:44:10.480 It accrued really poorly across the country,
00:44:10.480 --> 00:44:12.628 and so the study never finished.
00:44:12.630 --> 00:44:13.746 Accrual and it,
00:44:13.746 --> 00:44:14.490 kind of.
00:44:14.490 --> 00:44:17.034 Ended halfway through the data somehow
00:44:17.034 --> 00:44:19.359 is still not published from it.
00:44:19.360 --> 00:44:22.083 There was another study in the UK
00:44:22.083 --> 00:44:24.589 that looked at a similar question
00:44:24.589 --> 00:44:27.343 in a smaller way, but you know,
00:44:27.343 --> 00:44:29.870 I think partially why it didn’t accrue
00:44:29.940 --> 00:44:32.688 well was because there wasn’t the
00:44:32.688 --> 00:44:34.968 kind of multidisciplinary groups that
00:44:34.968 --> 00:44:37.224 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
NOTE Confidence: 0.88146096
00:45:12.176 --> 00:45:15.164 about what the role is for combination
NOTE Confidence: 0.88146096
00:45:15.164 --> 00:45:17.494 therapy in this intermediate stage.
NOTE Confidence: 0.88146096
00:45:17.500 --> 00:45:20.372 You know group and so I just wanted
NOTE Confidence: 0.88146096
00:45:20.372 --> 00:45:22.545 to mention a couple of studies
NOTE Confidence: 0.88146096
00:45:22.545 --> 00:45:25.080 that we have open now at Yale.
NOTE Confidence: 0.88146096
00:45:25.080 --> 00:45:28.329 So one of them is the Keynote 937 study.
NOTE Confidence: 0.88146096
00:45:28.330 --> 00:45:30.647 So this study is looking at Agilent
NOTE Confidence: 0.88146096
00:45:30.647 --> 00:45:32.659 Pember Lizum app versus placebo.
NOTE Confidence: 0.88146096
00:45:32.660 --> 00:45:35.468 So for patients that have had a complete
NOTE Confidence: 0.88146096
00:45:35.468 --> 00:45:36.964 radiologic response after surgical
NOTE Confidence: 0.88146096
00:45:36.964 --> 00:45:39.160 resection or local ablation of HCC,
NOTE Confidence: 0.88146096
00:45:39.160 --> 00:45:41.340 they're planning to enroll
NOTE Confidence: 0.88146096
00:45:41.340 --> 00:45:43.520 close to 1000 patients.
NOTE Confidence: 0.88146096
00:45:43.520 --> 00:45:46.268 In one to one randomization September,
NOTE Confidence: 0.88146096
00:45:46.270 --> 00:45:47.224 Liz, member,
NOTE Confidence: 0.88146096
placebo, which would be for one year and then they’ll be followed for survival with primary objectives of recurrence free survival in an 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, uh, so Genentech has this platform called Morpheus where it allows them to do a bunch of small protocols.
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 is totalism AB and there’s actually
00:48:05.479 --> 00:48:07.990 going to be 2 new arms opening soon
00:48:07.990 --> 00:48:09.465 which I can tell you more about.
00:48:09.465 --> 00:48:10.552 Once once we have those open this
00:48:10.552 --> 00:48:12.799 study we don’t have open yet,
00:48:12.800 --> 00:48:15.131 but once the two new arms open
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, 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 of treatment 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. From Doctor Rohit Gupta and the question is would you stop at ease or Bev completely if they do have very cell bleed on treatment?
Yeah, you know 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 study that looked at the combination versus a tease alone and you really don’t get the same responses with a tease. So I think if you could you would try to continue the combination if you were able to, 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?

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 a 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, I think that’s fine, you know.

Another question, thank you for your answer, thank you for your answer, 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 up the child because I don’t think that there really is a separate signature.

OK, more questions so.