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 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. Is discussed among us and 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 University and then a master in science.
She did her residency in the Montefiore Medical Center in New York City and your college fellowship are and where you? She donyale in 2010. And she’s now associate professor of internal medicine ecology. She has leadership positions at the Center for Gas, intestinal cancer, and she’s a member of our steering committee of our Liver Cancer program, and she is one of the person that actually. Give us their guidelines through her activity in the effort. In addition, Stacy is one of the really...
few medical 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-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.
00:04:28.860 --> 00:04:29.456 you know,
NOTE Confidence: 0.92804784
00:04:29.456 --> 00:04:30.946 and then thinking about where
NOTE Confidence: 0.92804784
00:04:30.946 --> 00:04:32.933 things are and then really thinking
NOTE Confidence: 0.92804784
00:04:32.933 --> 00:04:34.648 more broadly about where things
NOTE Confidence: 0.92804784
00:04:34.648 --> 00:04:36.218 are going in the feature.
NOTE Confidence: 0.92804784
00:04:36.220 --> 00:04:38.780 So we’ll come back to this slide later.
NOTE Confidence: 0.92804784
00:04:38.780 --> 00:04:40.040 But you know also,
NOTE Confidence: 0.92804784
00:04:40.040 --> 00:04:41.930 I feel like this reflects the
NOTE Confidence: 0.92804784
00:04:42.005 --> 00:04:43.888 time when I came to Yale 10
NOTE Confidence: 0.92804784
00:04:43.888 --> 00:04:46.229 years ago and it was really a
NOTE Confidence: 0.92804784
00:04:46.229 --> 00:04:48.054 transplant conference at the time,
NOTE Confidence: 0.92804784
00:04:48.060 --> 00:04:50.030 not a liver tumor board.
NOTE Confidence: 0.92804784
00:04:50.030 --> 00:04:53.282 But I went to weekly and I kind of sat in
NOTE Confidence: 0.92804784
00:04:53.282 --> 00:04:56.486 the back of the room right out of fellowship.
NOTE Confidence: 0.92804784
00:04:56.490 --> 00:04:58.105 And when someone kind of
NOTE Confidence: 0.92804784
00:04:58.105 --> 00:04:59.720 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.
00:05:30.729 --> 00:05:32.320 it if intent therapies,
NOTE Confidence: 0.92804784
00:05:32.320 --> 00:05:32.672 right?
NOTE Confidence: 0.92804784
00:05:32.672 --> 00:05:35.488 And then the local regional therapies for the
NOTE Confidence: 0.92804784
00:05:35.488 --> 00:05:38.094 Child Pugh for the for the BCLCB patients.
NOTE Confidence: 0.92804784
00:05:38.100 --> 00:05:39.460 And so you know,
NOTE Confidence: 0.92804784
00:05:39.460 --> 00:05:40.140 I think.
NOTE Confidence: 0.92804784
00:05:40.140 --> 00:05:42.520 Although this staging system isn’t perfect,
NOTE Confidence: 0.92804784
00:05:42.520 --> 00:05:43.788 it really reflects right?
NOTE Confidence: 0.92804784
00:05:43.788 --> 00:05:46.466 The you know the importance of thinking of
NOTE Confidence: 0.92804784
00:05:46.466 --> 00:05:48.972 the underlying liver function of the patient,
NOTE Confidence: 0.92804784
00:05:48.980 --> 00:05:50.424 their performance status and.
NOTE Confidence: 0.92804784
00:05:50.424 --> 00:05:52.590 The tumor characteristics and so starting
NOTE Confidence: 0.92804784
00:05:52.649 --> 00:05:54.833 at the beginning here with the sharp study,
NOTE Confidence: 0.92804784
00:05:54.840 --> 00:05:56.415 Which I’m sure everyone is
NOTE Confidence: 0.92804784
00:05:56.415 --> 00:05:57.360 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 never actually been shown in a randomized child to show a survival benefit. In this study we saw an overall survival benefit going from 7.9 to 10 years.
months with placebo to 10.7

and so based on this data, this became the new standard of care option and you could see also that there was a time to radiologic progression on this drug and just remember, you know Seraphim, right? It’s not chemotherapy in the exact strict sense of the term rate, but it’s a TKI and multi tyrosine kinase inhibitor, and because of that you know it’s really targeting multiple pathways. It’s kind of a dirty Drug and you know they’re not.
Although their oral and they’re taken daily, and they may not have some of the more serious side effects that some chemotherapy drugs have. They do have a lot of great toxicities that often affect our patients like fatigue. Sometimes decreased appetite, hand foot, skin reaction, diarrhea, right? Which are definitely important in the management of these 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 see that really all of the systemic criteria so you know patients have to have measurable lesions. BBC else stage B or C. Usually child Pugh a disease.
Some studies may have included some patients with B7 disease, but most are primarily child Pugh. A good performance status of zero or one, and then you know usual parameters for adequate organ function. They excluded patients that had more advanced disease like Portal, vein invasion and then they were stratified by region, whether they had Macrovascular invasion or extrahepatic spread and E COGS status and they were randomized one to one to live at nib.
which you know most patients received the 12 milligram dose to start, or saraf nib and the primary endpoint was overall survival with multiple secondary endpoints. And you could see that basically 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
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 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,
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
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

19
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
NOTE Confidence: 0.8380414
the conditional approval that there
NOTE Confidence: 0.8380414
would be randomized data in the future,
NOTE Confidence: 0.8380414
but this allowed patients to have
NOTE Confidence: 0.8380414
access to immune therapy for HCC,
NOTE Confidence: 0.8380414
an in a similar study.
NOTE Confidence: 0.8380414
The keynote 224 study very similar design.
NOTE Confidence: 0.8380414
This looked at pembrolizumab and
NOTE Confidence: 0.8380414
they separated the patients out in
NOTE Confidence: 0.8380414
a similar fashion with hepatitis B,
NOTE Confidence: 0.8380414
hepatitis C, and uninfected group.
NOTE Confidence: 0.8380414
And you could see again that in
NOTE Confidence: 0.8380414
you know this waterfall plot that
NOTE Confidence: 0.8380414
there were responses in all of the
NOTE Confidence: 0.8380414
groups and that they were pretty
NOTE Confidence: 0.8380414
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, 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. 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.
00:15:00.520 --> 00:15:03.070 rate by resist 1.1 there's also.
NOTE Confidence: 0.8179294
00:15:03.070 --> 00:15:04.950 Duration of response progression.
NOTE Confidence: 0.8179294
00:15:04.950 --> 00:15:07.770 Free response time to radio graphic
NOTE Confidence: 0.8179294
00:15:07.840 --> 00:15:10.492 progression and then they also looked
NOTE Confidence: 0.8179294
00:15:10.492 --> 00:15:12.766 at modified resist criteria and
NOTE Confidence: 0.8179294
00:15:12.766 --> 00:15:15.769 overall survival so this looks at the
NOTE Confidence: 0.8179294
00:15:15.769 --> 00:15:18.004 baseline demographics of this study.
NOTE Confidence: 0.8179294
00:15:18.004 --> 00:15:20.752 So in total there were 103
NOTE Confidence: 0.8179294
00:15:20.752 --> 00:15:23.408 patients on the Phase one study,
NOTE Confidence: 0.8179294
00:15:23.410 --> 00:15:24.392 predominantly male,
NOTE Confidence: 0.8179294
00:15:24.392 --> 00:15:27.338 which is the HTC population that
NOTE Confidence: 0.8179294
00:15:27.338 --> 00:15:30.485 we see about half the patients were
NOTE Confidence: 0.8179294
00:15:30.485 --> 00:15:33.694 in Asia and the other 40% were in.
NOTE Confidence: 0.8179294
00:15:33.694 --> 00:15:36.076 Japan or the US patients were
NOTE Confidence: 0.8179294
00:15:36.076 --> 00:15:38.320 split between E kog performance,
NOTE Confidence: 0.8179294
00:15:38.320 --> 00:15:41.280 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,
and then they also looked at AFP to see if that was potentially a. You know show different responses and that was about half with less than 400 AFP. About half the patients had prior taste and about a third had prior radiotherapy, and this Spider plot shows the responses to treatment and you could see that the green lines or the patients who had either a partial or complete response to treatment. 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 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,
00:17:32.790 --> 00:17:35.289 one data that I am brave 150
NOTE Confidence: 0.85702395
00:17:35.289 --> 00:17:37.484 study was designed and this is
NOTE Confidence: 0.85702395
00:17:37.484 --> 00:17:39.578 a randomized study then to look
NOTE Confidence: 0.85702395
00:17:39.578 --> 00:17:42.058 at the combination of a tease.
NOTE Confidence: 0.85702395
00:17:42.060 --> 00:17:44.846 Oh Bevause was given in the Phase
NOTE Confidence: 0.85702395
00:17:44.846 --> 00:17:46.999 one study randomized to Seraphim.
NOTE Confidence: 0.85702395
00:17:47.000 --> 00:17:49.464 Which at the time when this was started,
NOTE Confidence: 0.85702395
00:17:49.470 --> 00:17:51.675 it was still the standard of care
NOTE Confidence: 0.85702395
00:17:51.675 --> 00:17:54.838 and it was randomized 2 to one and
NOTE Confidence: 0.85702395
00:17:54.838 --> 00:17:56.983 again with the same stratifications.
NOTE Confidence: 0.85702395
00:17:56.990 --> 00:18:00.671 And so the I am brave 150 study was
NOTE Confidence: 0.85702395
00:18:00.671 --> 00:18:03.640 published back in June and based on
NOTE Confidence: 0.85702395
00:18:03.640 --> 00:18:06.120 that data, there was FDA approval.
NOTE Confidence: 0.85702395
00:18:06.120 --> 00:18:08.195 I'm actually showing you here.
NOTE Confidence: 0.85702395
00:18:08.200 --> 00:18:10.490 The updated overall survival and
NOTE Confidence: 0.85702395
00:18:10.490 --> 00:18:12.322 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
up for Seraphim data, which I find interesting, but I’m not sure how to explain that and then. 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.
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, hypertension, rash. Hypertension, which is mostly from the bevacizumab which we know from 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, 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 are used to checking blood pressure at every visit and checking your Infor for protein as we do with bevacizumab. Another disease groups. And importantly, you know for the phase one and phase three study all patients had to have an EGD within six months of initiating therapy, so you know. Now we think of really doing that exclusively for the patients who have underlying cirrhosis.
But for the studies they didn’t.

Distinguish between patients who did or did not have cirrhosis,

so all patients had an EGD within six months of starting therapy and they had to have verisys treated according to local standard of care,

and so importantly, looking at the upper GI bleeding rate in the combination versus Seraphim.

EBIT increased from 4.5% in Strafford, up to 7% with a tease.

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, right? 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 1 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 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 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 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 and that data is already been presented. There was an overall response rate of.
00:29:53.080 --> 00:29:56.131 36% but I just caution you that when the
NOTE Confidence: 0.80620193
00:29:56.131 --> 00:29:58.987 Phase one data was initially presented,
NOTE Confidence: 0.80620193
00:29:58.990 --> 00:30:00.166 the response rate.
NOTE Confidence: 0.80620193
00:30:00.166 --> 00:30:03.340 You know from the beginning was very high,
NOTE Confidence: 0.80620193
00:30:03.340 --> 00:30:04.592 even higher than this,
NOTE Confidence: 0.80620193
00:30:04.592 --> 00:30:07.938 and so you know as you get randomized data,
NOTE Confidence: 0.80620193
00:30:07.940 --> 00:30:10.214 the response rate often comes down
NOTE Confidence: 0.80620193
00:30:10.214 --> 00:30:12.745 so you know the final data for
NOTE Confidence: 0.80620193
00:30:12.745 --> 00:30:15.380 this may not be as high as this,
NOTE Confidence: 0.80620193
00:30:15.380 --> 00:30:17.456 ’cause often the patient selection for
NOTE Confidence: 0.80620193
00:30:17.456 --> 00:30:19.979 the Phase one study is very selective.
NOTE Confidence: 0.80620193
00:30:19.980 --> 00:30:22.635 An in the Phase one study they had a
NOTE Confidence: 0.80620193
00:30:22.635 --> 00:30:24.862 median overall survival of 2022 months
NOTE Confidence: 0.80620193
00:30:24.862 --> 00:30:27.410 and that was about 100 patients.
NOTE Confidence: 0.80620193
00:30:27.410 --> 00:30:30.050 And so I think it will be really
NOTE Confidence: 0.80620193
00:30:30.050 --> 00:30:31.976 interesting to see the combination
00:30:31.976 --> 00:30:33.170 data for this.

00:30:33.170 --> 00:30:33.900 You know,

00:30:33.900 --> 00:30:36.090 and then you could really kind

00:30:36.090 --> 00:30:37.790 of think about right?

00:30:37.790 --> 00:30:40.100 Which patient might be best suited

00:30:40.100 --> 00:30:41.640 for which combination therapy,

00:30:41.640 --> 00:30:43.602 and similarly the Cosmic 312 study

00:30:43.602 --> 00:30:45.953 is looking at cabins antonym plus

00:30:45.953 --> 00:30:48.282 atezolizumab versus rafanan, so again,

00:30:48.282 --> 00:30:50.437 you know another tyrosine kinase

00:30:50.437 --> 00:30:53.106 inhibitor plus plus PD one inhibitor and

00:30:53.106 --> 00:30:55.904 you know we know right cab is antonym

00:30:55.904 --> 00:30:58.196 is active in second line therapy.

00:30:58.200 --> 00:31:00.881 And as I mentioned there were some

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 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
candidate for addition with the 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 CTA for combination like in Melanoma. Typically the patients get four cycles with the combination and
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, 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
00:35:52.334 --> 00:35:55.799 you know what what you would want to do next.
NOTE Confidence: 0.8559677
00:35:55.800 --> 00:35:57.236 So if someone really,
NOTE Confidence: 0.8559677
00:35:57.236 --> 00:35:59.810 I think progressives quickly through a tease.
NOTE Confidence: 0.8559677
00:35:59.810 --> 00:36:00.508 Oh, Bev.
NOTE Confidence: 0.8559677
00:36:00.508 --> 00:36:02.951 I don’t know that going to a
NOTE Confidence: 0.8559677
00:36:02.951 --> 00:36:04.563 combination immune therapy you
NOTE Confidence: 0.8559677
00:36:04.563 --> 00:36:06.939 know regimen would be the best,
NOTE Confidence: 0.8559677
00:36:06.940 --> 00:36:08.740 but perhaps if someone responds
NOTE Confidence: 0.8559677
00:36:08.740 --> 00:36:10.180 and then eventually progresses,
NOTE Confidence: 0.8559677
00:36:10.180 --> 00:36:13.372 you may want to think about
NOTE Confidence: 0.8559677
00:36:13.372 --> 00:36:14.968 combination immune therapy.
NOTE Confidence: 0.8559677
00:36:14.970 --> 00:36:17.020 And.
NOTE Confidence: 0.8559677
00:36:17.020 --> 00:36:19.075 For the patients that tolerate
NOTE Confidence: 0.8559677
00:36:19.075 --> 00:36:21.130 a tyrosine kinase inhibitor and
NOTE Confidence: 0.8559677
00:36:21.202 --> 00:36:23.542 maybe have good control or decrease
NOTE Confidence: 0.8559677
00:36:23.542 --> 00:36:24.712 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 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? From the trial really, is it really applicable to these patients? So as a tease? And as the data that we are seeing, 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. 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. 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 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
targets at the bottom of the slide, right or very uncommon in HCC. I have sequence in patients this year, especially ones that had no underlying cirrhosis and this kind of confusing 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 abraco related disease. And we’ve seen some back one mutations, so I think it’s you know it’s interesting to find these select patients, although it’s not clear that they 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 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
NOTE Confidence: 0.85235196
00:41:59.395 --> 00:42:01.544 just in this advanced stage C group,
NOTE Confidence: 0.85235196
00:42:01.550 --> 00:42:03.518 you know we’ve now accumulated rates
NOTE Confidence: 0.85235196
00:42:03.518 --> 00:42:05.619 several different drugs in this category,
NOTE Confidence: 0.85235196
00:42:05.620 --> 00:42:07.846 so adding into seref and if now
NOTE Confidence: 0.85235196
00:42:07.846 --> 00:42:09.350 we have a tease.
NOTE Confidence: 0.85235196
00:42:09.350 --> 00:42:12.054 Oh, and Bev approved in the first line.
NOTE Confidence: 0.85235196
00:42:12.060 --> 00:42:13.755 Also Lynn VAT and approved
NOTE Confidence: 0.85235196
00:42:13.755 --> 00:42:15.450 in the first line cabins,
NOTE Confidence: 0.85235196
00:42:15.450 --> 00:42:17.145 antonym burgraff and IMMA ramucirumab
NOTE Confidence: 0.85235196
00:42:17.145 --> 00:42:18.840 approved in the second line.
NOTE Confidence: 0.85235196
00:42:18.840 --> 00:42:21.032 Also it be niveau right and then we
NOTE Confidence: 0.85235196
00:42:21.032 --> 00:42:23.635 have pen Bruen Niveau still kind of
NOTE Confidence: 0.85235196
00:42:23.635 --> 00:42:26.070 conditionally approved a single agent drugs.
NOTE Confidence: 0.85235196
00:42:26.070 --> 00:42:28.275 But I think those will be largely
NOTE Confidence: 0.85235196
00:42:28.275 --> 00:42:30.446 replaced soon by the multiple combination
NOTE Confidence: 0.85235196
studies of data that’s going to come out, and so we’ve really added a lot in this category here, but I think that even more importantly, right now we need to kind of think of the whole, you know, the whole staging system he ran. Really say now that we finally have more effective therapies. You know, in my mind, combination doesn’t just mean combination of two systemic therapies, but it’s really combination of. All the modalities that we use in this disease, with potentially systemic therapy,
and so you know, there's a lot of interest now. I'm thinking of Advent therapy, thinking of combination therapy with local therapy. This study is that it weren't done in the past. You know, looked at Saraf, and it's so there was an adjutant fit study that looked at Seraphim after reception. That study was negative, but as far as I know, I don’t think there’s a tyrosine kinase inhibitor approved in any
diseases adjutant therapy because,

you know,

when you think of the mechanism of action.

I don't think it's actually really

illuminating microscopic disease,

and so it's not surprising.

I guess in retrospect that

it wasn't a positive study.

There was also the first study that

I opened when I came here

was the E Card 1208 study which was

looking at the role of adding saraf

number placebo to sequential tastes.

And you know,

I think it's interesting 'cause going back.

You know,
to almost 10 years ago now 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 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 adjutant 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 where it allows them to do a bunch of small protocols. Kind of that can cycle into the
trial as there’s new combinations that look potentially interesting. So the competitor the comparator arm in this study is the combination of a tease. Oh and Bev. So all patients get that and then right now the experimental stage one. Looks at a drug added called to Raghuram AB and then the other one is totalism AB and there’s actually going to be 2 new arms opening soon which I can tell you more about. Once we have those open this study we don’t have open yet, 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,

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. Is a. 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. Hopefully the risk is very low. 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 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.
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
don’t get the same responses with a tease.
Oh alone.
So I think if you could you would
try to continue the you know the
combination 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? Azie anhyzer prophylaxis?

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 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, 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, 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 saw that also in the trial design and 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.