Our group tonight for this CME event. Sponsored by our Center for Gastrointestinal cancers here at Smilow Cancer Hospital in New Haven Hospital and Yale School of Medicine, so we’re delighted that you took some time out from. I know it is a busy time of year for many to join us. This evening we’re going to be focusing on gastroesophageal cancers. We have three talks tonight. It will give about 30 minutes
to each with some time in each
NOTE Confidence: 0.791430941428571

session for some questions,
NOTE Confidence: 0.791430941428571

and we’ll try to leave some time at
NOTE Confidence: 0.791430941428571

the end for questions as well in
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terms of the order of the talks,
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we’re going to start with Doctor Baffa,
NOTE Confidence: 0.791430941428571

then move on to Doctor Robert
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and then myself.
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I am doctor Lacey by way of introduction and
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I will introduce myself again at the end.
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So we’re going to,
NOTE Confidence: 0.791430941428571

without further ado,
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get started and Doctor Baffa is
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going to kick this off this evening.
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Doctor Baffa is a colleague that
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I work with very closely.
He is professor and chief of the Division of Thoracic Surgery here at the Yale School of Medicine and Cancer Center, and he is going to be speaking to us tonight about the impact of recent Trials on systemic therapy before and after esophagectomy. Thank you very much and again, thank you to everybody who is joining either live or after the fact and I will tell you that I’m a fast talker and I always give short talks. So if you feel like you did not get your moneys worth,
I don’t know what to tell you, but I will. My e-mail is daniel.boffa@yale.edu and if there’s anything I say that is unclear or you want to talk more about, please don’t hesitate to reach out to me. I have a couple of disclosures, so the. I’m going to talk 1st about preoperative therapy and then I will talk about post operative therapy in patients that have what is perceived to be resectable, esophago gastric cancer. So there was a study, the CLG B8 O eight O 3 trial that was pet guided therapy in the preoperative setting in terms of which chemoradiation
NOTE Confidence: 0.9312649275
00:02:42.085 --> 00:02:45.369 cocktail to be administered.
NOTE Confidence: 0.9312649275
00:02:45.370 --> 00:02:48.044 So this is this is a really
NOTE Confidence: 0.9312649275
00:02:48.044 --> 00:02:50.150 interesting study in my opinion.
NOTE Confidence: 0.9312649275
00:02:50.150 --> 00:02:52.575 I was fortunate enough to
NOTE Confidence: 0.9312649275
00:02:52.575 --> 00:02:54.515 be involved in this.
NOTE Confidence: 0.9312649275
00:02:54.520 --> 00:02:55.995 And I think it’s understanding
NOTE Confidence: 0.9312649275
00:02:55.995 --> 00:03:00.236 I think it was a cleverly designed study.
NOTE Confidence: 0.9312649275
00:03:00.240 --> 00:03:02.216 I don’t know that it was a huge,
NOTE Confidence: 0.9312649275
00:03:02.220 --> 00:03:03.252 really impactful study,
NOTE Confidence: 0.9312649275
00:03:03.252 --> 00:03:05.316 but I think the study design
NOTE Confidence: 0.9312649275
00:03:05.316 --> 00:03:06.630 was pretty interesting.
NOTE Confidence: 0.9312649275
00:03:06.630 --> 00:03:10.025 So the the fundamental principle that this
NOTE Confidence: 0.9312649275
00:03:10.025 --> 00:03:13.454 was based on is that if you give induction,
NOTE Confidence: 0.9312649275
00:03:13.460 --> 00:03:14.308 chemotherapy,
and radiation,

NOTE Confidence: 0.9312649275

about 25% of people will sterilize the cancer

NOTE Confidence: 0.9312649275

within the surgically removed specimen.

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But that means that three out of four.

NOTE Confidence: 0.9312649275

Patients actually have some form of

NOTE Confidence: 0.9312649275

resistance to that neoadjuvant treatment.

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And we know that the best

NOTE Confidence: 0.9312649275

prognosis is in patients who have

NOTE Confidence: 0.9312649275

a pathologic complete response,

NOTE Confidence: 0.9312649275

and so it doesn’t take much to connect

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those dots that if we can increase the

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path CR rate that there’s a potential

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that we could make people live longer.

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And.

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Different chemotherapies have been used

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for esophageal and gastric carcinoma
and there is potentially a different mechanism of resistance and so just because somebody’s resistant to one may not mean they’re resistant to both. So the question is what if you changed chemotherapy? If there was a way to know it wasn’t working, could you change it during the neoadjuvant course to something that’s more effective? So these are the two common regimens carboplatinum, paclitaxel and oxaliplatin. And five FU, and so they actually do both have platinum backbones,
but they do have different mechanisms of resistance and so. This is sort of the founding principle that if you give a chemotherapy regimen, we’re just going to call regimen a. And you assess mid treatment pet and if they don’t reduce the Max SUV’s by 35%, then the chance of you having a pathologic complete response is quite low. Sorry, one second here.
It seemed to have. There we go. It’s it’s only 5%.

However, if you are giving 1 regimen and you notice that there’s no pet response, but change to a different chemotherapy regimen for the chemo radiation phase, the null hypothesis is that we can take this 5% path CR rate and bump it up to 20%.

So that was the foundation for the CL GB study, and so this was in adenocarcinoma patients, was a phase two trial they had to at least be clinical stage T.

To and or have lymph node metastases now. One thing that’s just really
important is you could get into this trial being a T2 and zero.
That was the minority of the patients and I would say this study was not powered to look at that subgroup. So just because a group is in a trial does not mean the trial findings universally apply to every small subgroup. I think that’s important, and that’s been misinterpreted and that.
The patients had have a distal, esophageal, or GE junction cancer, and again, as I mentioned, they would get chemo. There would be an early pet assessment and if they had a response you would keep going.
If you didn’t, you would change to another chemo form of chemo radiation and then have an esophagectomy and about 3/4 of the patients in both arms went on to have an esophagectomy, so there’s certainly was some fallout. Between induction and moving on to Esophagectomy, and again the primary endpoint of this study was path CR. In the patients who were deemed non responders. So again, that’s that group we thought would have
00:07:08.774 --> 00:07:12.140 a 5\% path CR rate and so could we bump
NOTE Confidence: 0.804088352857143
00:07:12.140 --> 00:07:15.759 that up by changing the chemotherapy so.
NOTE Confidence: 0.804088352857143
00:07:15.760 --> 00:07:19.420 Green is starting with full Fox,
NOTE Confidence: 0.804088352857143
00:07:19.420 --> 00:07:24.019 but responding and continuing with full Fox.
NOTE Confidence: 0.804088352857143
00:07:24.020 --> 00:07:26.799 The the yellow is starting with folfox,
NOTE Confidence: 0.804088352857143
00:07:26.800 --> 00:07:30.064 but then changing the carboplatin paclitaxel
NOTE Confidence: 0.804088352857143
00:07:30.064 --> 00:07:33.320 blue is starting with Carbo Taxol,
NOTE Confidence: 0.804088352857143
00:07:33.320 --> 00:07:35.804 and if you continue in blue
NOTE Confidence: 0.804088352857143
00:07:35.804 --> 00:07:37.460 then you were responder.
NOTE Confidence: 0.804088352857143
00:07:37.460 --> 00:07:38.480 If you did not respond,
NOTE Confidence: 0.804088352857143
00:07:38.480 --> 00:07:40.646 then you changed a full box.
NOTE Confidence: 0.804088352857143
00:07:40.650 --> 00:07:42.687 So if you look at the path
NOTE Confidence: 0.804088352857143
00:07:42.687 --> 00:07:44.829 CR rate in the responders,
NOTE Confidence: 0.804088352857143
00:07:44.830 --> 00:07:46.410 there’s a pretty big difference.
NOTE Confidence: 0.804088352857143
00:07:46.410 --> 00:07:48.979 So of the people that got folfox,
NOTE Confidence: 0.804088352857143
00:07:48.980 --> 00:07:50.498 these are adenocarcinomas.
If you started with Folfox and you responded and that was 73 out of 129 were responders and you kept going the path CR rate was 40%, so that’s pretty good.

If you started with carboplatin, paclitaxel, and you responded and kept going with Carbo Taxol, you’re past CR. It was 14%. That’s pretty darn low, and I’m going to give you some context in terms of other recent trials. Now, the non responders.
Now this is the group we were trying to bump up from. 5% so if you started green, if you started folfox, you were deemed a non responder and changed the path CR 8. 18% so that’s pretty darn close to 20%. And however, if you were a non responder to carboplatin, paclitaxel, and you switched, you actually got 20%, this was actually a positive study. Again, because we were expecting a 5% path CR rate from historical data and
00:09:03.622 --> 00:09:05.878 both of these were significantly higher

00:09:05.878 --> 00:09:08.379 than what we would have anticipated.

00:09:08.380 --> 00:09:12.764 So I’m just some stats from CL GB 80803.

00:09:12.764 --> 00:09:14.316 The complete resection rate.

00:09:14.320 --> 00:09:16.960 So granted 3 out of four patients that

00:09:16.960 --> 00:09:19.574 started in each arm went on to get

00:09:19.574 --> 00:09:22.012 into Sophie Ectomy the path CR that

00:09:22.012 --> 00:09:24.282 the complete resection rate was 94%.

00:09:24.282 --> 00:09:25.488 That’s pretty good.

00:09:25.488 --> 00:09:27.096 That’s that’s pretty average.

00:09:27.100 --> 00:09:28.330 The mortality rate.

00:09:28.330 --> 00:09:31.719 This is the 90 day mortality rate is 3.3%.

00:09:31.719 --> 00:09:32.556 That’s quite low,

00:09:32.556 --> 00:09:35.060 so in the French and German trials though,

00:09:35.060 --> 00:09:38.644 they had double digit 30 day mortality.
So this is quite low. Usually the 90 day mortality is twice the 30 day mortality and so this is quite low. Five or six started with Carboplatinum paclitaxel, so that’s just a statistical aberration, but maybe a light signal and the five year survival for this study was about 45%. So if you look at the difference between responders and non responders. So again, how did people do based on whether they respond to that? Early pet, the responders, as you might think,
00:10:14.600 --> 00:10:18.878 would have had a better outcome.

00:10:18.880 --> 00:10:22.040 49% five year survival versus 39% and

00:10:22.040 --> 00:10:25.448 the median survival was almost twice as long.

00:10:25.448 --> 00:10:27.230 Now if you look at the

00:10:27.304 --> 00:10:29.128 different treatment groups,

00:10:29.130 --> 00:10:33.240 so the red is full fox.

00:10:33.240 --> 00:10:35.538 The dash is responder the the

00:10:35.538 --> 00:10:38.220 solid line is the nonresponder,

00:10:38.220 --> 00:10:40.868 so you can see those are the those

00:10:40.868 --> 00:10:43.120 are wider than the blue lines,

00:10:43.120 --> 00:10:47.056 which are the people that started

00:10:47.056 --> 00:10:49.024 with carboplatinum paclitaxel.

00:10:49.030 --> 00:10:51.571 So here’s how I put this study

00:10:51.571 --> 00:10:54.037 together so that that if you the

00:10:54.037 --> 00:10:56.451 path CR was more likely if you

NOTE Confidence: 0.824055006
started with full fox of all the patients that started with full Fox, they were more likely to have a path CR. So when you combine an average this out 31% versus 14% in the carboplatinum paclitaxel group, Now this is a bit odd because sorry, the in the cross trial which was. Carboplatinum, paclitaxel, the all the way through the paths CR8 was 29%. So something’s funny in that 14%. So it’s hard to know what to make of that. But at least in the in this study there was a difference based on whether you started with folfox
or carboplatinum paclitaxel.

But paths yard does not tell the story because when you actually look at the overall survival,

five year overall survival.

The mustard and there’s probably a fancy name for that color.

browish yellow, the.

They’re both around 4142%,

the Greens,

the full fox patients,

they’re all in the same ballpark,

so I don’t think if anything
you know we were. We were expecting this carboplatin group, which went all the way through without a Pats CR of 14%. They still had a 44 percent five year survival, so path CR definitely does not tell the whole story. Now the other question is this study. The biggest part of this study was a pivot, meaning if you use a pet to change what you’re going to give people, does that help you know? So these were two common chemotherapy regimens used with radiation that there was a pivot in place. So with this pivot,
NOTE Confidence: 0.86021555
00:12:51.346 --> 00:12:53.266 did we make anything better?
NOTE Confidence: 0.86021555
00:12:53.270 --> 00:12:55.514 So overall, the five year survival 
NOTE Confidence: 0.86021555
00:12:55.514 --> 00:12:57.924 in this study was about 45%, 
NOTE Confidence: 0.86021555
00:12:57.924 --> 00:13:01.364 so the pivot gets you about 45%. 
NOTE Confidence: 0.86021555
00:13:01.364 --> 00:13:03.740 However, the cross trial, 
NOTE Confidence: 0.86021555
00:13:03.740 --> 00:13:04.910 it’s pretty much the same, 
NOTE Confidence: 0.86021555
00:13:04.910 --> 00:13:06.575 and there that was carboplatinum 
NOTE Confidence: 0.86021555
00:13:06.575 --> 00:13:08.240 paclitaxel all the way through, 
NOTE Confidence: 0.86021555
00:13:08.240 --> 00:13:10.880 so it’s hard for me to say that 
NOTE Confidence: 0.86021555
00:13:10.880 --> 00:13:13.398 using PET to guide your therapy, 
NOTE Confidence: 0.86021555
00:13:13.400 --> 00:13:15.920 at least in this context, 
NOTE Confidence: 0.86021555
00:13:15.920 --> 00:13:18.678 that it really changed the overall survival. 
NOTE Confidence: 0.86021555
00:13:18.680 --> 00:13:20.612 Now that that doesn’t mean that 
NOTE Confidence: 0.86021555
00:13:20.612 --> 00:13:22.519 there’s never a role for this, 
NOTE Confidence: 0.86021555
00:13:22.520 --> 00:13:25.175 but it does mean pivoting 
NOTE Confidence: 0.86021555
between these two regimens, carboplatin and paclitaxel, and full fox.

Using trying to mimic this and thinking you’re going to make people live longer. I think that’s that’s a hard sell.

So what are the take home messages that the pet does predict? Resistance?

So I think that of the non responders in general they had lower response rates.

So if there was a better pivot, potentially this this there is potential for pet early pet response to predict overall response to chemo radiation. I think that this adds to a signal.
this is a very soft call,

and and Jill I'd love to get your feedback on this,

but I think this adds to a signal that

if you have a squamous cell carcinoma

that that really carboplatinum makes the most sense

and so this is the cross study.

Again,

this is I’m just saying it adds to a signal.

I’m not saying that this is an absolute but this is the the

squamous cell that got chemoradiation.

And squamous cell that got surgery only.

And you could see how wide apart those
bars are. The lighter Gray bars.

Those are the adenocarcinoma with and without induction therapy. So I think this is pretty impressive that with squamous cell the induction does have a profound widening. I think this adds to a signal that full Fox is better with AD. No that compared to. Carboplatin, paclitaxel, there are studies like protect fourteen O2 that are going to compare different induction regimens, but I think this adds to that signal.
So why do I say that? So if you look at the full fox, the people that started with full Fox the the lines are just more separated based on response, and so I think it does a better job stratifying people that are going to respond and not respond. That’s not telling you prognostically, it’s just saying if the whole point of this study is to be able to separate responders and non responders, it’s the the pet format. Seems to be better with folfox.
The blue lines are people that started with carboplatinum paclitaxel.

This is the cross study and if you this is the forest which basically looks at unplanned, analysis from the cross study. This is old now, but if you actually look at by the Histology and and to be clear, the majority of these patients were adenocarcinoma patients, it actually was not statistically significant in the ADNO group. Clearly the mortality reduction.

Is less impressive in adeno versus squamous cell, so again,
I’m not saying it’s wrong to give carboplatinum paclitaxel to adno, but I do believe this the CGB study adds to a signal that in adno full fox is actually a better way to go. So now I’m going to pivot to postoperative therapy and I’m going to talk just briefly about checkmates 577, nivolumab after completely resected, and this was giving nivolumab after completely resected, so they had negative margins. Esophageal cancer that had some residual disease. They were not anybody.
pathologic complete responder.

So this this they accrued between 16 and 19, a lot of different centers.

They had to be clinical stage two or three.

They received induction chemo of chemo that was platinum based.

They again they had to have a complete resection.

No positive margins and then they were randomized whether or not to start between one and four months.

They again they had to have some residual disease in the pathologic or specimen, so it could not be a complete.
NOTE Confidence: 0.84344467
00:17:51.627 --> 00:17:55.640 pathologic response. And so.
NOTE Confidence: 0.84344467
00:17:55.640 --> 00:17:58.646 It was nivolumab for four months.
NOTE Confidence: 0.866352902727273
00:18:00.780 --> 00:18:03.195 That was given every two weeks and
NOTE Confidence: 0.866352902727273
00:18:03.195 --> 00:18:06.171 then it became monthly after that and
NOTE Confidence: 0.866352902727273
00:18:06.171 --> 00:18:08.456 it continued either to progression
NOTE Confidence: 0.866352902727273
00:18:08.456 --> 00:18:11.578 or if it was terminated for toxicity
NOTE Confidence: 0.866352902727273
00:18:11.578 --> 00:18:15.030 or patients got to a year and again.
NOTE Confidence: 0.866352902727273
00:18:15.030 --> 00:18:17.850 This was designed for disease free
NOTE Confidence: 0.866352902727273
00:18:17.850 --> 00:18:21.530 survival and so this just highlights
NOTE Confidence: 0.866352902727273
00:18:21.530 --> 00:18:26.870 where the patients came from the.
NOTE Confidence: 0.866352902727273
00:18:26.870 --> 00:18:31.230 About 40% were from Europe.
NOTE Confidence: 0.866352902727273
00:18:31.230 --> 00:18:34.090 60% were esophageal and 40%
NOTE Confidence: 0.866352902727273
00:18:34.090 --> 00:18:37.519 were gastroesophageal junction.
NOTE Confidence: 0.866352902727273
00:18:37.520 --> 00:18:39.716 71% were adenocarcinoma.
NOTE Confidence: 0.866352902727273
00:18:39.716 --> 00:18:45.634 Now the the PDL 1 count so was
NOTE Confidence: 0.866352902727273
about 16% were PDL 1 positive.

Now that’s different.

Something Doctor Robert is going to talk about which is a complete positive score.

A composite positive score which is a different and in just to be clear in a post hoc analysis the that score was.

Positive in about 57% had five or more percent cells positive, so this looks like there was very little PDL one.

But actually when you use the composite score it’s actually was higher.

So the. So this was well tolerated so the there were no grade 5 adverse events.
About 1/3 of patients had any three or four adverse events. It was actually pretty similar between the placebo and then the volume Nob arm. This continued treatment. Was 9% in the Nomad and 3% in the placebo group. Umm? The sorry, so when we look at disease free survival, the blue line is the nivolumab arm and the red line is placebo. So you can see there was a really significant difference in the disease. Free survival if you look at the median disease free survival in the nivolumab group, it was basically twice that.
00:20:21.451 --> 00:20:23.800 of the placebo group.
NOTE Confidence: 0.8029525384
00:20:23.800 --> 00:20:27.730 When you look by Histology so.
NOTE Confidence: 0.8029525384
00:20:27.730 --> 00:20:31.937 The the the the blue lines are
NOTE Confidence: 0.8029525384
00:20:31.937 --> 00:20:35.669 the patients who got nivolumab.
NOTE Confidence: 0.8029525384
00:20:35.670 --> 00:20:39.720 The red lines are the placebo groups and when
NOTE Confidence: 0.8029525384
00:20:39.720 --> 00:20:44.029 you actually just break it down by Histology.
NOTE Confidence: 0.8029525384
00:20:44.030 --> 00:20:45.950 So if you look at adenocarcinoma,
NOTE Confidence: 0.8029525384
00:20:45.950 --> 00:20:49.630 the median disease free survival
NOTE Confidence: 0.8029525384
00:20:49.630 --> 00:20:51.240 was 19 versus 11 months.
NOTE Confidence: 0.8029525384
00:20:51.240 --> 00:20:53.221 And when you look at
NOTE Confidence: 0.8029525384
00:20:53.221 --> 00:20:57.367 squamous it was actually 29,
NOTE Confidence: 0.8029525384
00:20:57.370 --> 00:20:59.165 Which is something we’ve seen
NOTE Confidence: 0.8029525384
00:20:59.165 --> 00:21:01.661 before where there seems to be a
NOTE Confidence: 0.8029525384
00:21:01.661 --> 00:21:03.551 little bit more activity in the
NOTE Confidence: 0.8029525384
00:21:03.551 --> 00:21:05.448 squamous cell patients and again,
70% of the patients in the study were actually adino. When you look at the forest plot again, these are all unplanned subset analysis. When you look at Adno versus Swain, they were both significant. Adno was flirting with a non significance but was significant. When you look at PDL one, so the people that had PDL 1 less than one now granted this is probably just a power analysis but the people with PDL 1 less than one it was significant but they had 600 patients versus the patients who were greater than one.
and these are tumor cell PDL one. It’s actually not significant. That doesn’t necessarily make sense, but I think it’s got to be a power issue. Interestingly, if you the people who had node positive pathologic specimens, they seem to do a little bit better and have a bigger impact. The people that were no negative. Actually it did not reach significance. And again these are unplanned subset analysis. So it’s I don’t think these should be practice changing, but should inspire future.
deliberation and future trials. And if you were really on the fence.
As to what should somebody get immunotherapy if they were in a group where there really wasn’t significance, I think you can. That’s one perspective to consider. Older patients we’ve seen this before in different immunotherapy adjuvant trials. Although it was a hazard ratio less than one and this very well may have been a power issue, but again, if you had an older patient and you were on the fence.
00:22:59.650 --> 00:23:01.630 you know I think you could.
NOTE Confidence: 0.8029525384
00:23:01.630 --> 00:23:03.740 You can consider that the
NOTE Confidence: 0.8029525384
00:23:03.740 --> 00:23:05.428 impact might be less,
NOTE Confidence: 0.8029525384
00:23:05.430 --> 00:23:09.738 and if you’re her two positive.
NOTE Confidence: 0.8029525384
00:23:09.740 --> 00:23:11.420 This was a very small group.
NOTE Confidence: 0.8029525384
00:23:11.420 --> 00:23:14.084 There were only 63 patients so I don’t
NOTE Confidence: 0.8029525384
00:23:14.084 --> 00:23:16.817 know how much stock to put into this,
NOTE Confidence: 0.8029525384
00:23:16.820 --> 00:23:18.740 but just something to think about.
NOTE Confidence: 0.8029525384
00:23:18.740 --> 00:23:20.693 So there are a couple of there’s
NOTE Confidence: 0.8029525384
00:23:20.693 --> 00:23:25.118 a bunch of ongoing studies.
NOTE Confidence: 0.8029525384
00:23:25.120 --> 00:23:25.118 These are a couple interesting ones,
NOTE Confidence: 0.8029525384
00:23:25.120 --> 00:23:30.364 which is flot versus Cisplatinum 5 FU and
NOTE Confidence: 0.8029525384
00:23:30.364 --> 00:23:33.640 in patients that have resectable gastric
NOTE Confidence: 0.692280666764286
00:23:33.738 --> 00:23:35.798 and GE junction cancer,
NOTE Confidence: 0.692280666764286
00:23:35.800 --> 00:23:37.810 getting adjuvant Pembroke
NOTE Confidence: 0.692280666764286
00:23:37.810 --> 00:23:41.160 versus placebo and then keynote.
which is for either people who are have unresectable disease or don’t want esophagectomy, which I don’t know why anybody wouldn’t want an esophagectomy I giving definitive chemoradiation again with a one of the common backbones and then Pembroke or not so a lot of information. I appreciate your time. So this was a a chemotherapy talk by a non chemotherapy ologist so take it for what it’s worth. Thank you for your your attention.
Dan, thank you. That was great.

Really nice review of some very very important.

Studies, one of which is clearly practice changing adjuvant neevo huge advance in the field and advance that we’ve been waiting for I think a couple of decades, so really exciting to have the adjuvant therapy option with the volume up in these patients we are happy to take questions in this format.

It’s in the chat box so please put any questions in that you may have.

Dan, if I may, I have a couple

of for you, so the C LGB study.
Left us hanging with a lot of unanswered questions. And wish list for maybe how they had designed the study. But one just your opinion on the question of induction, chemoradiotherapy. There’s been no study that’s compared adding induction chemo priority if therapy versus just chemoradiotherapy followed by esophagectomy. It’s from a pragmatic perspective. We find it useful to start with induction, chemo, because often dysphagia resolves rapidly,
so we do it pretty routinely,
and I think based on the study you reviewed,
we have shifted towards full
Fox in the adenocarcinomas.
Do you have an opinion?
I'll just ask for
your opinion on whether you think
induction chemotherapy is important.
The survival statistics from
that study were impressive.
I think better than prior studies.
Could that in part be due to the induction.
The inclusion of induction, chemo?
Or do you think it just has
more to do with maybe full Fox
in the adenocarcinoma subset?
So, so the fact that there were that that roughly 1/4 of patients did not get an esophagectomy could be that. You know, anytime there’s attrition that could be could be appropriate. Patient selection patients progress and they avoided a surgery that didn’t help them. I think in my experience there are definitely patients who achieved a a superior nutritional status and had a they were better surgical candidates, ultimately because they got induction, chemo and then moved on to chemo radiation instead of just getting hammered right away. Clearly there also had patients that
got so much chemo by the time they got to the operating room they were. So they just really didn’t. They distorted, never recovered. And it increased the risk.

And so one thing I love about Connecticut, the medical oncologists have been really engaged and just say you know and I and been really open to this conversation. The medical oncologists have been really engaged and just say you know and I and been really open to this conversation. And often, you know, there’s no scientific way of doing this, but but a gestalt of are they? What’s the regimen that’s going to really get them to take advantage of all modalities?
And so I do think if they’re obstructive and then nutrition, trying to optimize them, I think in our experience the induction chemo is very effective. But I do think there are people who just get so debilitated from all of the induction to try to identify those people so that they don’t miss out on an opportunity of a curative and resection.

I have a question before we let Dan go, I don’t know how close to this part but in the trial with Nivolumab did anyone
have to withdraw due to immune related adverse events from the checkpoint?
Or was there a significant? Was there any incidents or could you talk about that at all?
Great question and I'm gonna. I'm Jill is going to know exactly what I'm talking about here,
 discontinuation of therapy was about 10 percent 910% and and I would say. I, I think that is an overly optimistic number.
We've now had the advantage of seeing people on nivolumab after Esophagectomy and I don’t think it’s a walk in the park.
I think it’s tolerated,
but I think it does. You know?

Unlike because we’ve because I do a lot of lung cancer and we give a ton of immunotherapy. I personally think it is a real thing to go through immunotherapy. After off Ectomy and I would guess that more than 10% of people have a hard time with it. But but Joe, what? What is your sense of that?

This is a learning curve for all of us because this is very new, so I think we don’t have vast experience yet in that study I
think was about 10% discontinuation for treatment related areas, and I would imagine that most of those were felt to be immune related. So I mean, I think in general we think Nevo is a well tolerated drug, a single agent with a low incidence of serious immune related AE, but I think you’re right, Dan. This is a new patient population. We’ve not done this before in large numbers, so I think to be continued, we’ll we’ll have to see how it plays out. Just one final question, and maybe this is the lead in for Marie’s talk you you showed
some of the information about PDL 1 scoring in this study? Was that done in the post treatment Pathologic specimen stand? Do you know off the top of your head? Yeah, that’s a great question, I don’t know. Because, you know, going to, I think educate us all about some of the challenges with PDL one, but I think 1 issue is that. We don’t really have a. I don’t think a clear understanding of what we would see with PDL 1 scoring pretreatment and then post chemoradiotherapy, but you have to imagine it’s
going to affect the results.

So all right, Dan,

Thank you very much.

That was really a great review

of really important studies.

We’re going to move on to our second talk.

We’re going to shift directions now and
take a very deep dive into immunotherapy.

And as I think, most of you know,
in the last two years we have
heard a lot about immunotherapy
and gastroesophageal cancers.
And we are deploying it quite regularly
now in the first line setting.
And there’s a lot of chatter about.
How do we use PDL one as a
NOTE Confidence: 0.830067296666667
00:31:13.662 --> 00:31:15.194 predictive biomarker in choosing
NOTE Confidence: 0.830067296666667
00:31:15.194 --> 00:31:17.269 an patients for immunotherapy in
NOTE Confidence: 0.830067296666667
00:31:17.269 --> 00:31:19.735 the first line setting and beyond.
NOTE Confidence: 0.830067296666667
00:31:19.740 --> 00:31:22.001 And Marie is going to shed some
NOTE Confidence: 0.830067296666667
00:31:22.001 --> 00:31:24.558 light on that very confusing topic.
NOTE Confidence: 0.830067296666667
00:31:24.560 --> 00:31:27.424 And then with that backdrop then I will
NOTE Confidence: 0.830067296666667
00:31:27.424 --> 00:31:30.456 then review some of the more recent studies.
NOTE Confidence: 0.830067296666667
00:31:30.460 --> 00:31:32.092 So Marie Doctor Robert,
NOTE Confidence: 0.830067296666667
00:31:32.092 --> 00:31:34.540 another wonderful colleague of mine that
NOTE Confidence: 0.830067296666667
00:31:34.612 --> 00:31:37.033 I get to work with on a regular basis.
NOTE Confidence: 0.830067296666667
00:31:37.040 --> 00:31:38.840 Is professor of pathology,
NOTE Confidence: 0.830067296666667
00:31:38.840 --> 00:31:39.290 medicine,
NOTE Confidence: 0.830067296666667
00:31:39.290 --> 00:31:42.068 and human and translational immunology here.
NOTE Confidence: 0.830067296666667
00:31:42.070 --> 00:31:44.966 And she directs our GI pathology program and,
NOTE Confidence: 0.830067296666667
00:31:44.970 --> 00:31:47.588 very importantly and relevant to her topic.
NOTE Confidence: 0.830067296666667
49
Tonight she is Co leading an important international study on interobserver agreement in PDL one CPS scoring and gastric cancer, so Marie.

Thank you, Jill.

And I’m still smiling despite being on doing that study. OK, so I think you can see my screen. Well, I’m delighted to be here with you today in person and those watching later on. And I want to thank Doctor Lacey for the invitation and Doctor Boffa for sharing the Virtual podium this evening. I hope that I will only spend about 20 maximum 25 minutes discussing really the
inside baseball nitty gritty in the weeds.

What does it mean to score a PD1 immunohistochemical stain

in gastric cancer and this would apply to other tumors as well,

and so the subtitle is the challenges and interpretation and how for a clinician,

how should one decipher the report?

These are my disclosures.

So by way of outline,

I’m just going to spend a moment just second on things you already know,

way better than me.

The rationale for blocking PD one

receptors on immune cells in cancer.
Spend the bulk of the time talking about.

An overview of the development of the PO1 immunohistochemical stain as a companion or complementary diagnostic for the use of checkpoint inhibitors,

and we’re really going to look very, very intensely at how Pedial Wednesdays are interpreted at the microscope,

and I will show you examples and ask you to do this with me.

And in doing so, I hope to. Sort of.

Unveil the challenges in applying the scoring criteria that are recommended by the Agilent Dako group for two are proportions.
Score what we’re really about today.

The combined positive score and all of that is about scoring tumor cells in immune cells.

And this will get to the question of Interobserver agreement and reproducibility of results.

Finally, I’ll hope to help decipher reports, at least the Yale reports and.

Touch on what I think would be, I think what everyone thinks who does this for a living is what would be great.

A future directions.

So this is the tried and true example.

There’s a cartoon.

There are many.
This happens to be photos from the Agilent Vehicle Training manual for pathologists.

I, just to remind everyone what are we? What are we standing here? What are we talking about? So PDL one and also PDL 2 Stanford Program cell death ligand. So the ligand is the thing sticking out of the cell. On the membrane and it’s expressed normally in normal cells, normal immune cells, epithelial cells, fibroblasts and endothelial cells and the ligate. The the receptor for this to the PD
NOTE Confidence: 0.953792594
00:35:09.452 --> 00:35:11.713 one which is the program cell death
NOTE Confidence: 0.953792594
00:35:11.713 --> 00:35:14.690 receptor is expressed on the surface of.
NOTE Confidence: 0.953792594
00:35:14.690 --> 00:35:17.189 Inflammatory cells CD 4 positive and CD
NOTE Confidence: 0.953792594
00:35:17.189 --> 00:35:20.190 8 positive T cells natural killer cells,
NOTE Confidence: 0.953792594
00:35:20.190 --> 00:35:21.504 B cells,
NOTE Confidence: 0.953792594
00:35:21.504 --> 00:35:22.161 macrophages,
NOTE Confidence: 0.953792594
00:35:22.161 --> 00:35:26.103 and dendritic cells and in health.
NOTE Confidence: 0.953792594
00:35:26.110 --> 00:35:29.673 The purpose of the PD one ligand
NOTE Confidence: 0.953792594
00:35:29.673 --> 00:35:34.748 is to bind to a T cell receptor
NOTE Confidence: 0.953792594
00:35:34.750 --> 00:35:38.369 and and and tell it I’m OK.
NOTE Confidence: 0.953792594
00:35:38.370 --> 00:35:39.408 This is me.
NOTE Confidence: 0.953792594
00:35:39.408 --> 00:35:43.070 This is you stop and cease and desist friend.
NOTE Confidence: 0.953792594
00:35:43.070 --> 00:35:47.570 And this prevents autoimmunity.
NOTE Confidence: 0.821920152857143
00:35:47.570 --> 00:35:50.006 Interesting when that breaks down not just
NOTE Confidence: 0.821920152857143
00:35:50.006 --> 00:35:52.529 because of drugs but from other diseases.
NOTE Confidence: 0.821920152857143
The then you can get bad autoimmunity. It is one of the mechanisms actually. As a side point is there’s the CLA 4 deficiency that can lead to severe colitis, for example. But in tumor growth, some tumor cells develop the ability and mimic normal cells by up regulating PD1 ligand on their membranes, and then they trick the cytotoxic T cell which binds via the PD1 receptor and it activates the cytotoxic T cell which is supposed to recognize this as something that doesn’t belong and kill it and so you all know this very very well and therefore the the rationale behind.
Anti PD One therapy is to give an antibody that will bind instead of the PD one ligand on a tumor cell. This will block these receptors and allow these cells to then not to say, "hey, you’re not me, you’re not self and attack." That’s the rationale.

So, I’m trying to put my pictures somewhere. This led to these discoveries about the wonderful science, some of which Yale did. The development led to the development of immunohistochemical PDL.

One stain as a companion or companion
meaning companion diagnostic means.

If you don’t have this result you can’t give the drug or complementary.

We want to know the result, but either way we’ll still use the drug diagnostic,

so immunohistochemical stains if you don’t know, they’re very.

These are a series of antibodies linked together to identify a molecule on a formalin fixed, or it could be frozen,

fixed piece of human tissue or any tissue that is in mostly in this setting.

Formalin fixed and paraffin
00:37:49.956 --> 00:37:52.380 embedded and cut onto a slide.
00:37:52.380 --> 00:37:54.372 And this is the of course on the manual they show beautiful stain.
00:37:56.120 --> 00:38:01.713 This is an example of a PD.
00:38:01.713 --> 00:38:05.778 One stain on a cancer and you see the brown is positive stain and it’s outlining the cell membrane,
00:38:03.579 --> 00:38:05.778 it’s membranous, strong,
00:38:05.780 --> 00:38:07.940 so it’s membranous, strong,
00:38:07.940 --> 00:38:09.020 membranous staining.
00:38:09.020 --> 00:38:12.156 If anyone looks at her too immunostains, it’s very similar when it’s this strong,
00:38:12.160 --> 00:38:14.078 it’s similar to what up 3 plus positive
00:38:14.080 --> 00:38:16.424 her two stain would look like strong membranous staining.
00:38:16.424 --> 00:38:18.817 member to staining on tumor cells.
00:38:21.000 --> 00:38:21.290 OK,
but that’s the manual.

And then there’s real life so,

I was very successful and LED

to in 2015 the Deco,

which is bought by Agilent few years later.

Firm DX anti PD12C3 assay which


The combined positive score

I’ll be defining all of this.

Was FDA approved for gastric and GJ

had no person Noma after phase two?

Keynote 59 trial.

So Agilent or Dayco developed

and and but this this.
This approval was based on pathologist at Merck and I'll talk about this in a moment. The scoring, the putting together of combined positive score. What was it? How to do it was done in the confines of a single company Merck. And the FDA approved their methodology. That’s how that got going. That’s how CPS came to be as a requirement. Was not tested outside of that. It’s important to know that so, but nonetheless, Agilent then developed training modules for work and day pathologists like myself and others to
train and learn how to look at.

Video 1 stains and produce these scores from the methods developed in house at Merck.

I will just mention that now there are multiple antibodies. I purposefully mentioned the specific antibody 22C3 because that’s the one that was approved by the FDA for this purpose and with CPS score and also TPS and inland.

There are multiple antibodies available and at Yale we use the E1L 3N.

Antibody that has been shown to have a homology and to work equally well as 22C3, and there’s also 28 eight SP 142.

Many proof of concept studies since
I was not involved in those I feel I can brag for my colleagues. We’re actually performed by Yale Smilow and pathology department faculty, and so it’s a nice legacy of progress. But I think it’s important. Those of us who look at this stain on a daily basis have come to, I would say almost universally, across the United States. In any case, and opinions are slightly different in Europe from the pathologist with whom I interact with. That what we are having trouble.
With reproducibility and with frankly performing the stain as it is laid out in the guidelines, I just like to share this with you. We do it, we do our very best. We follow the guidelines but I would like you to know about some concerns. About relying on this immunostain because I think we can move on, hopefully in the not so far future to something else, so it starts back from 2017 at ASCO. This presentation by Merck about the development of the combined positive score for the evaluation of PD one and solid tumors.
Using this antibody and what they discussed is that they had an interobserver agreement amongst their pathologists of 88%, which sounds pretty good further. For a cut off of of Cpiq score of 1, about 57% of the gastric cancers in their hands had a positive score. I've seen in in the literature and I would say in our hands it’s somewhere more between 30 and 50%, but that’s what they found. So that’s interesting that in their hands they got an 88% agreement. As at a cutoff of 1. But what what?
There are a few questions that this raises once we get into start doing this as we’ve been doing for some years now, there’s not much data on agreement at other cut offs, nor at what if and what if the case will come, which it may be coming that oncologists would like to have an exact value, not a cut off, like greater than one greater than five greater than 10. But was it 8 or 45? And and I’ve heard I’m in discussions now about what
we should be providing and this is because the indications keep changing and there’s new protocols and wonderful opportunities for patients to be treated with these medicines that may or may not depend upon certain criteria of MCPS. And I’m just very curious. I think we have the answer and we ask this question. How does agreement on combined positive score differ? From agreement on tumor proportion score, which is simply the percent of positive tumor cells over the
00:43:31.755 --> 00:43:33.105 total number of tumor cells,
NOTE Confidence: 0.796600026666667
00:43:33.110 --> 00:43:34.895 simple straight percentage and the
NOTE Confidence: 0.796600026666667
00:43:34.895 --> 00:43:37.200 hint is you’re not surprised by this.
NOTE Confidence: 0.796600026666667
00:43:37.200 --> 00:43:40.404 You already know is that pathologists
NOTE Confidence: 0.796600026666667
00:43:40.404 --> 00:43:43.252 agree much better on TPS.
NOTE Confidence: 0.796600026666667
00:43:43.252 --> 00:43:46.725 If you have 10 pathologists look at
NOTE Confidence: 0.796600026666667
00:43:46.725 --> 00:43:50.238 the same sample then they would on CPS.
NOTE Confidence: 0.796600026666667
00:43:50.240 --> 00:43:52.475 We’re going to go into why?
NOTE Confidence: 0.796600026666667
00:43:52.480 --> 00:43:54.475 But the the other you know concepts
NOTE Confidence: 0.796600026666667
00:43:54.475 --> 00:43:56.916 to to put out here is when when one
NOTE Confidence: 0.796600026666667
00:43:56.916 --> 00:43:59.138 puts out in an abstract that hey,
NOTE Confidence: 0.796600026666667
00:43:59.140 --> 00:44:01.540 this works and there’s great
NOTE Confidence: 0.796600026666667
00:44:01.540 --> 00:44:03.015 interobserver agreement, well.
NOTE Confidence: 0.796600026666667
00:44:03.015 --> 00:44:05.590 What was your training methodology
NOTE Confidence: 0.796600026666667
00:44:05.590 --> 00:44:09.053 in this specific setting and what is
NOTE Confidence: 0.796600026666667
00:44:09.053 --> 00:44:11.552 the training methodology in the the
rest of the world and in practicing medicine?

In fact, the methodology is voluntary. It the rigor varies widely, there’s no requirement that that it’s not registered with the FDA that we’ve done our training or not. This is honor system, so we’ve all done it all the graphologists if you all have gone through the training, but there’s no requirement that you repeated every year. What about drift over time after training, so it’s there’s a lot of questions. And the unfortunate fact that we
00:44:41.440 --> 00:44:44.502 seem to notice is that many samples.
NOTE Confidence: 0.798921287222222
00:44:44.502 --> 00:44:48.185 Hover near the cutoff so when it’s
NOTE Confidence: 0.798921287222222
00:44:48.185 --> 00:44:50.210 negative we’re all in agreement.
NOTE Confidence: 0.798921287222222
00:44:50.210 --> 00:44:52.014 When it’s wildly positive,
NOTE Confidence: 0.798921287222222
00:44:52.014 --> 00:44:53.818 and clearly you know.
NOTE Confidence: 0.798921287222222
00:44:53.820 --> 00:44:56.251 1020, etcetera score that’s easy
NOTE Confidence: 0.798921287222222
00:44:56.251 --> 00:44:58.008 because you’re way above any cut off.
NOTE Confidence: 0.798921287222222
00:44:58.010 --> 00:45:00.327 But we do have many samples that
NOTE Confidence: 0.798921287222222
00:45:00.327 --> 00:45:02.569 hover near a CPS cutoff of 1.
NOTE Confidence: 0.798921287222222
00:45:02.570 --> 00:45:05.740 And I know new cut offs of five are coming.
NOTE Confidence: 0.798921287222222
00:45:05.740 --> 00:45:07.060 I’m just going to highlight here.
NOTE Confidence: 0.798921287222222
00:45:07.060 --> 00:45:08.698 This is the manual that we use,
NOTE Confidence: 0.798921287222222
00:45:08.700 --> 00:45:12.696 and I’m going to show some figures and and
NOTE Confidence: 0.798921287222222
00:45:12.700 --> 00:45:15.535 language from this from the Agilent Deco.
NOTE Confidence: 0.798921287222222
00:45:15.540 --> 00:45:18.366 This is what we read and is a gorgeous
NOTE Confidence: 0.798921287222222
00:45:18.366 --> 00:45:20.454 picture of PD one standings pristine
and I'm also going to use material from a book written by friends of Mine, Sunil, Bobby and George Kumar predicted biomarkers in oncology and this is an excellent Treatise of the topic. This is not to get into the test tube and pipette phase of things, but it is important that we all remember that in any test that’s done in a laboratory there are called there’s a quality assurance aspect and this is they they in the and kumars book they talk about the predictive biomarker quality assurance cycle,
and I think it’s important to know that when you’re taking a sample from a patient. Usually in this setting it’s an endoscopic mucosal biopsy that undergoes tissue processing, first in formalin and through a series of solutions. In the regular Histology laboratory that have to be controlled. It’s put into paraffin, cut into sections, and then that’s the tissue processing. The pre analytic phase. Then there’s sustaining the analytic phase that has. There has to be QC and quality assurance of both the controls and the test tissue sample.
And then there’s post analytic.

That’s the interpretation, scoring and reporting.

So what kind of QC can we really apply?

And that’s a question to pose

yourself when I take you through this.

The result of a CPS score,

for example,

compared to a chemistry test of

a blood test in the lab and and
00:47:09.696 --> 00:47:12.190 what kinds of decisions might be
NOTE Confidence: 0.798921287222222
00:47:12.190 --> 00:47:15.038 made and how that’s done.
NOTE Confidence: 0.798921287222222
00:47:15.040 --> 00:47:16.587 I won’t walk through all this side,
NOTE Confidence: 0.798921287222222
00:47:16.590 --> 00:47:18.795 but but just to say those people
NOTE Confidence: 0.798921287222222
00:47:18.795 --> 00:47:20.984 who do just know that at the
NOTE Confidence: 0.798921287222222
00:47:20.984 --> 00:47:23.595 back of a test like this one and
NOTE Confidence: 0.798921287222222
00:47:23.595 --> 00:47:25.535 and hopefully every other one.
NOTE Confidence: 0.798921287222222
00:47:25.540 --> 00:47:29.124 Is a whole are people who understand.
NOTE Confidence: 0.798921287222222
00:47:29.130 --> 00:47:31.902 What needs to go into the pre
NOTE Confidence: 0.798921287222222
00:47:31.902 --> 00:47:34.260 analytic analytic and post analytic?
NOTE Confidence: 0.798921287222222
00:47:34.260 --> 00:47:36.055 Quality checks such that there
NOTE Confidence: 0.798921287222222
00:47:36.055 --> 00:47:37.850 are things that would indicators
NOTE Confidence: 0.880474148461538
00:47:37.915 --> 00:47:40.148 of unacceptable results that would cause us
NOTE Confidence: 0.880474148461538
00:47:40.148 --> 00:47:42.940 to pause and not report that and start over.
NOTE Confidence: 0.880474148461538
00:47:42.940 --> 00:47:45.229 I just want to highlight one here.
NOTE Confidence: 0.880474148461538
00:47:45.230 --> 00:47:48.690 Quality of tissue morphology.
So the tissue morphology in a biopsy is sort of decided by things that are out of our hands that they’re sample. How much tumor is in it versus normal benign or incites? You crush artifact from the biopsy, forceps, necrosis, thermal injury if caught early was used in obtaining the specimen, so we have no control over this and we don’t. We try very hard not to ask folks to go back and get more samples and put patients through procedures. We deal with what?
We have by and large and do the best we can, but it’s something to know about, so these are some statements from the Agilent Manual and this is the most important equation that we are living by for gastric and GJ cancer. So what is the combined positive score? It is as you know the number of Pedial 1 staining tumor cells, lymphocytes and macrophages over divided by the total number of viable tumor cells, and then we multiply that times 100 so you can see that we ought to be, you know, shouldn’t be too hard to get to something greater than one because
we’re multiplying by 100.

So they want us to get to 1.

So let’s take some definitions now for PDL 1,

scored tumor cell.

OK, well, what is that?

Well, it sounds pretty obvious,

but there are some caveats.

Not inside you, not dysplasia or carcinoma,

incites you and in the esophageal cancer

or gastric cancer coming from a backward,

often a dysplastic background on

top and the superficial mucosa

that is not to be counted,

and that is to be distinguished

from the invasive self coming right
off of that inside your component. That’s very challenging at times. Areas of necrosis are to be avoided and one must have a minimum of 100 viable tumor cells in the sample. To perform the stain. What is an immune cell for the purposes of this for CPS it’s consists only of lymphocytes and macrophages, plasma cells and neutrophils are not to be counted. Those are very common cells in the mucosa, especially plasma cells, fibroblasts and endothelial cells which are not inflammatory cells but are other stromal cells are not to be counted.
All of these things can pick up stain. All of them can pick up a PD. One stain can be positive. So we already said what 2 reports and CPS is. I want to just point that outside of the GE of the GE junction and gastric cancer in the GI tract, we're doing PD one on many things and there because CPS or TPS have not been codified. We report simply the percent immune cells and percent tumor cells staining, and we'll talk about that when we get to reports, OK? Fine,
so that’s those are our marching orders.

How do we do it?

Well, the minimum of 100 cells we look at various magnifications. This is important if the specimen includes more than one biopsy in the jar, which it always does.

And we put all that on one slide, all the tissue on the slide needs to be evaluated. Generate a single CPS score. And if we’re doing it on a resection, the entire every single tumor cell, every immune cell should be evaluated. And that’s when in tumor.
We have a lot of dos and don’ts include and don’t include in the numerator and denominator.

And specifically, what are we grading? Well, for tumor cells we’re looking at membranous staining, only not cytoplasmic. And we are to count a cell as positive if it has any partial. Or complete linear membrane staining. So half the cell or the whole cell. Any part of the cell any membrane is staining. Of greater than one plus intensity.
So what’s interesting is that this is not defined. This is a completely subjective 1 + 2 + 3 plus partial complete. And for the immune cell lymphocyte or macrophage membranous staining and cytoplasmic staining count, again with any basically any amount of staining. You’re to count that cell. So let’s go through now and see how to do this with some real world samples. Here’s a biopsy set of biopsies all in one jar, ten eleven you know 12 ish. Biopsy fragments of various sizes.
I can tell at this magnification that they basically all came all have tumor in them is very generous endoscopist, so we’re meant to do an immunostain and count every single one of these pieces. So let’s see how that’s done. This is one piece at a slightly higher magnification. The bigger poofy cells are tumor cells. The small purple dots are inflammatory cells. Here it is at higher magnification. These are tumor cells the the bigger cells, they’re bigger nuclei, a little bit paler, and the smaller purple dots are immune cells, so I just want you to know.
the oncologist watching.

There is no ocular micrometer or software to do this counting. We are literally at a microscope with maybe an arrow. Basically, guesstimating estimating that that the numbers of denominator how many tumor cells are here. So that is what I want to communicate to you about the precision. How do we do this? Some people do a gestalt. I do a counting guesstimate and on the training in the online training with a guide, someone teaching us how to
train at Agilent at Dayco.

That's as good as they had to offer.

That's what we are meant to do,

so I will count off 100 cells by hand,

at the microscope with the fellow.

Count to 100 and then I do this.

I don’t want to scare you,

but that’s what we do.

203 hundred, 405 hundred 600.

Literally,

this is what we have to work with.

this is what we have to work with.

There is nothing better.

Then when we put side by

side as I’ve done here,

the tumor cells a high power view of
the tumor cells with some immune cells.

I would just like to point out that some of these immune cells are plasma cells, and we're not to count plasma cells, only lymphocytes and macrophages. The macrophages are always quite hard to recognize and distinguish from a fibroblast or endothelial cell. This is the PDL one stain in this example. So we get a sense. Here's a Member in this staining, probably a tumor cell, so that's one. There are some other cells with some membrane and I'm not sure what this one is, but you know, chances are it's meant to be counted.
That's two and we're getting into some things here that have a lot of stain that's very dark where it's hard to distinguish what cell type it is and how many cells are here. So this is what is challenging when you get big clumps like this, there's a lot of standing here. This is this is here's that same vessel. It's stuff here. It's probably immune cells, and some of them are lymphocytes, some are not. So we do the best we can. In this example, there's some pretty, you know, honeycomb pretty clear cut,
membranous tumor staining.

And we could probably could certainly get to cut offs where we’re helped a lot by the fact that we are only for the most part giving a cut off of less than or greater than one not an exact number. So one can guess that this degree of staining and then your time timing by 100 the equation we’re going to get to greater than one.

So I think this saves us. But if we’re going to get to cut off some 5. And exact numbers. It’s different. In this example, the tumor cells are here and these are this very nice example,
because these are all lymphocytes.

Morphologically,

I feel pretty comfortable about that.

And the PDL one stain in this area

anyway shows negative tumor staining,

but lots of lymphocytes staining,

so even if I'm not sure it's really

impossible to count how many are positive,

but one can do their best with this

sort of an estimate and get to a score.

In terms of a cutoff of greater less

than one. Couple more examples.

I want to show this is a biopsy,

which is real life biopsy with the usual.

Sometimes we get folds in the slide etcetera.
In the section there’s a lot of insights you display Asia here. This is not cancer, that’s dysplasia. This is cancer. There is some cancer here. This probably is cancer. These three glands. Then there’s some inside you. So when you Pivot to the PDL. One stain one has to be. It’s challenging to count only what we think is invasive cancer, not dysplasia. And only the immune cells around the cancer, not the immune cells around the dysplasia. So these are just some of the challenges. In this example, these again are tumor cells.
And there's some stroma around this is the PDL one stain and there is some positive staining and this is cytoplasmic, not membranous. So if this is a tumor cell, it is not to be counted. Here's some membranous staining, probably a tumor cell. But there's some other staining that is cytoplasmic here and there and I don't know what the cells are. I don’t know. I can’t tell morphologically. Even going back and forth are those lymphocytes. These are actually smooth.
muscle cells with a faint stain. 

So it does. Get quite challenging. 

Finally, 

we’re asked this is a metastatic colon cancer to the liver. 

Just the concept of. 

How much material there can be? 

This is only about 1/5 of the 

tumor on the slide, 

and here we’re counting just percent 

tumor and percent immune cells and making 

tumor cell staining here, 

very specific point on this slide. 

There’s not a lot of. 

There’s almost no tumor cell staining here, 

but you can see some faint brown even at this 

magnification surrounding some of the cancer,
and these are immune cells and a lot of these are lymphocytes, others are neutrophils.

This is the PDL one stain. This is a vessel that’s staining and there is some cytoplasmic staining of variety of things. Not sure what all these cells are, but you know we would do our best but the the other point about this is that. When we’re giving a PDL one CPS score. We just have to guesstimate the number of positive tumor and the number of positive immune cells.
We don’t have to give the denominator of what is the total immune cell count and you can imagine how challenging it would be for us to try to count the immune cells in any section, let alone a large section. So percent immune cell is really quite challenging to feel good about. So in summary, I think I’m being the bearer of not very comforting news here. This is our reality in every academic pathologist with whom I’ve ever spoken across numerous centers is in complete agreement with this and we are.
cage for something better.

So in summary, there are the challenges with PDL 1 scoring.

You know, recognizing tumor cells from stroma,

cautery and other artifacts,

faint staining and in the immune

cells it’s really hard to distinguish

the limbs and macros from other

cells and a variety of other things.

The agreement at cut offs is, I think,

already can be quite challenging,

but reproducibility for exact scores.

Should that be be requested,
would I would expect that to be even less agreements and I’m saying, well I think it’s an 8.

And Jill mentioned something that I think there’s basically no data on. What about the variability within the tumor? Even even in a single tumor within biopsy fragments or within a resection. And what about? Should we do a primary or a metastasis? Pre or post therapy? So those are really valid questions. Uh, almost done. Just how to decipher report.
OK, we’re giving it our best shot.

We do this test every day and we will continue to do so as requested until something better comes along.

But at Yale, in any case, our reports, I think, can probably be somewhat confusing, and I’m sorry if that’s the case.

We try to give for gastric and GGJ a score based upon the cutoff of 1 and say it’s positive or negative.

And what the what?

The equation consists of? In, in, and in isopropyl that cut off his ten etcetera depends on
the organ system elsewhere in the GI tract we when asked to do this. Since there’s no cutoff agreement, one just gives the.
The percent of immune cells and percent of tumor cells staining, albeit the challenges that I, despite the challenges that I’ve mentioned. And I just want to make a point here that while you can impute. A tumor proportion score from this information because the the percent of tumor cells is TPS. That is what TPS is. But you can’t impute a CPS should you want to from this, because.
The CPS is just the absolute number of positive immune cells. It is nothing to do with the denominator of the total number of immune cells staining at any intensity, so you can’t add these together or in some way figure out you’re not getting the number of immune cells, which is what you need. The absolute number, which is what you need for a CPS.

You’re getting the percent of immune cells stain.

Future directions we would be thrilled to get as quickly as possible to automation with
artificial intelligence and other software,
and I think this is coming to remove the subjective interpretation from this process.
I'm always comforted to hear from Jill that if one needs to treat a patient with a checkpoint inhibitor, it is possible to do so regardless. Of what the score is, but we still feel quite a burden that we may be giving a result that is, is not could potentially not be accurate about a cutoff that you're counting on, and therefore the the sort of the hope given to the patient about a response. We would like that to be real. But it does beg the question.
Are there situations where PD one stain may not be needed to treat, and if that’s the case, be great not to ask for it.

Further, in addition to what I think you know, and I have to mention, Dave Rim always in a talk like this for all the wonderful work that he and his lab have done. And I he has a quantitative pathology laboratory yield that I hope will, I assume is working very hard on getting to automation. But in in fact there’s other
research and Kurt Shelper in our department with Leaping Chen. Of course they recently published in Cell in 2019. They’re digging even deeper, you know, because after all there are those. Folks with checkpoint inhibitors who don’t respond and he’s there, the group is getting into other discoveries of other potential important molecules. Such as fibrogenic like fibrinogen like protein and its interaction like protein and its interaction with lymphocyte activation gene 3. So that’s very exciting, and hopefully they’ll be more things.
I just wanted to share some references that I referred to in this talk and thank you.

I hope it’s not too alarming, but I think it’s a great opportunity for pathologist to share what’s really going on behind that CPS clip.

There was a question in the chat box which I think you preemptively answered about. There must be scanning software and artificial intelligence that can do this.

This just seems like such an opportunity for pathologist to share what’s really going on behind that CPS clip.
01:04:47.330 --> 01:04:48.680 onerous burden on you all.
NOTE Confidence: 0.858157674736842
01:04:48.680 --> 01:04:50.755 And at the end of the day, as you said,
NOTE Confidence: 0.858157674736842
01:04:50.755 --> 01:04:52.345 it’s not really as quantitative as
NOTE Confidence: 0.858157674736842
01:04:52.345 --> 01:04:54.299 we all think it might be when we
NOTE Confidence: 0.858157674736842
01:04:54.299 --> 01:04:56.118 look at forest plots with cut offs.
NOTE Confidence: 0.858157674736842
01:04:56.120 --> 01:04:57.548 So it looks like that is something
NOTE Confidence: 0.858157674736842
01:04:57.548 --> 01:04:59.430 that’s in the works, and I
NOTE Confidence: 0.8389574734
01:04:59.490 --> 01:05:02.232 think people. I know people are
NOTE Confidence: 0.8389574734
01:05:02.232 --> 01:05:05.983 working on this and and it I agree
NOTE Confidence: 0.8389574734
01:05:05.983 --> 01:05:08.725 with the person asking the question.
NOTE Confidence: 0.8389574734
01:05:08.730 --> 01:05:09.966 There will be a better way.
NOTE Confidence: 0.918112289
01:05:11.390 --> 01:05:12.660 All right, well I will
NOTE Confidence: 0.918112289
01:05:12.660 --> 01:05:13.930 carry on and thank you.
NOTE Confidence: 0.918112289
01:05:13.930 --> 01:05:18.018 That really lays the foundation for my talk.
NOTE Confidence: 0.918112289
01:05:18.020 --> 01:05:20.092 And now we’re going to talk about how
NOTE Confidence: 0.918112289
01:05:20.092 --> 01:05:23.018 we use this information in making very

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important decisions for our patients.

So we can all see my screen.

So I’m Jill Lacey.

I’m a medical oncologist at the Yale School of Medicine and Smilow Cancer Center.

I’m involved in caring for patients with gastrointestinal cancers and do have a strong interest in gastroesophageal cancers.

So my topic tonight is, is it time for chemo immunotherapy for all of our patients, or should we slow down, put the brakes on? And here are my conflicts, so I’m going to be focusing solely on first line treatment,
not second line and beyond, and the role of immunotherapy in the first line treatment of metastatic gastroesophageal cancers. I'm going to review the data for chemoimmunotherapy, and when I say chemoimmunotherapy here, I'm talking about a standard chemotherapy doublet with or without an immune checkpoint inhibitor. And all the studies have been with. I'm going to talk about the data in squamous cell carcinoma and the data in adenocarcinoma, which is different.
Then I’m going to review some of the data for chemotherapy free immunotherapy in the first line setting. We’ve heard a lot about the controversy surrounding PDL one's predictive biomarker, so I will just highlight those and then I will have some conclusions of my own and some of the questions and future directions that we are facing. So.

Enhancing did you click on your talk? I had. There you go. OK, so immune. Checkpoint inhibitors.
I think as many know in gastroesophageal cancers have really had a checkered history. Had some pretty inconsistent and conflicting results. Certainly in the second and third line setting and also in the first line setting. There are many reasons for this. This is really a heterogeneous group of tumors. In every respect we've just heard about the imperfections of PDL one, and yet we are continue to use it to make to design studies and to make treatment decisions and then of course the trial designs. Any trial design is never perfect.
and I think there have been a lot of imperfections in the ways that the studies have been designed. You know, in large part baked into the cake and for pragmatic reasons. But that said, I think in the first line setting, some consistent and reproducible data have emerged, especially in squamous cell carcinomas. As I said, I'm focusing on the first line setting at present in the United States, we have FDA approvals for two iOS...
the second line setting and beyond,
both in squamous cell carcinomas
of the esophagus,
one with pembrolizumab with the
PDL 1 score is 10% or greater.
That's CPS and nivo PDL 1 agnostic,
so I'm going to talk now about the
data in squamous cell carcinoma.
So I just need to remind you as we go
through this that when we talk about
esophageal cancer so often historically,
the studies have included both
squamous cell and adenocarcinoma.
So mixed Histology studies
really based on the anatomy,
but in reality these are
very different diseases.

Many differences as are highlighted here and actually not that many similarities,
symptoms, overarching treatment algorithms and and prognosis, and I think.
What’s really emerged is that, yes, these are very different diseases.
This is from the tumor profiling and molecular analysis that we’re seeing with esophageal squamous and adenocarcinoma.
So the squamous subtype really resembles from A at a molecular level, and a genomic profiling level, squamous cell carcinomas of other organ sites.
Whereas adenocarcinomas of the esophagus resemble the chromosomal instability subtype. The four subtypes of gastric cancer.

So really there’s no biologic or scientific rationale, I think at this point in clinical trials for combining squamous and adeno esophageal cancers. It’s a maybe a pragmatic reason, but not really a biological reason. And I think if that’s important to keep in mind as we look at some of this data. So turning now to squamous cell carcinomas. This is remarkable.
There have been in the last two years 5 completed published large randomized phase.

Three trials of chemotherapy doublets versus a chemotherapy doublet plus a PD1 inhibitor, and they are listed here, and these studies have all shown really a consistent improvement in overall survival with the addition of a. I’m sorry that is PD1 inhibitor to chemotherapy remarkable consistency and two of these studies have led to FDA approvals in the United States in squamous cell carcinoma.
I'm going to focus in on Checkmate 648. This is the largest study by far, and this is the study that led to the FDA approval of Nevo with chemo and squamous cell carcinomas. The study design was a three-arm study with chemotherapy, fluorouracil, cisplatinum as a control against chemo plus Nevo and then a third arm without chemo of Nevo. The results are highlighted in this somewhat. So in terms of the overall survival, there was a benefit in both the PDL.
01:11:12.106 --> 01:11:14.150 one TPS 1% or greater population,

01:11:14.150 --> 01:11:16.334 which was their first primary endpoint

01:11:16.334 --> 01:11:19.419 about a six month improvement in survival.

01:11:19.420 --> 01:11:22.381 Truly a stunning result with a hazard

01:11:22.381 --> 01:11:24.670 ratio of .54 and also improved


01:11:26.830 --> 01:11:30.141 This is really dramatic data for this

01:11:30.141 --> 01:11:32.899 very difficult disease and again major.

01:11:32.900 --> 01:11:34.292 Events in the field.

01:11:34.292 --> 01:11:36.380 Also there was benefit in terms

01:11:36.454 --> 01:11:38.634 of survival for all randomized

01:11:38.634 --> 01:11:41.422 patients of about two 2 1/2 months

01:11:41.422 --> 01:11:45.040 with a hazard ratio .74.

01:11:45.040 --> 01:11:47.074 And of course everyone is interested

01:11:47.074 --> 01:11:48.794 in the subset analysis that

NOTE Confidence: 0.862154936071429

115
are often flawed small numbers. But if you look at the subsets here, I think what jumps out is that almost all subsets benefited. Interestingly, females and it’s a small set. A number of patients in squamous there did not appear to be a benefit that’s been seen in other studies, and importantly, that very important biomarker that we’re all now relying on PDL one. And so that’s that’s blown up here on this slide. And so if you look at CPS first. The only group that did not appear to benefit in terms of hazard ratio
less than one was a CPS less than one, and that was only 9% of the patient, so all the others were. The hazard ratio was less than one. If you look at TPS, this is interesting in the group less than one. There did not appear to be a benefit and by TPS less than one is about half the patient, so the data is a little bit, I think hard director head around, but. In the CPS less than one, there was a higher response rate. There was longer response duration,
and it’s possible that a survival benefit may emerge with longer follow-up.

So in the other studies, just to run through, you know what these look like. Three of them conducted in Asia, three global. These are all big studies. Keynote 590 stands out in that it was a mixed Histology study of adenosquamous. The 2/3 of them being squamous. Different PD1 inhibitors were used in each of these studies. Different chemotherapy backbones were used, although most were cisplatinum, based with either 5 or fewer CARBO paclitaxel.
Different PDL, one cut points for primary analysis, different assays. But what’s remarkable is the similarity in survival benefit in all of these studies of a couple of months with quite similar hazard ratios. Jupiter 06 being most impressive, so this is a very consistent finding and I think that really drives home the point of the value PD 1 inhibitors and squamous cell cancers. And for those of you that like Kaplan Meier plots, those are depicted graphically here for these studies.
Now how does PDL 1 fit into this?

So again we’re getting conflicting results.

I reviewed the PDL one story with 648 where did appear that the benefit was greater with higher PL and scores,

especially TPS.

We did not appear to see that same phenomenon in Jupiter 06 or in Orient 15,

but there was an association with Epoxy and PDL one and escort the escort study.

So again not completely consistent.

But overall,

I think these are really impressive results,

if you look at the forest plots

and again the the big picture here
01:14:41.932 --> 01:14:43.811 is the the hazard ratio is less than one in almost all of these studies in all PDL 1 subsets.

01:14:48.290 --> 01:14:50.514 So my take away message is that PD one inhibitors added to chemotherapy and this disease improves survival and the magnitude of benefit has been similar across different studies with different PD1 inhibitors and different chemo backbones and the study did lead to the FDA approval.

01:14:58.259 --> 01:15:00.256 For me, vote and that is a a PDL 1 agnostic.

01:15:02.562 --> 01:15:05.110 So your respective of PDL one expression. And we also have an approval from Keynote 590 for Pembroke.
Also, irrespective of PD L1 expression in esophageal squamous as well as adeno. So I’m going to pivot now to adenocarcinoma, and here the story is a little less clear. The data is more conflicted and I would say that conclusions certainly can be made with caveats, but it’s a little bit more of a challenging story, I think. So here we have 5 randomized phase three studies, all similar designs of chemotherapy doublets against chemotherapy. Plus PD1 inhibitor. Two of these studies,
01:16:00.022 --> 01:16:00.748 keynote 62,
01:16:00.750 --> 01:16:02.700 which was using Pembroke with
01:16:02.700 --> 01:16:05.650 chemo and also had a chemo through
01:16:05.650 --> 01:16:07.935 free arm of Pembroke alone.
01:16:07.940 --> 01:16:10.175 Traction four was a negative
01:16:10.175 --> 01:16:12.390 study and then Checkmate 649,
01:16:12.390 --> 01:16:13.230 keynote 590,
01:16:13.230 --> 01:16:15.330 and adenocarcinoma subset and Orient
01:16:15.330 --> 01:16:18.083 16 were all viewed as positive studies
01:16:18.083 --> 01:16:21.713 and the two the two Checkmate 649 and
01:16:26.060 --> 01:16:27.060 I think in the aggregate,
01:16:27.060 --> 01:16:28.860 even though there is conflicting
01:16:28.860 --> 01:16:29.580 results here,
01:16:29.580 --> 01:16:31.325 there’s a trend towards improved
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outcomes with the addition of PD1 inhibitors to chemotherapy in the adenocarcinoma Histology as well as squamous, and again I'm going to highlight Checkmate 649. And because, this led to an FDA approval and you have seen the design of 648, this is very similar chemo as the control arm chemo plus anevo and then a chemo free arm of. Nivo and IPI and here the ippy doses 3 megs per keg and neevo 1. The chemotherapy free arm was closed early due to futility and they carried
on with the other two arms and then the key points in terms of results are shown here. They primary end point was in the CPS 5 or greater subset and that was positive with a three month improvement in survival and again this is in this disease. Pretty impressive. We haven’t seen this kind of result. In decades, except in the her two positive group with a hazard ratio, .71 was also positive study in all randomized patients about a
two month improvement in survival with a hazard ratio of .8.

So this was a positive study.

Now everybody is interested in the PDL subsets and is there a benefit in PDL?

One negative and low and that data is shown here and so you can see that in the PDL one CPS less than one, the hazard ratio just is just under one but not impressive and the same thing with less than five. But if you look at responses the response rates are higher in all PDL 1 subsets including less than one and less than five.

So again,
this study strongly suggests that there is a relationship between PD L1 expression and efficacy from the addition of a PD1 inhibitor. So again, here are the the five studies. And in terms of how they look in terms of geography, there they were all large studies except the keynote 590 adenocarcinoma subset. Most of them were focused on GE, but Checkmate 649 fortunately included Asopus and keynote. And they used again different chemo
backbones and different PD1 inhibitors, and for the positive studies the hazard ratios in the overall patient population were quite similar and hazard ratios are not significant in keynote 62 and Attraction 4. And these are the Kaplan Meier curves for the two negative studies. They really, really were negative studies. When you look at the hazard ratio you ask the question. Well, the negative studies did the PDL 1 high subset benefited? That did not seem to be the case and in the. Other studies we don’t really have good
data in the PDL negative or low subset, so it’s hard to draw a lot of conclusions other than from Checkmate 649 about PDL quantification and benefit. Now it’s a different story in patients who are mismatched pair definition or MSI high, and I think this is a really interesting and important story that deserves highlighting. So in in both Keynote 62 which looked at Pembroke chemo versus Pembroke chemo and Checkmate 649 Nevo chemo. They looked at retrospectively at the small numbers of patients that were MSI high. These numbers are small but look at these results.
They're really dramatically favorable and dramatically similar with almost identical hazard ratios, and so I think there's no question that chemoimmunotherapy should be given to all patients without other contraindications who have mismatch repair, deficient MSI high tumors. This is a huge story, I think. In my opinion, New England Journal of Medicine Worthy, but I think definitely worth highlighting. So can we explain the discrepancies in these studies? I would say I'm challenged.
to really rationally.

Explain the discrepancies.

We can talk about biology because gastroesophageal adenocarcinoma from a biological perspective is very heterogeneous.

We've identified the four major molecular phenotypes, but that's just I think the tip of the iceberg, and we know, of course, that MSI high and B positives will be the ones likely to respond.

A lot of challenges in the trial design.

You know, excluding esophageal adenocarcinoma or excluding, different chemo backbones.
And then of course, the impact of post study treatment. I think the explanation for the very negative attraction for study was that many of those patients did get PD1 inhibitors in the second and third line and beyond. Now, how about her two positive gastroesophageal cancer? All those studies that we just reviewed excluded her two positive patients, so we now have pretty exciting data in this patient population, with the inclusion of a PD1 inhibitor with chemotherapy and trastuzumab. This is the keynote 811 study.
Also got a lot of publicity appropriately, so simple design, trastuzumab, chemo versus trastuzumab, and on what we. See here are the response data and you can see very high response rate. Very deep responses with Pembroke added to chemo and Herceptin. Higher response rate and a complete response rate. That’s very impressive at 11% versus 3%. This study led to the provisional approval of Pembroke, added to trastuzumab and chemo and her two positive.
gastroesophageal adenocarcinomas.

So obviously this is provisional.

We are waiting for.

PFS data and overall survival data.

To see what the final impact is going to be.

So we have three FDA approvals now

gastroesophageal adenocarcinomas.

So Pembroke from Keynote 590,

which did not include gastric cancers.

Neevo based on Checkmate 649 and

Pembroke added to trastuzumab.

Chemo based on keynote 811.

All of these studies.

All of these approvals by

the FDA are PDL 1 agnostic.

Which is, I think,
interesting and can be debated. So my take away message in the last few minutes is that adding a PD1 inhibitor to chemotherapy and adenocarcinomas improves overall survival in most studies, but not all. That benefit has been seen with different PD1 inhibitors. Chemo doublets and different PD, one cut offs. I think we can conclude safely that efficacy diminishes with decreasing PD L1 expression. And so, how do we use this information? So I think that most patients with adenocarcinoma should be offered
first line chemoimmunotherapy. But I recognize that we are conflicted about what to do with patients who have no PD L1 expression or low PD L1 expression. So just for a few minutes for the last few minutes I’m going to pivot to the data in guest Russophile deal cancers for first line immunotherapy without chemotherapy. So chemotherapy free immunotherapy and there are three randomized phase three trials that have addressed this question with the control arm of chemotherapy against an experimental arm of immunotherapy without chemotherapy.
So we’ve heard about Checkmate 648. Squamous cell carcinoma that had the ippy Nevo chemo free arm. We’ll discuss in a minute led to FDA approval just this past month for it being EVO in squamous cell carcinomas for adenocarcinomas. We have Checkmate 62 which looked at chemo versus Pembroke and Checkmate 649 again which looked at a chemotherapy free dual immunotherapy Nevo. These studies in adenocarcinoma were considered. Negative studies and we do not have FDA approval.
And then again I’m going to highlight the data in MSI high adenocarcinomas. So we’ve seen the Checkmate 648 and 649 designs very similar except for the dosing of Yippee Nevo, 3 megs per kig in adenocarcinoma, one Mig per kig ippy in squamous cell carcinomas, and side by side. Here are the Captain Meyer plots for overall survival and in their primary endpoint of PD L1 positive tumors and then down below all randomized patients. And so, in adenocarcinomas, this was viewed as a negative study, median survival, the same.
Although you can see the curves do separate at later time points, I think which is interesting.
The response rate was notably substantially lower.
Would it be neevo different story and squamous cell carcinoma?
This is a positive study with a significant improvement in overall survival in PDL and positive patients and also in all randomized.
Patients so no approval for apnea and adenocarcinoma, but it is approved in squamous cell carcinomas.
Now what are the red flags here for squamous cell carcinoma? So a big red flag is this crossing of the curve survival curves in the first six months so a higher rate of death and patients getting immunotherapy alone versus chemotherapy. And we don’t know the full explanation for that. We can come up with some plausible explanations, but we’re not certain. I think we’ll get more information from this study about that. If you compare immunotherapy alone versus chemotherapy immunotherapy in 648,
01:26:46.018 --> 01:26:48.454 which is not fair by our statistically,

01:26:48.460 --> 01:26:50.770 it does look like the

01:26:50.770 --> 01:26:52.618 survival curves are similar,

01:26:52.620 --> 01:26:55.399 but the duration of response and the

01:26:55.399 --> 01:26:57.540 responders does appear to be longer.

01:26:57.540 --> 01:27:01.010 With dual immunotherapy

01:26:59.622 --> 01:27:02.907 When you look at immunotherapy versus chemo,

01:27:01.010 --> 01:27:02.907 you have the very predictable expected

01:27:02.910 --> 01:27:05.484 differences in treatment related AE.

01:27:05.484 --> 01:27:07.450 But there were fewer treatment

01:27:07.450 --> 01:27:09.105 related AE's leading to treatment


01:27:11.616 --> 01:27:13.850 So this is really exciting.

01:27:13.850 --> 01:27:16.850 This has led to the first FDA approval

01:27:19.506 --> 01:27:21.394 of chemotherapy free treatment for squamous cell of the esophagus,
NOTE Confidence: 0.860198533888889
01:27:21.394 --> 01:27:23.319 and for those that like the forest plots here we go.
NOTE Confidence: 0.860198533888889
01:27:23.320 --> 01:27:24.976 Most subsets benefited, but again in the TPS.
NOTE Confidence: 0.860198533888889
01:27:24.976 --> 01:27:26.310 Less than one, the hazard ratio was .96.
NOTE Confidence: 0.860198533888889
01:27:26.310 --> 01:27:30.966 Now in adenocarcinomas we have another study and this was did
NOTE Confidence: 0.860198533888889
01:27:30.970 --> 01:27:36.160 Not lead to FDA approval.
NOTE Confidence: 0.860198533888889
NOTE Confidence: 0.860198533888889
01:27:40.363 --> 01:27:41.978 Pembroke was non inferior to chemo but again you see those troubling survival curves crossing.
NOTE Confidence: 0.860198533888889
01:27:41.980 --> 01:27:50.547 So with the higher rate of death
NOTE Confidence: 0.860198533888889
01:27:50.547 --> 01:27:52.432 early on and so right now there’s no approval for immunotherapy
01:27:59.171 --> 01:28:01.160 alone and adenocarcinomas.

01:28:01.160 --> 01:28:03.968 We have to talk about the MSI high patients.

01:28:03.968 --> 01:28:06.287 though with adenocarcinomas and again.

01:28:06.290 --> 01:28:07.994 We have keynote 62 where they went back and looked at this and

01:28:07.994 --> 01:28:10.091 went back and looked at this and


01:28:17.670 --> 01:28:20.640 and very similar outcomes with really


01:28:22.620 --> 01:28:26.337 Again, I think this is a huge story,

01:28:26.340 --> 01:28:28.972 and so it it begs the question

01:28:28.972 --> 01:28:30.100 could could we?

01:28:30.100 --> 01:28:33.020 Should we consider immunotherapy loan

01:28:33.020 --> 01:28:35.211 as first line treatment in patients with

NOTE Confidence: 0.860198533888889
MSI high guest Raphael adenocarcinoma?

NOTE Confidence: 0.860198533888889

So a story to be continued.

NOTE Confidence: 0.860198533888889

And also I think of course

NOTE Confidence: 0.860198533888889

begs the question you know,

NOTE Confidence: 0.860198533888889

are we going to be curing these patients?

NOTE Confidence: 0.860198533888889

With MSI high guest reseal endocarp sinoma,

NOTE Confidence: 0.860198533888889

either with immunotherapy

NOTE Confidence: 0.860198533888889

alone or chemoimmunotherapy,

NOTE Confidence: 0.860198533888889

so to to conclude to the

NOTE Confidence: 0.860198533888889

base to the question.

NOTE Confidence: 0.860198533888889

Chemoimmunotherapy for all or not so fast.

NOTE Confidence: 0.860198533888889

So I think here are the considerations

NOTE Confidence: 0.860198533888889

squamous versus adeno it matters

NOTE Confidence: 0.860198533888889

PDL one matters I think,

NOTE Confidence: 0.860198533888889

especially in adenocarcinoma,

NOTE Confidence: 0.860198533888889

but as we heard so brilliantly from
Marie it is such an imperfect biomarker. Is it good enough to guide us to select patients in whom we will not give immunotherapy? This is a really troubling question for us as clinicians in terms of anatomic site for adenocarcinomas. I don’t think we have any data yet that esophagus versus GE junction versus Gastro is gastric is the issue. I think MSI mismatch repair deficiency Trump’s PDL one. All those patients should get chemoimmunotherapy and similarly for her too regardless of PD L1.
Those patients now inclusion of Pembroke I think is reasonable. We’re waiting for survival data. So here are my conclusions. So for a sophal squamous I am offering chemoimmunotherapy to most of my patients irrespective of PD L1 and for the adenocarcinomas I am taking a similar approach but I am very circumspect about what we may be helping patients. If the PDL 1 score is 0 or very low. If we do I think it has to be
01:30:25.622 --> 01:30:27.698 with circumspection and caution.

01:30:27.700 --> 01:30:30.955 I think particularly you know after the
information that we heard from Marie about
some of the challenges with this biomarker.

01:30:30.955 --> 01:30:34.161 Chemotherapy free immunotherapy, for whom?
And in what settings?

01:30:34.161 --> 01:30:37.630 So this is very exciting.

01:30:37.630 --> 01:30:40.190 It is approved it be neevo and squamous
and cell carcinoma irrespective of PD one.

01:30:40.190 --> 01:30:41.282 But again that cautionary note we
are seeing increased deaths compared
to chemo in the first six months.

01:30:41.282 --> 01:30:42.647 So that gives one pause.

01:30:42.650 --> 01:30:45.362 And I think careful patient
selection is the key.
But I don’t think we know yet how to select patients. Is it PD one or PDL? One score? Is it the tumor burden so you know again, I think. To be continued. This is an interesting story. And then for gastric adenocarcinomas, we’re not there yet for immunotherapy alone, as the initial treatment. I think even in MSI high patients, I think it’s still would be chemoimmunotherapy. So where we go from here? I think the questions are are obvious. I think adenocarcinoma we just do need more better data.
We have the keynote 859 and other large randomized phase three trial of chemo versus chemo, plus pember. We're going to learn a lot from that study. It's a huge study. Clearly, as Marie articulated we do need a better biomarker period. And now the next phase. This is a big advance. Forward for us. I mean really huge when you look at the history of the treatment of metastatic gastroesophageal cancers.
So now we need more effective immunotherapy agents or immunotherapy combinations. And now we're going to be moving into the realm of adding immunotherapy to other targeted therapies. Some studies that were planned or underway have now had to be redesigned. In light of this data. Adding immunotherapy to a targeted therapy and chemotherapy, and I've highlighted 2 studies such studies that will be open here at Smilow Cancer Center shortly. And of course, now the widespread use of PD1.
inhibitors in the first line setting really changes the landscape in the second line setting and beyond in terms of how we design those studies and how we’re going to be treating those patients so much work to be done. But this is an incredibly exciting era. For those of us. Who treat this these diseases and thank you for your attention, and I’m happy to take any questions in the chat box, but I know we are overtime so I’m happy to take questions by e-mail. I know Dan shared his mind as the
01:33:15.924 --> 01:33:17.640 typical Yale e-mail jill.lacey@yale.edu
NOTE Confidence: 0.6983145
01:33:22.030 --> 01:33:22.878 Still, I will ask
NOTE Confidence: 0.93279395
01:33:22.890 --> 01:33:26.120 a question to close. Thank
NOTE Confidence: 0.982170548
01:33:26.130 --> 01:33:27.390 you so much for that.
NOTE Confidence: 0.9483689
01:33:28.940 --> 01:33:32.630 Really. Sort of exhaustive and and
NOTE Confidence: 0.9483689
01:33:32.630 --> 01:33:34.240 deep dive into the differences
NOTE Confidence: 0.9483689
01:33:34.299 --> 01:33:36.389 between squamous and the salvageable.
NOTE Confidence: 0.9483689
01:33:36.390 --> 01:33:38.882 And it’s so interesting to see about
NOTE Confidence: 0.9483689
01:33:38.882 --> 01:33:41.968 the PDL 1 scores and where they are
NOTE Confidence: 0.9483689
01:33:41.970 --> 01:33:44.420 making sense and where they may not.
NOTE Confidence: 0.9483689
01:33:44.420 --> 01:33:45.520 Might not be making sense.
NOTE Confidence: 0.894460095
01:33:46.460 --> 01:33:48.110 Are you ever in a situation
NOTE Confidence: 0.928063653333333
01:33:48.120 --> 01:33:51.023 where, Despite that, it’s sort of the
NOTE Confidence: 0.928063653333333
01:33:51.023 --> 01:33:53.105 deregulated to order this the PDL?
NOTE Confidence: 0.928063653333333
01:33:53.105 --> 01:33:54.920 One stain that you might say you
NOTE Confidence: 0.928063653333333
01:33:54.920 --> 01:33:56.660 know I’m going to proceed without it?
01:33:56.660 --> 01:33:59.000 I’m going to do for XYZ.

01:33:59.000 --> 01:34:01.168 Reason is that is that ever a part of the conversation at this point.

01:34:01.170 --> 01:34:03.228 Yeah, so you’re getting at the heart of what we struggle with in the clinic. I.

01:34:14.200 --> 01:34:21.042 My bias is to include immunotherapy as I concluded in the slides for most patients with gastroesophageal cancers with metastatic disease.

01:34:21.042 --> 01:34:23.290 Not that I know that it’s benefiting everybody, because I certainly know that it’s absolutely not.

01:34:23.290 --> 01:34:25.538 Able to sort out those patients that are getting no benefit,
01:34:38.700 --> 01:34:41.598 so this is not like a K rest mutation
NOTE Confidence: 0.92267488
01:34:41.598 --> 01:34:44.124 in colorectal cancer that’s very
NOTE Confidence: 0.92267488
01:34:44.124 --> 01:34:46.356 black and white and very clear.
NOTE Confidence: 0.92267488
01:34:46.360 --> 01:34:49.035 There’s not benefit to adding
NOTE Confidence: 0.92267488
01:34:49.035 --> 01:34:50.640 cetuximab or panitumumab.
NOTE Confidence: 0.92267488
01:34:50.640 --> 01:34:53.538 This is much more ambiguous and nuanced,
NOTE Confidence: 0.92267488
01:34:53.540 --> 01:34:57.500 so I I think we’re just not there yet.
NOTE Confidence: 0.92267488
01:35:00.580 --> 01:35:03.202 Key opinion leaders you know will
NOTE Confidence: 0.92267488
01:35:03.202 --> 01:35:05.879 agree to disagree about this point,
NOTE Confidence: 0.92267488
01:35:05.880 --> 01:35:14.528 and I know that people have different
NOTE Confidence: 0.92267488
NOTE Confidence: 0.92267488
01:35:16.580 --> 01:35:19.051 We’re we’re all I would say we’re
NOTE Confidence: 0.92267488
01:35:19.051 --> 01:35:21.755 all struggling and so I think at
NOTE Confidence: 0.92267488
01:35:21.755 --> 01:35:24.399 this point it’s just keep at it.
More studies, more data.

Looking for better biomarkers? Useful for us to know.

This pathologist, because of our struggles with interpreting that stain. Eventually it’s not needed. That’ll be great.

I can’t speak for all oncologists. Obviously. I do know that some oncologists if the PDL ones, if there is no PDL one anywhere, it’s just flat out, it’s just flat out, no PDL one are not including immunotherapy because there’s
there are toxicities

the treatment discontinuation rate was higher in all these studies

in the immunotherapy arm and that makes sense because you’re adding in a whole another class of toxicities that may lead to treatment discontinuation and of course we start chemo immuno and have a treatment related immune adverse event and are are withdrawing the drug.

It’s also a cost issue but I think that’s a health economics issue for individual decision.

making for patients you know unless
it’s personal financial toxicity.

I think it’s a little hard for me to argue well, it’s costly to our healthcare system, so I’m going to withhold immunotherapy if it’s personal financial toxicity.

That’s of course a different story, so that’s kind of how I think about it. But everybody I think looks at this differently and right now I don’t think anyone has has the right right answer, or there’s a truly a wrong answer.

Well, you touched on something the completely negative stain.
We can agree on that and definitely I know they're oncologists and some of our key opinion leaders in the field who feel we should. That's a setting where very comfortable withholding anything you can rely on. Our result is what I meant that we can reliably. We can agree this is negative. Actually all right, we are beyond the hour. Thanks everyone who stayed to the end for your attention. And again, I think we're all happy to take questions by e-mail.
and have a good evening. Thank you very much everyone. Thank you Jill.