[MUSIC PLAYING]

**SPEAKER 1:** And our next speaker is Ursina Teitelbaum.

**URSINDA TEITELBAUM:** So I will break down the tracts as they do in ASCO with colorectal and non-colorectal focusing initially on the plenary session with the results of CALGB/SWOG 80405.

So this was the final design. And I say that because the original design actually included, in 2004, a third arm with chemo plus combination biologics cetuximab and bevacizumab. What's interesting about this study is when they first put it together we didn't know about KRAS wild type and its significance in prognosis of response to epidermal growth factor receptor inhibitors.

What's also notable here is that the chemotherapy backbone was dealer's choice. So you could choose-- the physician could choose which backbone they wanted. And then they would go on to be randomized between initially three and ultimately two arms.

The question in 2004 for colorectal cancer regarding the optimal first-line treatment is still somewhat relevant. At that time, as we know now, still FOLFIRI and FOLFOX are known to have similar efficacies, but different toxicities.

In 2004 bevacizumab was approved for first-line, cetuximab for second or third line, and bevacizumab and cetuximab thought to be an active combo. Median overall survival at that time was roughly 20 months.

A lot can happen in 10 years. In 2004 Barrack Obama was just leaving the Senate, Facebook was just leaving Harvard. And since then we have learned that KRAS mutation predicts resistance to epidermal growth factor receptor inhibitors, and in fact, may predict for poor prognosis.

We've learned that combination biologics, meaning bevacizumab and cetuximab or panitumamab are in fact harmful. And that we have new drugs in these intervening 10 years, new technologies, and new ways to use old drugs.

But we're still very much in the same position of not knowing the optimal front-line treatment definitively and in fact anyone that's followed the colon cancer literature knows that there's a wide array of studies with varying and conflicting outcomes.

So many people asked, why did it take 10 years? Again, the original design was part of the issue. And it had to be and closed in amended to reintegrate the KRAS wild type phenotype. And that was open then for another three years.

Roughly 300 patients were accrued prior to the amendment, and 800-plus after. The data was just released in January 2014. The criteria at that point were untreated patients, expanded to include wild types-- this is exon 2 wild types codon 12 and 13, and I'll get to that in a moment.

These patients had to have preserved organ function. Again, it was dealer's choice in the intent was palliative, but there was incorporated in there a strategy to resect all patients that were potentially resectable. And that may have impacted the ultimate survival data.

Again, primary endpoint was overall survival. And the assumption was that roughly overall survival would mirror the past with 22 to 27 a half months, accrual goal of 1,140 patients.

The patient characteristics for well matched. And the reason I actually put this slide up was to point out that, similar to North American treatment choices, 3/4 of the patients were selected for FOLFOX and 1/4 for FOLFIRI. So that's just across both arms was matched and matches our treatment patterns.

The progression-free survival was essentially superimposable between the two arms comparing bevacizumab or cetuximab. And the overall survival was similarly equivalent. And what I want to call your attention to here is the really high overall median survival of greater than 29 months, which was the highest documented value in any study to date.

The toxicities were what you would expect based on the profiles of the biologics. Patients think that the EGFR inhibitors had higher incidence of rash and diarrhea. And those that got the bevacizumab had a higher incidence of hypertension.

There was a very elegant quality of life study embedded in this with a hypothesis that patients on the cetuximab would be less satisfied with their appearance, with a lower overall quality of life. And what's interesting here is that while initially the skin satisfaction, as you would predict, was lower, it started to equalize out.

If you look at the timeline, months three to nine are when a lot of these symptoms abate, or patients become better at managing them. And the global quality of life numbers were fairly equivalent. Part of this attributed to the fact that patients that are on EGFR inhibitors know that rash may predict for better outcome. So they maybe reporting better satisfaction with their treatment.

So generally speaking, this is practice affirming. Survival on chemotherapy plus cetuximab was no different than chemo and bevacizumab in first line treatments. This was in patients with KRAS wild type, codons 12 and 13. And so either one can be considered options for front-line therapy.

It establishes a very high benchmark for survival in both arms. And some of this may be attributed to a really broad clinical trial of great centers. So it's hard to know. And we have a rich database to analyze selected subsets to get more information.

It still highlights the puzzle of front-line chemotherapy in colon cancer. We had to, actually-- data leading up to this study, the GERCOR data, the [INAUDIBLE] data that suggested FOLFOX and FOLFIRI were equivalent.

We've had subsequent studies that looked at OPUS and COIN. There's a whole slew of others that looked at FOLFOX, which is FOLFOX plus cetuximab. So we had some data in this setting including biologics [INAUDIBLE]. But truly, when you look at this study compared to the others, the numbers are far and ahead, exceeding all of the other studies.

So how do we compare them? Again, the survival is much [INAUDIBLE]. Perhaps these patients were better selected. Perhaps it was the academic setting. Perhaps it was because over 10% of them were-- excuse me-- resected for cure. And a very high number, 88%, went on to second-line therapy. So this may be the other piece that predicted for their survival.

Looking at the role of expanded RAS analysis is very interesting. I think the answer is yes. And these may very well change how we practice. It should actually change. Because the caveat of this study is that for KRAS exon 2, 12 and 13 mutations, this applies. But now we know that NRAS may also predict for resistance.

In fact, we have a colorectal cancer pie that we are just elucidating now and may actually help explain why some of our patients don't do as well as we anticipate. I would actually argue that we should to expanded RAS testing for all of our patients.

And in fact, there was some controversy with the presentation of this data ASCO because European package inserts require knowledge of NRAS before treating with an epidermal growth factor receptor inhibitor.

So this may underestimate the populations we should or shouldn't treat. And I say shouldn't treat because some of these mutated patients may have worse prognosis with these biologics. So again, I would say it's negative but informative.

It reaffirms our dealer's choice of backbone chemotherapy. It reaffirms it in terms of a study as we look at value added and cost considerations this may change. But at this point, we can choose.

We know that either biologic is equivalent in a wild type KRAS exon 2 patient. I do think expanded RAS analysis will change this. And again, the highest median survival thus far, 29-plus months really sets the benchmark.

Looking at the non-colorectal highlights, this one was a little harder and less obvious. I picked one pancreas cancer study because I think it points to another way to look at biomarkers or lack thereof to help guide the care of our patients.

And the last two actually I call the promise and perils of anti-angiogenesis in non-colorectal cancer. This was a really elegantly done randomized double-blind phase 2 study of ruxolitinib or placebo together with capecitabine in patients second-line that had failed [INAUDIBLE] with metastatic pancreas cancer.

I just want to state quickly about JAK-STAT signaling. It's a novel approach to cancer therapy. We've already shown benefit myelofibrosis. And the effect is mediated by reducing the levels of inflammatory cytokines and improving the symptom profile of patients. And ruxolitinib is an inhibitor of JAK1 and JAK2, and blocks the signaling mediation of these proinflammatory cytokines.

We know very well, those of us that treat pancreas cancer, that systemic inflammation is commonly observed. And we can say anecdotally and by trials that it's associated with poor survival.

We see these patients with weight loss, muscle wasting, quickly declining performance status. And these are the ones that generally have elevated CRP. And this has a known prognostic significance that is namely poor.

And again, this is just another table that shows that when inflammatory markers are higher than the median, the median survival is markedly lower, at times 1/2 of what you see with patients with inflammatory markers that are lower than the median.

JAK-STAT signaling inhibition showed some promise in combination with capecitabine in pre-clinical models. And it led to this study design out of Duke. Patients with pancreas cancer preserve performance status who had failed [INAUDIBLE] and randomized them to either capecitabine versus capecitabine with roxulitinib.

And overall survival difference at first glance wasn't really that impressive, to be truthful. But they planned this prospective analysis. They actually showed that patients that had elevated CRP and low albumin actually did much better when they were treated with this agent that mediated inflammatory cytokines. And in fact, this is where the survival benefit was shown, in those patients at specifically had high CRP defined as greater than 13 low albumin. And this was clinically significant.

This brings to bear this modified Glasgow Prognostic Score, which is actually a well characterized clinical measure of inflammation in cancer. The reason this is important is our pancreas cancer patients have no great biomarkers. They have no mutation analyses that are predictive or prognostic.

But a CRP and an albumin are easily drawn blood tests that are accessible to everyone and cheap to do, and in fact, combined show that there is a benefit in those patients with elevated CRP, both in survival and clinical benefit. Ruxolitinib in pancreas cancer showed combination activity with capesitobine.

There's some question marks about what the right backbone to pair it with is. It's tolerable. And in those patients that were the sickest, it actually performed the best. And again, it is tough to get tissue in pancreas cancer for molecular profiling, and these are readily accessible biomarkers. So I think this has a lot of promise.

And in fact, phase 3 programs are being extended. We actually have a study that we're participating at Penn right now that has [INAUDIBLE] as the backbone, and they're using it in other studies including modified Glasgow Performance Score-based patient selection.

Very briefly, to what some may say were disappointing aspects of ASCO or updates-- and again, this is what I call the perils and promise of anti-angiogenesis in specifically gastric cancer here and HCC.

Turning gears to gastric cancer, we know that bevacizumab works in colorectal cancer. And so the question was, how can we improve the outcomes for esophageal gastric patients? Bevacizumab turned out to be very disappointing in the AVAGAST study.

And then attention then turned to ramucirumab. And this is the AVAGAST design, just to set the stage, where they looked at front-line advanced patients and gave a front-line regiment versus bevacizumab, essentially no benefit.

You know that ASCO 2014 didn't have a lot of highlights when I'm pulling to GI ASCO, but this is where the rainbow study was presented that actually showed a benefit in second-line patients with gastric cancer or GE junction cancer patients that have progressed on front-line, platinum, or 5-FU therapy, and randomized them to paclitaxel or paclitaxel plus ramucirumab.

And this showed a benefit in terms of both overall survival and medium progression-free survival of about 2.3 months, which was clinically significant. The update at ASCO just helps enhanced understanding with a subset analysis that shows that actually the benefit, while seen both in Japanese and Western populations, significantly favors patients in the Japanese subgroup, though safety profiles were comparable.

And so the other ramucirumab study combined with FOLFOX was another front-line study. This was a negative study looking at patients front-line therapy with FOLFOX, which is an established regiment.

And again, bad disease, VEGFR2 is a critical receptor, the hope was that this, based on the efficacy and second-line studies, would apply to first-line. But it did not, and this was a negative study which was a disappointment.

So where are we with VEGF and gastric adenocarcinoma? So we know with the target VEGF ligand, bevacizumab, no difference in overall survival. Targeting the VEGFR 2, ramucirumab, positive in combination second-line with Paclitaxel. Front-line combination with FOLFOX was a disappointment.

And I don't know that ending with paracellular is ever a positive, but the STORM study was practice affirming. And very briefly, since I think I'm at the end of my time, this was a placebo-controlled trial of adjuvant sorafenib after resection or ablation.

And I think, sort of knowing what we know now about HCC and cytotoxic versus cytostatic therapies, this had patients that were completely resected or ablated. It did not include transplanted patients, although it may potentially be extrapolated to those patients in time. No residual HCC, and they were randomized to either Sorafenib twice daily or placebo. Overall survival thankfully for the patients, essentially superimposable.

And what I will say is they were smarter than we were. So I think the point here is patients did equally well with or without. There was absolutely no improvement in time to relapse or overall survival. And again, patients were smarter than we were. They self-discontinued Sorafenib at a very high rate to probably their benefit in terms of side effects.

And the truth is in these resected and ablated and transplanted patients, they're doing quite well with the therapies that are available to them. I get referred a lot of these patients, and I'm very happy to say now that I don't have to give you or Sorafenib, that won't help you.

And in fact, we don't know how it will effect-- there are in fact studies looking at Sorafenib portal hypertension and ascites and different things. It may harm you. So I can very happily tell patients, I will watch you along with your hepatologists. Thank you.