

Gastrointestinal cancers: new standards of care from landmark trials

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ASCO 2017 was very eventful with many groundbreaking studies reported across numerous tumor types and subspecialties. Gastrointestinal cancers were no exception. Dr Daniel Haller, former editor of the *Journal of Clinical Oncology*, discusses some of these breakthroughs in this interview. They include adjuvant therapy in colorectal cancer with the IDEA trial detailing 3 versus 6 months of adjuvant therapy and the subgroup in which 3 months of therapy might be adequate. The right and left colon primary location is becoming more important. Right colon cancers seem worse than left and there are mutations that might explain this. In gastroesophageal cancer, the FLOT trial looked quite promising for response and progression-free survival. Data that led to an FDA approval for checkpoint inhibitor therapy in MSI-high colon cancer was particularly interesting especially given that MSI-high tumors might enjoy a higher response rate. The BILCAP adjuvant trial for biliary cancer demonstrated surprisingly impressive results with capecitabine postoperatively in these difficult patients.

DR HENRY I am Dr David Henry, the Editor-in-Chief of *THE JOURNAL OF COMMUNITY AND SUPPORTIVE ONCOLOGY* (JCSO; JCSO-online.com). I'm with Dr Dan Haller, former Editor-in-Chief of the *Journal of Clinical Oncology* and currently the Editor-in-Chief of American Society of Clinical Oncology (ASCO) University. He is also my friend and former mentor at University of Pennsylvania Abramson Cancer Center, where he is Professor Emeritus.

We're going to talk about colorectal cancer and a lot of things that came out of the ASCO meeting this year that were practice changing, or certainly interesting and worth further discussion. I thought we'd start talking about the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration, in which for patients with colorectal cancer who were considering adjuvant postoperative therapy, there was a discussion of 3 cycles versus 6 cycles of FOLFOX (fluorouracil [5-FU] plus oxaliplatin) or XELOX (capecitabine plus oxaliplatin, also CAPOX) (Figure 1).¹ Could you comment on what they did, and how that study turned out?

DR HALLER The IDEA collaboration was the brainchild of the late Dan Sargent, a biostatistician

who was at the Mayo Clinic. It was his idea, since 6 international groups were all testing the same question of 3 months for oxaliplatin to 6 months of oxaliplatin, to combine the data in an individual patient database – which is the best way to do it – so there were these six trials that were all completed.



Dr. Haller

Three of them were individually reported at ASCO this year, and then the totality was presented at the plenary session – the first time in 12 years that a gastrointestinal (GI) cancer trial made the plenary session. The whole point, obviously, is neuropathy. With 6 months of FOLFOX or XELOX, about 13% or more patients will develop grade 3 neuropathy, even if people stop short of the full-cycle length, and that is a big deal for the 50,000 patients or so who get adjuvant therapy. At the plenary session, the data were presented and the next day three individual trials were presented and discussed by Jeff Meyerhardt (of Dana-Farber Cancer Institute, Boston).

There were 6 different trials: a few included rectum, some included stage II, some used CAPOX and FOLFOX-4 or 6. The only trial that used only FOLFOX was the Cancer and Leukemia Group B (CALGB) trial in the United States (US). There was a lot of heterogeneity, but when Dan was around, I asked him whether that was a problem, and he

presented and the next day three individual trials were presented and discussed by Jeff Meyerhardt (of Dana-Farber Cancer Institute, Boston).

Received for publication October 2, 2017. Correspondence: David H Henry, MD; David.Henry@uphs.upenn.edu. Daniel G Haller, MD, FACP, FRCP; Daniel.Haller@uphs.upenn.edu. Disclosures: The authors report no disclosures or conflicts of interest. Published online Month XX, 2017. ©2017 Frontline Medical Communications. doi: <https://doi.org/10.12788/jcs0.0377>

said on the contrary, was a better thing because it allowed for real-life practice.

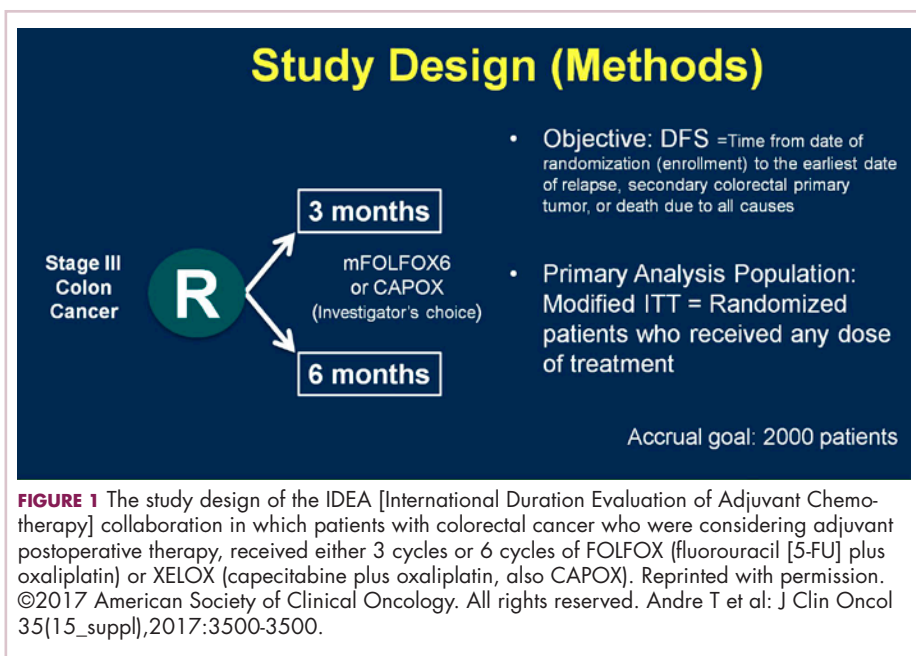
The primary endpoint of the study was to look for noninferiority of 3 months versus 6 months of treatment. The noninferiority margin was at a hazard ratio of 1.12, so they were willing to barter down a few percentage points from benefit. If you looked at the primary disease-free survival analysis, the hazard ratio was 1.07, which was an absolute difference of 0.9%, favoring 3 months of therapy. But because the hazard ratio crossed the 1.12 boundary, it was considered inconclusive and not proven.

If you looked at the regimens, CAPOX outperformed FOLFOX. That's a regimen we don't do much in the US. We tend to use more FOLFOX, but CAPOX looked better. What they then did was look at the different subsets of patients, and the subsets that it was obviously as good in was the group that had T1-3N1 disease, where 3 months of therapy was clearly just as good as 6 months of therapy, with only a 3% risk of grade 3 neuropathy.

DR HENRY That would be one to three nodes?

DR HALLER Exactly. That's about 50% of patients. In the T4N2 patients, neither regimen did very well and the 3-year disease-free survival was in the range of 50%, which is clearly unacceptable. Jeff discussed two things. Why could CAPOX be better? If you do the math, when you do CAPOX, you get more oxaliplatin during the first few months of therapy, because it's 130 mg every 3 weeks, rather than 85 mg every 2 weeks. His conclusion was, "for my next patient who has T4N2 disease, I'll offer 6 months of FOLFOX." The study that really needs to be done in these patients is FOLFOX versus FOLFIRINOX (folinic acid, 5-FU, irinotecan, oxaliplatin) or FOLFOXIRI (folinic acid, 5-FU, oxaliplatin, irinotecan), because we're clearly not doing well with this population of patients. But for the T1-3N1 disease, discuss the toxicities and logistics of CAPOX or FOLFOX with the patient. They'll probably offer 3 months of CAPOX.

He discussed the two new trials. One is a study called ARGO, which is being done by the National Surgical Adjuvant Breast and Bowel Project, where people get standard adjuvant chemotherapy, and they're then randomized to either 24 months of regorafenib 120 mg per day or a placebo. This is an attempt to recreate the transient benefit from bevacizumab in the NSABP C-08 trial. It's accruing slowly because regorafenib has some toxicity associated with it, but it probably will be completed. Will it continue the benefit as seen in the 12 months of bevacizumab and C-08? We'll see.



The other, more interesting study is being done in the cooperative groups looking at FOLFOX plus atezolizumab, one of the checkpoint inhibitors. The difficulty here is that only 15% of people with stage III disease have microsatellite instability (MSI)-high tumors, but it's certainly compelling. This is a straight up comparison. It's 6 months of FOLFOX in the control arm, or 6 months of FOLFOX plus atezolizumab concurrently for 6 months, and then an additional 6 months of atezolizumab. These are both very fascinating ideas.

DR HENRY To go back to one of your original points, this 3 versus 6 months: the neuropathy is significantly less in those getting the 3 months?

DR HALLER It went to 3%.

DR HENRY We all see that is very bothersome to patients. Before we leave colorectal, I must ask about the right-sided versus left-sided colorectal cancer that we hear a lot about now. Could you comment on how right-sided is worse than left-sided, and do we understand why?

DR HALLER There are two things to consider. If you look back even to simple trials of 5-FU or biochemical modulated 5-FU from 20 years ago, there were clear differences showing worse prognosis in patients with right-sided tumors, so that's one point to be made. It's been consistently seen but never acted upon. Then, the explanation for it, possibly, is that the right colon and left colon are two biologically different organs – and they are. Embryologically, the right colon comes from the midgut and the left colon comes

from the hindgut, and there were several presentations at ASCO and at prior meetings showing that when you look at different mutations, they differ between the right and left colons. The right-sided tumors are more MSI-high and more *BRAF*-mutated, left-sided mutations less so.

Then, people started analyzing many of the very large colon cancer trials, including the US trial CALB/SWOG C80405 and the FIRE-3 trials in Europe, where backbone chemotherapy of FOLFIRI or FOLFOX was given with either cetuximab or bevacizumab in RAS wild-type patients. For one study, C80405, they saw that for cetuximab, on the right side, the median survival was 16.7 months and on the left side, it's 36 months – a 20-month difference. In fact, if you look at the totality of the data, 16.7 almost looks like cetuximab is harming them, as if you were giving it to a RAS-mutated patient, but they were not. They were all RAS wild-type.

For bevacizumab, the right side was 24 months; the left side was 31.4 months. If you look at the left, cetuximab was 36 months and bevacizumab was 31.4 months, so it appears left-sided tumors should get more cetuximab than they are now getting in the US with a 5-month difference, but that decrement is much different on the right, where there's an 8-month benefit for bevacizumab compared with cetuximab. There is a very good review by Dirk Arnold, who looked at a totality of 6 studies to really examine this more carefully.²

The National Comprehensive Cancer Network has chimed in on this, and is suggesting that for the 25% of people who have right-sided tumors, epidermal growth factor receptor (EGFR) agents not be considered in first-line therapy. NCCN did not go as far to say that EGFR agents should be given on the left side. As I said, the differences are much more impressive in the right, so this is a real sea change for people to consider which side of the tumor affects outcome.

Deb Schrag (Dana-Farber Cancer Institute) presented data at last year's ASCO not only for stage IV disease showing the same thing, but also stage III disease where there are also right-versus-left differences in terms of recurrence, with a hazard ratio on the right side of about 1.4 compared with the left-sided tumors. Maybe it should be true that 3 months is especially good if you're treating left-sided tumors, and maybe the right-sided tumor needs to be also calculated with the factors we just talked about. These are two big changes in an area in which we literally haven't made any change since FOLFOX was introduced a decade ago.

DR HENRY That's really fascinating, and if not practice changing, then practice challenging. Staying with the mutations idea, in my patients, I'm checking the RAS family and the *BRAF* mutation, where I've learned that's a particularly bad mutation. I wonder if you might comment on the Kopetz trial, which took a cohort of *BRAF* mutants and treated them (Figure 2).³ How did that turn out?

DR HALLER It turned out well. We're turning colon cancer into non-small cell lung cancer in that we're getting small groups of patients who now have very dedicated care. The backstory here is that there was some thought that you should be treating mutations, not tumor sites. Drugs such as vemurafenib, for example, which is a *BRAF* inhibitor, worked well in melanoma for the same mutation that's in colon cancer, *V600E*. But when vemurafenib was used in the *BRAF*-mutant patients – these are 10% of the population – median survivorship was one-third that of the rest of the patients, so roughly 12 months. People looked like they were doing worse when vemurafenib was used. They had no benefit.

Scott Kopetz at MD Anderson (Houston, Texas) is a very good bench-to-bed-and-back sort of doc. He looked at this in cell lines and found that when you give a *BRAF* inhibitor, you upregulate EGFR so you add an EGFR^T inhibitor. He did a phase 1 and 1B study, and then in the co-operative groups, a study was done – a randomized phase 2 trial for people who had the *BRAF-V600E* mutation failing first-line therapy, and then went on to receive either irinotecan single agent or irinotecan plus cetuximab or a triple arm of irinotecan, cetuximab, and vemurafenib. There was a crossover, and so the primary endpoint was progression-free survival. It accrued rapidly.

Again, small study, about 100 patients, but for the double-agent arm, or cetuximab–irinotecan, the median survivor-

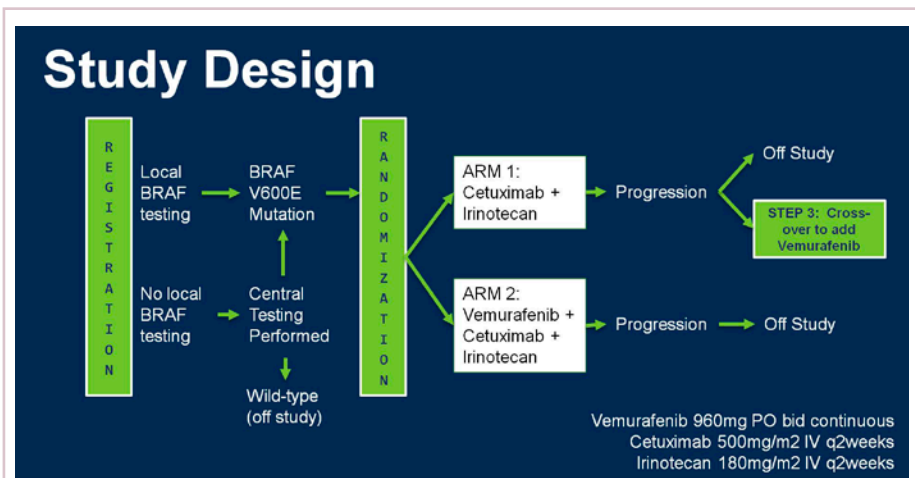


FIGURE 2 The design of the SWOG S1406 study in which patients with *BRAF*-mutant metastatic colorectal cancer were randomized to receive irinotecan and cetuximab with or without vemurafenib. Reprinted with permission. ©2017 American Society of Clinical Oncology. All rights reserved. Kopetz S et al. *J Clin Oncol* 35(4_suppl),2017:520-520.

ship was 2 months. It was 4.4 months for the combination, so more than double. The response rate quadrupled from 4% to 16%, and the people who had disease control tripled, from 22% to 67%. Many of these patients had bulky disease, *BRAF* mutations. They need response, so this is a very important endpoint.

Overall survival was not different, in part because it was a crossover, and the crossover patients did pretty well. This is going to move more toward first-line therapy, because we don't talk about fourth- and fifth-line therapies, TAS-102 or regorafenib. These patients don't make it to even third line. We're chipping away at what we think is a very homogeneous group of peoples' metastatic disease. They're obviously not.

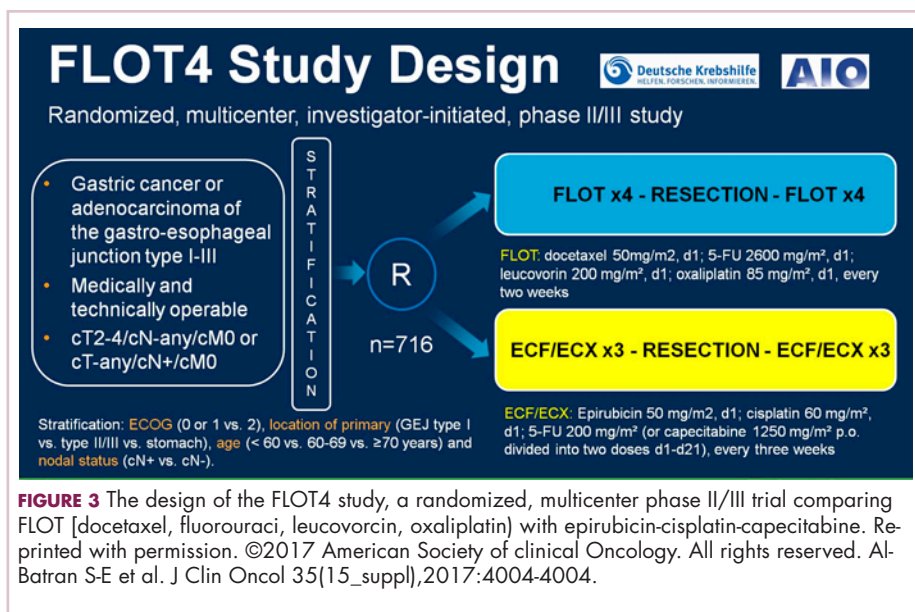
DR HENRY In the *BRAF*-mutant patient, the vemurafenib might drive them toward EGFR, and then the cetuximab could come in and handle that diversion of the pathway. Fascinating.

DR HALLER The preferred regimen in first-line therapy for a *BRAF* mutant might be FOLFIRI, cetuximab, and vemurafenib, especially on the left side.

DR HENRY Certainly makes sense. We'll continue the theme at ASCO of "new standard of care." Let's move to gastroesophageal junction. There was a so-called FLOT (5-FU, leucovorin, oxaliplatin, Taxotere) presentation in the neoadjuvant/adjuvant setting, 4 cycles preoperatively and 4 cycles postoperatively. Could you comment on that study?

DR HALLER Gastric cancer for metastatic disease has a very large buffet of treatment regimens, and some just become entrenched, like the ECF regimen with epirubicin (epirubicin, cisplatin, 5-FU), where most people don't exactly know what the contribution of that drug is, and so some people use EOX (epirubicin, oxaliplatin, capecitabine), some people use FOLFOX, some people use FOLFIRI. It gets a little bit confusing as to whether you use taxanes, platinum, or 5-FU or capecitabine.

The Germans came up with a regimen called FLOT – it's sort of like FOLFOX with Taxotere attached. They did a very large study comparing it with ECF or ECX (epirubicin, cisplatin, capecitabine; Figure 3).⁴ The overall endpoint with over 700 patients was survival. This is an adjuvant regimen. Only 37% of people got ECF or ECX postoperatively, and 50% of the FLOT patients got the regimens postoperatively. One of the reasons FLOT



might be more beneficial is that more people were given postoperative treatment, and it's one reason why many adjuvant regimens are being moved completely preoperatively, because so few people get the planned treatment. The FLOT regimen improved overall survival with a *P* value of .0112 and a hazard ratio of 0.77. The difference was 35 months versus 50 months. With the uncertainty as to what epirubicin actually does and the fact that it's been around for a while and that fewer people receive postoperative treatment, with that 15-month benefit, if you're using chemotherapy alone, and there's no radiotherapy component for true gastric cancer, this is a new standard of care.

DR HENRY I struggle with this in my patients as well. This concept of getting more therapy preoperatively to those who can't get it postoperatively certainly resonates with most of us in practice.

DR HALLER If I were redesigning the trial, I would probably say just give 4-6 cycles of treatment, and give it all preoperatively. In rectal cancer, there's the total neoadjuvant approach, where it's being tested in people who get all their chemotherapy first, then chemoradiotherapy, then surgery, and you're done.

DR HENRY Yes, right. Thank you for mentioning that. Staying with the gastric GE junction, you couldn't get away from ASCO this year without hearing about the checkpoint inhibitor immunotherapies in this population. In the CHECKMATE-142 trial with nivolumab versus placebo, response rates were good, especially in the MSI-high (microsatellite instability). Could you comment on that study?

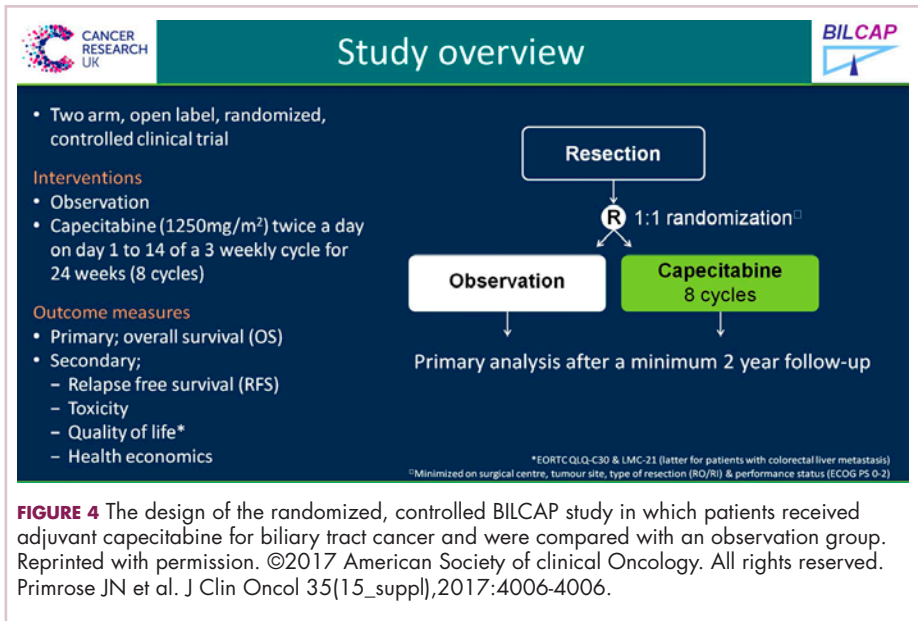


FIGURE 4 The design of the randomized, controlled BILCAP study in which patients received adjuvant capecitabine for biliary tract cancer and were compared with an observation group. Reprinted with permission. ©2017 American Society of clinical Oncology. All rights reserved. Primrose JN et al. J Clin Oncol 35(15_suppl),2017:4006-4006.

DR HALLER We already know that in May and July 2017, pembrolizumab and nivolumab were both approved for any MSI-high solid tumor based on phase 2 data only, and based on response. That’s the first time we’ve seen that happen. It’s remarkable. For nivolumab, the approval was based on 53 patients with MSI-high metastatic colon cancer. So these were people who failed standard therapy and got nivolumab by standard infusion every 2 weeks. The overall response rate was almost 30% in this population, which is typically quite resistant to any treatment, so one expects much lower response rates with anything in that setting – chemotherapy, TAS-102, regorafenib, et cetera (Table).⁵ More importantly, as we’re seeing with Jimmy Carter with checkpoint treatment (for melanoma that had metastasized to the brain), responses lasted for more than 6 months in about two-thirds of patients, even a complete response, so this is just off the wall. I mean, this is not what you would expect with almost any other treatment. The data are the same for atezolizumab and for pembrolizumab. What seems to be true is that in the GI tumors and colon cancer, MSI-high seems more important than expression of PD-1 or PD-L1 (programmed cell death protein-1 or programmed cell death protein-ligand 1).

In different tumor sites, PD-1 or PD-L1 measurement may be important, but in these tumors, and in colorectal cancer, it looks as if MSI-high is the preferred measurement. Recently ASCO, together with the American Society for Clinical Pathology, College of American Pathologists, and Association for Molecular Pathology, came out with guidelines on what you should measure in colorectal cancer specimens. Obviously, one is extended RAS. They say you should get *BRAF* for prognosis, but it may also be a prognostic factor that leads you to treat, which ultimately makes it a predic-

tive factor, so the data from Kopetz might suggest that will move up to something you also must measure. If patients have the *BRAF* mutation, it’s important they know that it’s a poor prognostic sign. But if they come in with literature saying they might live 36 months when their actual outcome is about a third of that, you need to frame your discussion in that regard and make sure they understand it.

The guidelines also suggested getting MSI-high, and certainly prognostically in early-stage disease, but now it’s going to be a predictive factor, so in the month in which these recommendations are made, two of them are already out of date. They also didn’t include human epidermal growth factor receptor 2 (HER2), and what we’ve heard from the HERACLES (HER2 Amplification for Colorectal Cancer Enhanced Stratification) trial is that for

those patients who got the trastuzumab and pertuzumab combination – and this is another 5% of patients – almost the same data was seen as in the MSI-high patients with checkpoint inhibitors. That is double-digit response rates and durable responses. As I said, we’re very much nearing in colorectal cancer what’s now being done in non-small cell lung cancer.

DR HENRY Indeed. Could you comment on the BILCAP study and adjuvant capecitabine for biliary tract cancer?

DR HALLER There are large meta-analyses looking at adjuvant therapy for biliary tract cancers typically from fairly small, fairly old studies that all suggest that in certain stages of resected biliary tumors, either bile duct or gall bladder, adjuvant treatment works, and typically either chemotherapy and radiotherapy, or chemotherapy alone, but not radiotherapy alone.

Capecitabine has been used for metastatic disease for years, mostly by default, and because most GI tumors have some response to fluoropyridines. But we’re finally able now to do large trials in biliary tumors, so this trial was a very large study with almost 450 patients from the United Kingdom over an 8-year period. About 20% were gallbladder, so the R0 surgery was about 60%, R1 at about 40% (Figure 4).⁶

The endpoint of the study was survival advantage, and when they did the protocol analysis, the survival for the treated population was 53 months and for the observation arm, 36 months, so that was a hazard ratio of 0.75, which is acceptable in an adjuvant study. It’s simple drug to give, and usually tolerable, so this will represent a new standard of care. Of course, in the advanced disease setting, the gemcitabine–cisplatin combination is the standard of care for

metastatic disease. It's a little more toxic combination, but we know that's standard. There's an ongoing study in Europe called the ACTICCA-1 trial, and this is gemcitabine–cisplatin for 6 months versus not capecitabine, but a control arm. My guess is if the capecitabine study was positive, that this also will be a positive trial, because gemcitabine–cisplatin is probably more active. Then, we'll have 2 standards, and I don't think anyone is going to compare capecitabine with gemcitabine–cisplatin.

What you'll have are two regimens for two different populations of patients. Perhaps for the elderly and people who have renal problems, capecitabine alone will give them benefit, and then you'll have gemcitabine–cisplatin, which may be just a more toxic regimen, but also more effective for the younger, healthier people with fewer comorbidities.

DR HENRY Great data and a small population, but a population in need. That moves us on to pancreatic cancer, and I don't know if this is happening nationwide, but in my practice, I'm seeing more. These patients tend to present beyond surgery, so they have metastatic or advanced pancreatic cancer. Any comment on where you think this field is going?

DR HALLER We were a bit bereft of new pancreatic cancer studies at ASCO this year. We're certainly looking more at neoadjuvant therapy for pancreatic cancer, primarily because of ease of administration and the increased ability to tolerate treatments in the preoperative setting. There aren't many people that get downstaged, but some are. Unfortunately, even in the MSI-high pancreas, which is a small subset, they

Pt	Local Testing		Central Testing	Clinical History of LS
	Method	Result		
1	IHC	dMMR	MSS	NA
2	IHC	dMMR	MSS	No
3	IHC	dMMR	MSS	Yes
4	IHC	dMMR	MSS	Yes
5	IHC/PCR	dMMR (IHC)/MSI-H (PCR)	MSS	NA
6	IHC	dMMR	MSS	Yes
7	IHC	dMMR	MSS	No
8	PCR	MSI-H	MSS	NA
9	IHC/PCR	dMMR (IHC)/MSI-H (PCR)	MSS	NA
10	IHC	dMMR	MSS	No
11	IHC	dMMR	MSS	NA
12	PCR	MSI-H	MSS	NA
13	IHC	dMMR	MSI-L	NA
14	IHC	dMMR	MSS	NA

TABLE In the CHECKMATE-142 trial with nivolumab versus placebo (n = 74), 14 patients had a central test that did not match local test results of whom 3 with a clinical history of LS were identified locally as dMMR but centrally as MSS. Reprinted with permission. ©2017 American Society of Clinical Oncology. All rights reserved. Kopetz S et al. J Clin Oncol 35(15_ suppl),2017:3548-3548.

don't seem to get as big a bang out of the checkpoint inhibitors as in other tumor sites, so I'm afraid I didn't come home with much new about this subset of patients.

DR HENRY We've covered a nice group of studies and practice-changing new standard-of-care comments from ASCO and other studies. Thank Dr Dan Haller for being with us and commenting. This podcast and discussion are brought to you from THE JOURNAL OF COMMUNITY AND SUPPORTIVE ONCOLOGY, the JCSO. I'm Dr David Henry, and you can listen to this and other archived articles or podcasts at JCSO-online.com. Thanks for listening.

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