



## INTERNATIONAL SOCIETY OF GASTROINTESTINAL ONCOLOGY (ISGIO)

**THE 17TH ANNUAL MEETING** of the International Society of Gastrointestinal Oncology (ISGIO) was held as a 2-day virtual event on October 2-3, 2020. This multidisciplinary educational conference is dedicated to presenting and discussing some of the latest advances in the field of gastrointestinal cancer research.

*ONCOLOGY*<sup>®</sup> sat down with the co-chairs of the conference, Tanios S. Bekaii-Saab, MD, section chief for Medical Oncology in the Department of Internal Medicine at Mayo Clinic in Phoenix, Arizona, and Daniel G. Haller, MD, professor of medicine emer-

itus, Abramson Cancer Center at the Perelman School of Medicine at the University of Pennsylvania, in Philadelphia, to discuss the abstracts that were presented, and the role of the conference itself.

Bekaii-Saab noted that the conference has taken on a “GI year in review” role and has become one of the premier GI cancer meetings.

“I think another thing is that ‘bigness’ is not always great,” said Haller. “I think people can get tired of ASCO and ESMO, with them being so large. I think one of the nice things here is that

[when we’re in person] the fact that the audience can mingle with the experts and not necessarily have to see them from far away. So, the intimacy and the ability to have those one on ones, that’s always been one of the selling points.”

“Exactly,” added Bekaii-Saab. “And, to that point, I’d say that the focus of ISGIO, essentially what it was built for, is to continue growing the next generation of GI oncologists. This is the one GI meeting in the world where junior colleagues take center stage. So, it’s a great place to mentor.”

➤ **TURN TO PAGE 469** for the ISGIO Abstracts presented at the 2020 conference

# National Clinical Trial Network Gastrointestinal Cancer Trial Mentions in Electronic Physician Resources

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**BACKGROUND.** Physicians look to various electronic resources to aid in management of patient treatment. Although national guidelines encourage clinical trial participation for patients with cancer, it is unclear if physician-facing resources help guide physicians to appropriate trials in which to enroll their patients. If resources do not mention appropriate open clinical trials, physicians miss a major management strategy.

**METHODS.** A list of open gastrointestinal cancer trials as of July 15, 2020, was obtained from the National Clinical Trial Network (NCTN). Physician facing electronic resources including UpToDate, DynaMed, WebMD, Medscape, theMedNet, WebMD, and ClinicalKey, were queried for each trial. The long name of the trial, trial name, any abbreviation associated with the trial, and definitive type of gastrointestinal cancer characteristics qualifying for the trial were searched for

in the database. Relevant management topics within each resource were also reviewed for mention of any open trial. A spreadsheet was constructed and trial mentions were tabulated.

**RESULTS.** The 23 trials were found mentioned 12 times across all 6 resources. This resulted in clinical trials being mentioned an average of 9% in each resource, with a range of 0% to 30%. A total of 30% of open NCTN gastrointestinal trials were

TABLE. Mentions of Trials Within Physician Facing Electronics Resources

Trial	Up to date	DynaMed	WebMD	MedScape	MedNet	ClinicalKey
EA2174	No	No	No	No	No	No
NRG-GI007	No	No	No	No	No	No
EA2183	No	No	No	No	Yes	No
NRG-GI006	No	No	No	Yes	No	No
S1922	No	No	No	No	No	No
A021502 (ATOMIC)	No	No	No	No	Yes	No
NRG-GI004 (COMMIT)	Yes	No	No	No	Yes	No
A021703 (SOLARIS)	No	No	No	No	No	Yes
NRG0GI002 (TNT)	No	No	No	No	Yes	No
EA2182 (DECREASE)	No	No	No	No	No	No
EA2165	No	No	No	No	Yes	No
EA2186 (GIANT)	No	No	No	No	No	No
A021806	No	No	No	No	No	No
S1815	No	No	No	No	No	No
EA2187	No	No	No	No	No	No
NRG-GI003	No	No	No	No	Yes	No
RTOG-1112	No	No	No	No	Yes	Yes
EA2142	Yes	No	No	No	No	No
A02162 (CABINET)	No	No	No	No	No	No
EAY131 (MATCH)	No	No	No	No	No	No
S1609 (DART)	No	No	No	No	No	No
Percent mentioned	9%	0%	0%	4%	30%	9%

mentioned on the MedNet, the highest of any platform. No trials were mentioned on DynaMed and WebMD. Clinical trial mentions did not always correlate with recommendation of enrollment or promotion of participation in the trial. The majority of mentions were found by searching the specific trial name.

**CONCLUSION.** Participation in clinical trials is almost always advised for patients

with cancer. However, access to open trial information is minimal within physician-facing electronic resources. Information on open or appropriate clinical trials rarely accompanies the recommendation for research participation. With extensive probing of physician-facing databases, open clinical trials were mentioned only 9% of the time (range of 0%-30%). The lack of exposure of open clinical trials in physician facing electronic databases

increases the difficulty of adherence to the recommendation of clinical trial enrollment as a management strategy. In addition to missing a major management strategy, the lack of representation of the trials may be a barrier to appropriate referrals. ■

**DISCLOSURES:** The authors report no relevant disclosures.

#### COMMENTARY

**Daniel G. Haller, MD** The table the authors created shows us that access to information on open clinical trials within physician sourcing resources is minimal at best, with clinical trials mentioned less than 10% of the time. I think 1 of the things that we as clinicians all need to do if we have involvement with these resources is to push for greater representation of the open clinical trials, which might be a barrier to appropriate referrals.

## Patterns of Use and Clinical Outcomes With Long-Acting Somatostatin Analogs for Neuroendocrine Tumors (NETs): A Nationwide French Retrospective Study in the Real-Life Setting

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**BACKGROUND.** Lanreotide autogel/depot (LAN) and octreotide long-acting release (OCT) are long-acting somatostatin analogs (LA SSAs) used to treat neuroendocrine tumors (NETs). Previous studies have shown differences in dose and persistence between these LA SSAs.<sup>1,2</sup> A recent analysis of the National System of Health Data (SNDS), a national French claims database, suggested that higher LA SSA doses and more syringes were used with OCT than LAN, translating into higher overall treatment costs for patients receiving OCT.<sup>3</sup> Here, we report further analysis aiming to explore patterns of use (dispensing and administration), as well as clinical outcomes, of first-line LAN compared with OCT in the French real-life setting.

**METHODS.** This was a retrospective analysis of LA SSA use in patients with NETs conducted in 2020 using claims data from the SNDS Database, which covers ~99% of French residents.<sup>4</sup> Patients were classified as having NETs if they had full insurance coverage for a long-term disease or a hospitalization linked to a NETs ICD-10 code. Included patients were aged 18 years or greater, initiated LAN or OCT treatment between 2009 and 2016 (indicated by no LA SSA treatment in the previous 12 months) and received at least 6 subsequent dispensing of first-line LAN or OCT during the first year of treatment. Patterns of use and clinical outcomes were compared between patients receiving LAN and OCT, including average monthly dose,

use of rescue medication (short-acting SSA), treatment persistence (proportion of patients remaining on treatment), and treatment duration (in months).

**RESULTS.** The final study population comprised 4417 patients with NETs, including 2,090 who initiated treatment with OCT and 2327 who initiated treatment with LAN. Patient characteristics were broadly similar between both treatment groups. Significantly fewer patients in the LAN group had an average monthly dose above the recommended dose compared with patients in the OCT group (3.0% vs 7.3%;  $P < .0001$ ; Chi-squared test). In the first year of treatment, patients in the LAN group had significantly lower use of rescue medication (short-acting SSA)

compared with patients in the OCT group (73/2327 [3.1%] vs 208/2090 [10.0%];  $P < .0001$ ; Chi-squared test). Patients in the LAN group showed significantly higher treatment persistence in the first year (74.5% [95% CI, 72.7%-76.2%] vs 65.6% [95% CI, 63.5%-67.6%]) through the fifth year (32.1% [95% CI, 29.6%-34.5%] vs 23.9% [95% CI, 21.8%-26.1%]), compared with patients in the OCT group. Median treatment duration was significantly longer for patients in the LAN group compared with patients in the OCT group (21 [interquartile range, 12-39] vs 19 [interquartile range, 9-40] months;  $P < .0001$ ; Mann-Whitney test).

**CONCLUSION.** LAN was associated with lower rescue medication use, greater treatment persistence and longer treatment duration than OCT. It should be

noted that this was an observational study that did not control for potential confounding factors, and results should be interpreted in light of limitations inherent to a database analysis. These results suggest potential economic and clinical advantages of LAN over OCT in the management of NETs, which should be further explored in specific studies. ■

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**DISCLOSURES:** BH, XMTT, FM: employee of Ipsen; MZ, CN, MZ, FF: employee of CEMKA, which received a grant from Ipsen to analyze the SNDA database; LM: Ipsen (consulting), Novartis (consulting, research funding), Pfizer (consulting).

#### COMMENTARY

**Daniel G. Haller, MD** One of the interesting aspects of this is the real-life setting in the French system, in which 99% of the French population is covered, so they know exactly how many doses are given and there's no barrier to obtain data. What this study suggested is that the long-acting agents were more efficacious, with lower use of rescue medication needed than octreotide, which suggests potential economic benefits to this treatment pattern as well.

## Concurrent Everolimus With Hepatic Transarterial Bland Embolotherapy (Evero-Embo) in Patients With Metastatic Well-Differentiated Neuroendocrine Tumors

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**BACKGROUND.** Intraarterial therapies in patients with well-differentiated neuroendocrine tumors (NETs) show improved treatment responses and disease control with predictable and manageable toxicities. Systemic targeted therapies, such as everolimus (Afinitor) and sunitinib (Sutent), are commonly held 2 to 4 weeks prior to and after

procedures. Embolotherapy induces anoxic injury whereas everolimus effects cell growth, proliferation, and survival. Combining these modalities may result in effective debulking of significant hepatic disease and/or delaying progression. Safety and response rates of concurrent use of everolimus with bland hepatic transarterial

embolization (TAE) have been previously reported (ASCO 2019). Historically, bland TAE and chemoembolization have median hepatic progression-free survivals (mPFS) of about 9 and 18 months, respectively. We hypothesize that by continuing everolimus during and after bland TAE, hepatic mPFS will exceed 18 months.

**METHODS.** A review of clinical and radiographic data was conducted for all sequential patients who underwent evero-embo between September 2016 and April 2018 at the University of Kentucky Markey Cancer Center. An independent radiologist performed response evaluation criteria in solid tumors (RECIST) measurements. To be included in this study, patients were required to have had systemic everolimus for 1 month or longer prior to embolization and to be on everolimus immediately post procedure.

Patients with at least 20 months post procedure follow-up were included for mPFS analysis.

**RESULTS.** A total of 51 TAEs with concurrent systemic everolimus were performed in 34 patients with NETS. Mean objective radiographic response was  $58.0 \pm 16.5\%$  (SD). Hepatic progression, per RECIST, has not been observed. Of the 34 patients, 23 had 24 or more months of follow-up post procedure; 2 patients were censored when peptide receptor ra-

diotherapy began. A mPFS of 27 months was observed.

**CONCLUSION.** Evero-embo results in a hepatic mPFS exceeding that of bland TAE or chemoembolization. With a median follow-up of 27 months, hepatic progression has not been observed. Additional follow-up is necessary to determine the actual mPFS and median overall survival. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

#### COMMENTARY

**Daniel G. Haller, MD** I think the takeaway here is that certainly embolization has a role in hepatic metastases, especially in neuroendocrine tumors. This study looked at not only the toxicity patterns for the combination, but also the response rates of evero-embo, and I think the results were very encouraging. The objective response rate was about 58%, in a single institution study in 51 patients with no progression in any of the patients. The median progression-free survival is over 2 years, which is really quite long. So, the combination is not only safe, but it seems to be effective as well.

## Analysis of DNA Damage Response Gene Alterations and Its Association With Tumor Mutational Burden in Asian Colorectal Cancer

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**BACKGROUND.** Colorectal carcinoma (CRC) is 1 of the most commonly diagnosed cancers in the world. Carcinomas with DNA damage response and repair (DDR) gene alterations are always observed with higher genomic instability and further lead to higher tumor mutational burden (TMB). In addition to improving sensitivity of tumor cells to poly (ADP-ribose) polymerase inhibition, somatic DDR alterations have also been demonstrated to predict response to immune checkpoint inhibitors in patients with different cancers. However, DDR defects are not well characterized in Asian patients with colorectal cancer.

**METHODS.** We systematically analyzed

somatic alterations from 242 Asian patients with colorectal cancer to provide a comprehensive view of DDR mutations with next-generation sequencing (NGS) using a 539-gene panel, including 66 DDR genes. In addition, the correlation between DDR and TMB was assessed by the Chi-square test with significance level of  $P < 0.01$ .

**RESULTS.** In total, DDR alterations were found in 35.1% (85/242) of cases. *PRKDC* (9.1%), *ATM* (8.7%), and *BRCA2* (7.0%) were the most commonly altered DDR genes in this series, followed by *ATR* (5.4%), *MSH3* (5.4%), *MSH6* (5.0%), *POLE* (5.0%), and *RAD50* (5.0%). More than 1 DDR gene alteration was found

in 36 (14.9%) of cases. Tumor mutation burden in this cohort ranged from 0 to 344.12 muts/Mb with a median value of 4.41 muts/Mb, and the population was divided into 2 groups: high TMB (TMB-H,  $\geq 6.62$  muts/Mb) and low TMB (TMB-L,  $< 6.62$  muts/Mb) using the top quartile threshold. It was demonstrated that those tumors with DDR gene mutations showed significantly higher rates of TMB-H than the wild cases (50.6% vs 16.6%;  $P < .001$ ). Overall, 29 genes involved in the DDR pathway were confirmed to be significantly associated with TMB-H in colorectal cancer ( $P < .01$ ). In addition, high microsatellite instability (MSI-H) was observed in 4.5% (11/242) of DDR-altered CRC cases, whereas

MSI-H was not detected in DDR-wild-type (WT) cases.

**CONCLUSION.** These study results confirm that DDR defects are relatively common and occurred more frequently in TMB-H

patients than in TMB-L group, which suggests that the subgroup of CRCs with DDR mutations may have a higher likelihood of response to immunotherapy. The clinical benefit from immunotherapy of CRC patient population with the DDR

gene mutations can be validated in further clinical trials. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

#### COMMENTARY

**Tanios S. Bekaii-Saab, MD** This study does confirm that, overall, DNA damage repair alterations are common in colorectal cancer, and are targets worth investigating. It is interesting because there is quite a discussion around the role of DDR [DNA damage response]-targeting agents alongside immune therapy. It was also interesting to see that the DDR effects seem to occur more frequently with TMB-H [[tumor mutational burden-high] than in TMB-L [low], which opens the way for examining the role, perhaps, of PARP inhibitors or other DDR-targeting agents plus immune therapies.

**Daniel G. Haller, MD** I think 1 thing you may be able to take away from this is that DDR measurements could be an additional part of an algorithm to choose patients for immunotherapy, apart from MSI [microsatellite instability]-high, TMB, or PDL-1 positivity.

## Treatment Patterns and Outcomes of Systemic Therapy for Microsatellite-Stable Metastatic Colorectal Cancer in the United States

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**BACKGROUND.** Colorectal cancer (CRC) is the third most common cancer worldwide and second most common reason for cancer-related deaths. About 50% to 60% of patients diagnosed with CRC develop metastases. Of the patients with metastatic CRC (mCRC), roughly 90% to 95% have microsatellite stability (MSS) and 5% to 10% have a high degree of microsatellite instability (MSI-H). Even though the genetic drivers of MSS mCRC are well documented, most of these alterations do not currently have effective targeted therapies. The treatment patterns of patients diagnosed with MSS mCRC have not been assessed using US real-world data and there is a need to understand the most common treatment patterns—as well as duration of treatment

(DOT)—to support the pioneering of novel treatment combinations.

**OBJECTIVES.** This study was designed to evaluate treatment patterns and DOT for patients with MSS mCRC in the US. Treatment patterns and DOT have not been assessed in this population and are needed to support pioneering of novel treatment combinations.

**METHODS.** A retrospective observational study using the Flatiron Health electronic medical records database was conducted among patients with MSS mCRC who received first-line therapy on or after January 1, 2013. Descriptive statistics were used for treatment frequencies, treatment sequences, and DOT. DOT was defined

as the time between start and end dates for therapy.

**RESULTS.** In this study, 7636 patients with MSS mCRC and first-line treatment were identified. Mean age was 62 years, 55% were male, 63% were white, 65% had stage IV disease at initial diagnosis, and 72% had an Eastern Cooperative Oncology Group score of less than 2. Among patients tested for mutations, 45% had positive *KRAS*, 5% had positive *NRAS*, and 7% had positive *BRAF*. Overall, 56% of patients subsequently received second-line treatment and 28% received third-line treatment. The most common regimen was FOLFOX plus bevacizumab (Avastin) (34%) as first-line treatment, FOLFIRI plus bevacizumab (26%) in

second line, and TAS-102 (14%) in third line. The most common sequence for first line to second line was FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab (22%) and for first line to third line was FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab followed by TAS-102 (4%). Median DOT was 5.1 months (95% CI, 5.10-5.29) in

first line, 3.7 months (95% CI, 3.68-3.94) in second line, and 3.0 months (95% CI, 2.79-3.09) in third line.

**CONCLUSION.** Patients with MSS mCRC predominantly received bevacizumab plus chemotherapy in first- and second-line treatment, with a high proportion continuing bevacizumab through progression.

There was no predominant third-line treatment regimen and median DOT was less than 3.0 months, highlighting the unmet need for more effective third-line treatment options. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

#### COMMENTARY

**Tanios S. Bekaii-Saab, MD** This study confirms the patterns of practice in the United States, which, unlike Europe, predominantly uses bevacizumab in addition to chemotherapy in the first line. Despite the right versus left data and the emergence of EGFR inhibitors, the United States remains the land of bevacizumab (Avastin). There could be multiple factors for that, including the rush to start treating patients before having the genomic analysis such as *RAS* mutations.

**Daniel G. Haller, MD** Certainly, the predominant use of bevacizumab is driven by the fact that half of the patients in this study showed *RAS* mutations and shouldn't get an EGFR inhibitor. The advice I offer in my lectures is to just start your baseline, backbone chemotherapy. Then, when *RAS* testing is available, start the appropriate antibody. It's not like a clinical trial, in which you have to give all treatment on day 1.

## Tumor-Informed Assessment of Molecular Residual Disease and Its Incorporation Into Practice for Patients With Early- and Advanced-Stage Colorectal Cancer (CRC-MRD Consortia)

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**BACKGROUND.** Circulating tumor DNA (ctDNA) testing (often referred to as liquid biopsies) can be used for the assessment of molecular residual disease (MRD) in patients with early-stage, advanced and/or metastatic colorectal cancer (CRC). The clinical utility of ctDNA as a noninvasive biomarker has been well established in

the literature for MRD detection and for stratifying patients based on their risk of developing relapse. Prospective evaluation of this methodology in clinical practice has been limited to date.

**METHODS.** A personalized and tumor-informed multiplex PCR assay (Signatera

16-plex bespoke mPCR NGS assay) was used for the detection and quantification of ctDNA for MRD assessment.

We analyzed and present results from an ongoing early adopter program of ctDNA testing across the spectrum of CRC management.

**RESULTS.** Here, we present a total of 535 unique CRC patients with colon (n = 432), rectal (n = 77), and other lower gastrointestinal cancers (n = 27; anal, appendiceal, small bowel). Most of the patients were male (57%; n = 307) with an average age of 61 years. MRD positivity rates and ctDNA quantification (mean tumor molecules/mL) are shown in Table 1. ctDNA detection was significantly associated with stage of disease ( $P < .0001$ ; Chi-square: 50.94, df = 3). Additionally, in patients with radiologically measurable active metastatic disease, ctDNA detection rate was 100%. On the contrary, patients with advanced/metastatic disease who had a partial response to treatment or no evidence of disease (NED) showed 60% and 33% ctDNA positivity, respectively. In the neoadjuvant (presurgical/pretreatment) setting, ctDNA detection was also 100% in oligometastatic CRC patients.

**CONCLUSION.** This is the first large, real-world study reporting on the results from a clinically validated MRD assay. For the first time, we delineate MRD rates and quantify ctDNA concentration in patients with early-stage, advanced, and/or metastatic CRC. We found that ctDNA detection postsurgically was significantly associated with the stage of the disease. Furthermore, we provide evidence that effective ongoing treatment in patients with CRC may be correlated with ctDNA clearance. ■

**DISCLOSURES:** PK would like to acknowledge research funding from Advanced Accelerator Applications, Array BioPharma, Bristol Myers Squibb, Celgene; consultancy/advisory board: Natera and Foundation Medicine. FD would like to

**TABLE 1. MRD Rates and ctDNA Quantity in Patients With Early-stage, Advanced and metastatic CRC**

Stages	MRD rates	Quantity of ctDNA (Mean tumor molecules (MTM)/mL)		
		Mean	Median	Range
<b>Stage (I-III) CRC; n = 300</b>				
<b>Neoadjuvant setting</b>	4/5 (80%)	21.04	11.69	0.24-60.55
<b>Stage I (T1-2N0)</b>	2/15 (13%)	2.65	2.65	0.13-5.18
<b>Stage II (T3N0)</b>	3/53 (5.6%)	1.63	1.74	1.33-1.84
<b>Stage II (T4N0)</b>	4/14 (28.6%)	136.24	0.44	0.31-543.77
<b>Stage III, low-risk (T1-3N1)</b>	3/32 (9.3%)	2.43	1.23	0.13-872.2
<b>Stage III, high-risk (T4, N1-2, T Any, N2)</b>	15/38 (39.4 %)	61.17	1.23	0.13-872.2
<b>During adjuvant therapy</b>	2/38 (5.2%)	1.37	1.37	0.27-2.47
<b>Surveillance</b>	4/103	36.65	4.76	2.29-134.8
<b>Metastatic CRC; n = 41</b>				
<b>Progressive/ active disease</b>	16/16 (100%)	203.75	7.51	0.13-2149.96
<b>Stable disease/ partial response</b>	9/15 (60%)	7.06	1.23	0.17-51.03
<b>No evidence of disease</b>	4/12 (33%)	232.07	21.41	0.62-884.83
<b>Oligometastatic CRC; n = 93</b>				
<b>Neoadjuvant setting</b>	9/9 (100%)	3045.04	36.53	0.49-27,077.71
<b>MRD (postsurgical)</b>	26/53 (49%)	454.15	5.61	0.11-13,274.05
<b>During adjuvant treatment</b>	5/15 (33%)	4.54	2.21	0.48-17.75

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## COMMENTARY

**Tanios S. Bekaii-Saab, MD** This continues to confirm that the presence of minimal residual disease indicates an almost certain risk of disease recurrence or progression. The study also does provide evidence that treatment may be correlated with circulating free DNA [cfDNA] clearance. But there's an important caveat here: clearing cfDNA in the more advanced setting does not necessarily lead to cure after a response. So, we have to be very careful about what that means. To put this in the big perspective, these remain observations, and until they're validated in prospective randomized trials, they should not be applied to the clinical practice.

## Serial Circulating Free DNA Testing Can Detect New Genetic Alterations in Patients Undergoing Treatment for Pancreas Cancer

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**BACKGROUND.** Pancreatic ductal adenocarcinoma (PDAC) is still a challenge with poor prognosis. As the disease progresses, new genetic changes may occur leading to more aggressive and less treatment responsive cells, resulting in secondary treatment resistance. The ability to detect these changes without using invasive techniques can potentially help to identify genetic targets with therapeutic implications and more enrollments in clinical trials. In this study, we aimed to evaluate the genetic landscape of circulating free DNA (cfDNA) in PDAC patients over time.

**METHODS.** From December 2014 through October 2019, 357 samples collected from 282 patients with PDAC at Mayo Clinic underwent cfDNA testing using Guardant 360, which detects single nucleotide variants, amplifications, fusions, and specific insertion/deletion mutations in up to 73 different genes. Therapeutic

relevance (TR) was defined as possible treatments within OncoKB levels 1-3B and R1.

**RESULTS.** Among 282 patients, 40 patients had at least 2 serial samples of cfDNA at the time of diagnosis and progression, 60% (24/40) were female, and age ranged from 43 to 86 years with a median age of 66 years. In addition, tissue-based profiling was available at baseline in 28/40 (70%). *KRAS* and *TP53* were the most common gene mutations found in patients with both liquid and tissue biopsy results (42%). Overall, 23/40 (57.5%) of patients developed new genetic alterations that were captured by cfDNA during the time of progression: 7/40 (17.5%) with VUS alterations, and 16/40 (40%) with pathogenic alterations. None of these new genetic alterations were detected on the baseline tissue profiling. Therapeutically relevant alterations were seen in 12 of the 40 patients (30%), including

*EGFR* (7.5%), *PIK3CA* (5.0%), *RET* (5.0%), *MET* (5.0%), *BRCA1* (2.5%), *PDGFRA* (2.5%), *ERBB2* (2.5%), and *FGFR2* (2.5%). These patients received a second-line regimen in the form of chemotherapy upon progression, and no patient was enrolled in a clinical trial targeting these alterations/pathways.

**CONCLUSION.** In PDAC patients, serial cfDNA testing can detect new genetic alterations in 40% of patients upon progression that could potentially have therapeutic relevance in 30% of cases. All such mutations were absent on both baseline tissue and liquid biopsies, suggesting tumor evolution might be responsible for resistance mechanisms. Larger studies are needed to investigate whether such findings can translate in improvement of clinical outcomes. ■

**DISCLOSURES:** All the authors declare that they have no conflict of interest.

### COMMENTARY

**Daniel G. Haller, MD** This study adds to the literature looking at the evolution of alterations and appearance of mutations that, in other tumors, can be actionable. For patients who may have had serial cfDNA testing, some genetic alterations that appeared upon progression may have been suppressed, because they were very small clones, or shedding little into the circulation, but ultimately they were detected. These were mostly *KRAS* and *TP53* mutations, and they did correlate with progression of disease. Unfortunately, as most of the mutations that were reported were not actionable, the problem remains: What can we do with these findings?

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