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REVIEW

Tracking the 2015 Gastrointestinal Cancers Symposium: bridging cancer biology to clinical gastrointestinal oncology

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Abstract: The 2015 Gastrointestinal Cancers Symposium (San Francisco, CA, USA; January 15–17) is the world-class conference co-sponsored by the American Society of Clinical Oncology, the American Society for Radiation Oncology, the American Gastroenterological Association Institute, and the Society of Surgical Oncology, in which the most innovative research results in digestive tract oncology are presented and discussed. In its twelfth edition, the meeting has provided new insights focusing on the underpinning biology and clinical management of gastrointestinal malignancies. More than 3,400 health care professionals gathered from all over the world to share their experiences on how to bridge the recent novelties in cancer biology with everyday medical practice. In this article, the authors report on the most significant advances, didactically moving on three different anatomic tracks: gastroesophageal malignancies, pancreatic and biliary cancers, and colorectal adenocarcinomas.

Keywords: colorectal cancer, gastric cancer, ramucirumab, pembrolizumab, target therapy, onartuzumab, AMG 337

Introduction

Significant studies have been presented at the 2015 Gastrointestinal Cancers Symposium, an outstanding appointment that is held every January in San Francisco, CA, USA. Although this year the practice-changing results were limited, results of many studies have markedly contributed to the expansion of our knowledge in the biology of gastrointestinal malignancies and to fine-tune the available treatment options.

Aims of this report are to recall and comment on the most significant preclinical and clinical studies that have been presented at the scientific venue, which will continue the major progress made in the past decades.[1] In the gastroesophageal track, we will present and reason on the available results of the studies testing mesenchymal epithelial transition (MET) factor inhibitors (AMG 337 and onartuzumab) and programmed cell death receptor 1 ligand (PD-L1) inhibitors (pembrolizumab) in patients with upper gastrointestinal tract diseases. In the second section of the manuscript, we will describe how a comprehensive molecular profiling of biliary tract cancers may be used as a tool for treatment and prognostic stratification, update on the method for refining optimal candidates for sorafenib in hepatocellular carcinoma (HCC), and discuss how to expand valuable treatment options in pancreatic carcinomas, including the novel MM-398 and PF-04136309. In the final section focused on colorectal cancers (CRCs), we will face the most recent advances in molecular selection for targeted therapies and understand that CRC has many underlying drivers, as well as the opportunity to identify targets responsible for drug resistance and the possibility of reshaping the

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Table 1 Significant clinical trials presented at the Gastrointestinal Cancers Symposium 2015 investigating novel agents in gastric, liver, and colorectal carcinomas

Authors	Phase	Treatment line	Design	Primary end point	Trial outcome
Kwak et al[7]	I	Refractory	AMG 337, single arm	Safety	Good tolerance, RR: 62%
Shah et al[8]	II, randomized	First-line	FOLFOX ± onartuzumab	PFS	HR
Zhu et al[22]	III, randomized	Second-line	Ramucirumab vs placebo	OS	HR: 0.67; (95% CI: 0.51–0.90*; *P*=0.0059)
Cheng et al[24]	II, randomized	First-line	Dovitinib vs sorafenib	OS	HR: 1.27; 95% CI: 0.89–1.80; *P*=ns
Palmer et al[25]	II, randomized	First-line	Nintedanib vs sorafenib	TTP	HR: 1.05; 95% CI: 0.63–1.76; *P*=ns
Tabernero et al[34]	III, randomized	Second-line	FOLFIRI + ramucirumab vs FOLFIRI + placebo	OS	HR: 0.84; (95% CI: 0.73, 0.98); *P*=0.0219
Xu et al[35]	II, randomized	Refractory	Famitinib vs placebo	PFS	HR: 0.58; *P*=0.0034

Notes: *A prespecified subgroup analysis according to baseline alpha-fetoprotein (AFP) level suggested that patients with baseline AFP ≥400 ng/mL might derive benefit from ramucirumab treatment vs placebo (OS HR: 0.67, 95% CI: 0.51–0.90; *P*=0.0059).
Abbreviations: CI, confidence interval; HR, hazard ratio; ns, nonsignificant; OS, median overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression.

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paradigm of sequential approach in multimodality therapies. Notable advances that may challenge the current paradigms in the management of rectal cancers are also presented. Results are summarized in Table 1.

Steps ahead in upper gastrointestinal malignancies

Recent advances in the understanding of gastric cancer biology and the comprehensive molecular analysis performed by the Cancer Genome Atlas (TCGA), which allowed recognizing four distinct disease subtypes,[2] have served as the rationale for the development of novel targeted agents.[3] Overexpression or amplification of the MET factor has been observed in gastric cancer[4] and been correlated with unfavorable clinical outcomes.[5] Compared to the proportion of genes identified by immunohistochemical (IHC) detection of overexpression, the rate of detection of activating mutations or amplifications of *MET* gene is higher,[6] defining a small group of tumors with aggressive clinical behavior regardless of disease stage. AMG 337 is a highly selective, orally available MET inhibitor that showed promising preclinical activity. In a multicenter, Phase I, open-label trial, 80 patients with MET-amplified tumors and good performance status (PS) received increasing doses of AMG 337 monotherapy, defining 300 mg/day as the maximum tolerated dose.[7] In the small subset of 13 heavily pretreated patients with *MET*-amplified gastroesophageal tumors exposed to AMG 337, the investigators observed a notable 62% rate of response. Interestingly, the response was fast and usually detectable within 4 weeks from treatment start, which may be a remarkable advantage for symptomatic patients. The experimental treatment had a favorable profile of tolerability. Dose-limiting toxicities were severe hypertension, headache, and increased amylase activity; the most common side effects were headache (45%), nausea (32%), vomiting (21%), fatigue (14%), and peripheral edema (12%); headache (9%) and fatigue (4.5%) were the most frequent severe adverse events.

Onartuzumab is a recombinant, fully humanized, monoclonal anti-MET antibody. Results of the randomized Phase II trial testing upfront FOLFOX6 with onartuzumab at the dose of 10 mg/kg or FOLFOX6 plus placebo were presented.[8] One hundred and twenty-three patients with advanced gastroesophageal cancer were enrolled from 25 centers; key eligibility criteria included no previous treatments for metastatic disease, Eastern Cooperative Oncology Group (ECOG) PS status of 0 or 1, and retention of organ function. MET-positive patients, defined as those with ≥50% of tumor with moderate–strong intensity staining by centrally reviewed IHC, were well balanced in the two arms: 28% in the experimental arm vs 33% in the control arm. Stratification factors were histological subtype and previous gastrectomy. At data cutoff, 96 out of 121 randomized patients had progression-free survival (PFS) events, 74% of those exposed to FOLFOX and onartuzumab and 82% of those receiving FOLFOX and placebo. The primary end point, PFS, in the intention-to treat population, was not met (6.77 months in the onartuzumab arm, 6.97 months in the placebo arm; hazard ratio [HR]: 1.08, 95% confidence interval [CI]: 0.71–1.63). In addition, the preplanned analyses in the MET-positive population generated similarly disappointing results: median PFS was 5.95 months for those exposed to FOLFOX6 and onartuzumab vs 6.8 months for those treated with FOLFOX6 and placebo (HR: 1.38). No differences were found despite the use of different definitions for MET positivity.

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The addition of onartuzumab was not beneficial, regardless of patients' race, and produced more adverse events. It is unclear whether these negative results suggest a failure of the strategy or the unreliability of the current definition of MET positivity. In fact, while it is reasonable not to consider IHC MET overexpression a good driver for patient selection, it should also be recalled that a large Phase III trial testing onartuzumab was prematurely interrupted because of failure of the drug in lung cancers,[9] and another randomized study testing rilotumumab in the advanced disease setting failed to meet the primary trial end point.[10]

Targeting the immune checkpoints in solid malignancies is becoming a major methodological approach. T-lymphocytes may recognize and eliminate cancer antigens, while immune checkpoints such as cytotoxic T-lymphocyte-associated antigen (CTLA)-4 and programmed cell death (PD-1) receptor and its ligands (PD-L1, PD-L2) are able to suppress the activity of T-lymphocytes. Therefore, enhancing antitumor immunity by blocking PD-1 is now an attractive reality. Pembrolizumab, a highly selective IgG4k, humanized monoclonal antibody against PD-1, has recently received approval from the US Food and Drug Administration for the treatment of advanced melanoma after the failure of ipilimumab administration or BRAF V600E-mutant melanoma in progression following BRAF inhibitor administration.[11] Because the high expression of PD-L1 on tumor gastric cells[12] and macrophages can suppress immune surveillance and permit neoplastic growth,[13] the molecule has become an interesting target even in gastric cancer. Preliminary data of the KEYNOTE-012 gastric cohort study, in which pembrolizumab (MK-3475) was given at 10 mg/kg every 2 weeks to 39 patients with PD-L1-positive advance gastric cancer, were recently presented.[14] The trial enrolled heavily pretreated Asian (19) or non-Asian (20) patients, wherein 67% received ≥2 treatment lines. Overall response rate (RR) was 30.8% (95% CI: 17.0–46.6) and 41% of patients experienced a decrease in tumor burden. Aim of the abstract presented at the 2015 Gastrointestinal Cancers Symposium was to analyze the relationship between PD-L1 expression and clinical outcome in patients with advanced disease treated with pembrolizumab.[15] Muro et al[15] found a significant association between PD-L1 expression level and objective response rate (ORR; one-sided P=0.10). Median overall survival (OS) was not reached, but the 6-month OS rate was surprisingly high (69%). Though described as easily manageable by the authors, the toxicity profile appears a bit challenging, with five severe adverse events (peripheral sensory neuropathy, fatigue, decreased appetite, hypoxia, and pneumonitis) and one drug-related death (hypoxia). Because the immune-related response may not be fully captured by conventional response criteria,[16] it would be interesting to assess the response with immune-related response criteria to further confirm the activity of pembrolizumab. On the basis of the KEYNOTE results, a Phase III randomized trial that compares pembrolizumab to paclitaxel in patients with recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma who progressed after first-line treatment has been planned.

Perioperative chemotherapy is a standard of care in locally advanced gastroesophageal cancer in Europe.[17,18] In the MAGIC population, the human epidermal growth factor receptor 2 (HER2) positivity was not a prognostic or predictive factor.[19] In the NEOHX study,[20] 36 patients with HER2-positive locally advanced gastric adenocarcinoma entered the Phase II trial to explore the combination of trastuzumab and chemotherapy in this setting. Patients were treated with three preoperative cycles of standard XELOX plus trastuzumab (loading dose 8 mg/kg, instead of 6 mg/kg), followed by definitive surgery. In the postoperative phase, patients received three other cycles of the same combination regimen and eventually 12 cycles of trastuzumab monotherapy. The primary end point of the study was 18 months disease-free survival (DFS). Median age at trial entry was 63 years. R0 resection was reached in 78% of the patients (three cases had a pathological complete response), median DFS rate at 18 months was 71%, 2-year OS rate was 75%, while median DFS and OS had not been reached. The trial results are very interesting in this biologically selected population and may promote the use of trastuzumab in resectable gastric cancer patients.

Significant advances in HCC, pancreatic cancer, and ciliary tract adenocarcinoma

Ramucirumab is a humanized monoclonal antibody that specifically blocks the vascular endothelial growth factor receptor 2 (VEGFR2).[21] The REACH trial is a randomized Phase III study investigating ramucirumab as a single agent for the treatment of advanced HCC after failure of first-line sorafenib.[22] Unfortunately, the trial did not meet its primary end point. In fact, median OS was 9.2 months for ramucirumab vs 7.6 months for placebo. Interestingly the prespecified subgroup analysis suggested that baseline alpha-fetoprotein (AFP) level might be a predictive marker for ramucirumab efficacy. Among 250 patients with baseline AFP ≥400 ng/mL, OS HR was 0.67 (95% CI: 0.51–0.90;

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P=0.0059) (Table 1). Median OS was 7.8 months for ramucirumab vs 4.2 months for placebo. Accordingly, in patients with a baseline AFP ≥1.5× the upper limit, OS was 8.6 months for ramucirumab vs 5.7 months for placebo and the HR was 0.749 (95% CI: 0.603–0.930; *P*=0.0088). In the REACH trial, AFP baseline levels seemed to be correlated with clinical outcome during ramucirumab treatment. Hopefully, the impact of this novel treatment approach will be proved prospectively in future clinical trials incorporating findings from the REACH study.

Casadei Gardini et al[23] presented a new prognostic factor for advanced HCC patients receiving sorafenib. The authors hypothesized that the antiangiogenic compound might induce an inhibition of endothelial nitric oxide synthase (eNOS) activity by blocking the VEGFRs, with a consequent decrease of the production of nitric oxide, which is correlated with tumor angiogenesis, invasion, and metastasis. On the basis of this assumption, *eNOS* polymorphisms were retrospectively investigated in 54 HCC patients receiving sorafenib. Patients carrying the *b* allele (five repetitions of 27 bp) of *eNOS* were found to have improved OS. The variants *4aa* (four repeats of 27 bp in homozygosis), *4ab*, and *4bb* were associated with a median OS of 5.7 months, 13.9 months, and 23.6 months, respectively (*P*=0.016). For *eNOS-786*, the presence of the *T* allele was associated with a statistically significant, longer median OS (15.6 months vs 13.9 months, respectively; *P*=0.031).

Two Phase II randomized studies with novel antitumor agents were presented.[24,25] Dovitinib was tested in patients with advanced HCC in an attempt to overcome the fibroblast growth factor receptors (FGFRs)-activated mechanism of resistance, which is considered an escape pathway for sorafenib activity. Nonetheless, dovitinib failed to prove superior to sorafenib in the first-line treatment of HCC. In the Phase II trial presented by Cheng et al[24] OS was 34.6 weeks for dovitinib and 36.7 weeks (23.3 weeks–49.3 weeks) for sorafenib (HR: 1.27; 95% CI: 0.89–1.80). Palmer et al[25] presented disappointing results for the triple angiokinase inhibitor nintedanib. In a randomized Phase II trial, time to progression (TTP) was similar between nintedanib and sorafenib (TTP: 5.5 months vs 3.8 months; HR: 1.05; 95% CI: 0.63–1.76). Accordingly, median OS was similar between the treatment arms (11.9 months vs 11.4 months; HR: 0.88; 95% CI: 0.52–1.47) (Table 1).[25]

Prajapati et al[26] proposed a novel staging system for patients with advanced HCC treated with doxorubicin drug-eluting beads transarterial chemoembolization. In the multivariate analysis, the independent factors for survival were Child-Pugh class, ECOG PS, number of HCC lesions, index HCC (iHCC) size, site of portal or hepatic venous thrombosis, extrahepatic metastasis, and serum creatinine and AFP levels. Consequentially, the Clinical, Imaging, and Serum examination (CIS) staging system was proposed. According to the study findings, patients were grouped into different stages with different outcomes. The OS of stages I, II, III, and IV was 40.4 months, 24 months, 10.6 months, and 2.6 months, respectively ($P<0.0001$).

A prognosis model was also suggested for patients with locally advanced unresectable pancreatic cancer included in the LAP 07 trial.[27] In the multivariate analysis, the independent factors for OS were age, pain, albumin levels, and Response Evaluation Criteria in Solid Tumors (RECIST) size. Three risk groups were identified: lower risk (n=17; median OS: 18.8 months; group of reference); intermediate risk (n=166; median OS: 13.4 months); higher risk (n=187; median OS: 11.8 months). This easy-to-use prognostic model might be relevant for treatment decision in clinical practice and future trial design. Novel potential therapeutic options for metastatic pancreatic cancer have been suggested from analyses of randomized trials. In the three-arm NAPOLI-1 trial,[28] 417 patients who had failed a gemcitabine-based first-line treatment were randomized to MM-398 (nanoliposomal encapsulation of irinotecan), 5-fluorouracil (FU) plus leucovorin (LV), or a combination of MM-398 and 5FU/LV. The primary end point of the trial was OS. The analysis in the per-protocol population (patients who received at least 80% of the target dose in the first 6 weeks and did not violate any inclusion/exclusion criteria) confirmed the favorable OS, PFS, and ORR for the combination MM-398+5FU/LV arm relative to the control 5FU/LV arm with a manageable safety profile, whereas single-agent MM-398 was not superior to 5FU/LV.

A Phase I trial investigated the role of PF-04136309 (a novel C–C chemokine receptor type 2 inhibitor) in combination with FOLFIRINOX for locally advanced pancreatic cancer.[29] Among 23 evaluable patients, 21 (91%) completed all six cycles; 12 (52.2%) obtained a RECIST-defined partial remission, whereas the remaining 11 (48%) had stable disease. Curative resections were achieved in four patients out of five with borderline resectable disease and in two with locally advanced pancreatic cancer. Globally, these very initial findings suggest that PF-04136309 and MM-398+5FU/LV should undergo further investigation in pancreatic cancer.

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Relevant information about the genomic landscape of biliary tract cancer was derived from an analysis including >500 hundred patients.[30] The primary aim of the study was to identify crucial molecular markers as potential candidates for targeted agents. Findings from this analysis showed that intrahepatic cholangiocarcinoma (IHCCA), extrahepatic cholangiocarcinoma (EHCCA) and gall bladder carcinoma (GBCA) share genomic alterations in cell cycle regulation (*CDKN2B*) and chromatin remodeling (*ARID1A*). IHCCA features FGFR fusions, isocitrate dehydrogenase (*IDH*)-1/2 substitutions, *BRAF* substitutions, and *MET* amplification, with a low *KRAS*-mutation frequency. EHCCA and GBCA feature *ERBB2* amplifications (GBCA > EHCCA) and *PIK3CA*/*MTOR* pathway alterations. EHCCA has a high *KRAS*-mutation frequency, whereas the *KRAS* genomic alteration in GBCA is low. Knowledge of relevant genomic alterations will be a fundamental starting point in designing future clinical trials in this setting.

We believe that new data deriving from the 2015 Gastrointestinal Cancers Symposium on HCC, pancreatic cancer, and biliary tract cancer will serve as relevant integration to our scientific knowledge about this heterogeneous group of neoplasms. Although the search for novel therapeutic targets represents a priority in this setting, we should remember that an improvement in the use of already available treatment options is equally important.[31,32] Recent presentation of results from an analysis of polymorphisms in the angiogenic pathway of HCC patients receiving sorafenib should be integrated with already known data in this area and with clinical data defining prognostic groups.[32,33] Similar considerations are applicable to data presented on patients with pancreatic cancer and biliary tract cancer.

Colorectal cancers: integrating novel drugs in innovative strategies

Results of the treatment with new antiangiogenic agents have been reported. Two studies suggested that ramucirumab and famitinib might soon be added to the armamentarium for metastatic CRC. The RAISE trial demonstrated that the addition of ramucirumab to second-line FOLFIRI chemotherapy resulted in a significant delay in disease progression and prolongation of survival in patients with metastatic CRC who had previously failed a first-line therapy containing bevacizumab.[34] The study included 1,072 patients with metastatic disease randomly assigned to ramucirumab (a human immunoglobulin G-1 monoclonal antibody that targets the extracellular domain of VEGFR2) plus FOLFIRI every 2 weeks per cycle (n=536) or placebo plus FOLFIRI every 2 weeks per cycle (n=536). The primary end point was OS. Ramucirumab reduced the risk for death by 16% (HR: 0.84; *P*=0.0219) and prolonged survival by a median of 1.6 months compared with FOLFIRI alone (median OS: 13.3 months vs 11.7 months). In addition, ramucirumab reduced the risk of disease progression by 21% (HR: 0.79; *P*=0.0005).

The efficacy and safety of famitinib, a small multitarget receptor tyrosine kinase inhibitor, which primarily inhibits VEGFR2, cKit, and PDGFR, were evaluated in a multicenter, randomized, double-blind, Phase II trial.[35] The study included 154 advanced CRC patients, who were randomly assigned in a 2:1 ratio to receive either famitinib or placebo. All patients had previously failed at least two lines of standard therapy. The primary end point was PFS. Famitinib increased median PFS from 1.5 months to 2.8 months (HR: 0.58; 95% CI: 0.41–0.86; *P*=0.0034). No statistical difference was observed in median OS with famitinib vs placebo (7.5 months vs 7.6 months; HR: 1.10; 95% CI: 0.76–1.60; *P*=0.605). The safety profile of famitinib was similar to that of other anti-VEGFR agents. Although these studies indicate that there will be alternative treatment options for metastatic CRC in the near future, they represent confirmations of the previously consolidated strategy of chemotherapy and antiangiogenic agent combination in unselected patients.[36] During this edition of the conference, a significant convergence was also demonstrated in refining molecular selection to increase the effectiveness of targeted therapies and particularly in developing a "beyond-*RAS*" strategy;[37] many works from all over the world have explored new screening, predictive biomarkers, and targeted therapies for metastatic CRC patients.

Preliminary data from two multinational screening platforms show that collaborative genomic analysis beyond the *RAS* is feasible and might be used to run next-generation trials with targeted agents. The European Organisation for Research and Treatment of Cancer (EORTC) Screening Patients for Efficient Clinical Trial Access in advanced colorectal cancer (SPECTAcolor), a pan-European network, has already analyzed 406 patients in the first year and has planned to use next-generation sequencing for 360 key cancer alterations.[38] A nationwide genomic screening project in Japan has evaluated a total of 361 tumor samples in the first 6 months to detect rare mutations such as *PI3KCA* and *BRAF* mutations.[39]

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Some other studies have shown that a strategy "from bench to bedside" is being pursued. The combination of the EGFR inhibitor panitumumab with the BRAF inhibitor vemurafenib for *BRAF*-mutant metastatic CRC has shown interesting hints of activity.[40] Two of 12 evaluable patients (13%) had confirmed long-lasting partial responses, whereas 8 patients (53%) had stable disease. The combination was well tolerated, with acneiform rash, fatigue, and arthralgia being the most frequent treatment-related adverse events. On the basis of the same assumption that activation of the EGFR pathway is the leading cause of failure of anti-*BRAF* monotherapy, a randomized Phase II trial of irinotecan plus cetuximab with or without vemurafenib is also currently ongoing.[41]

Because another mechanism of resistance to anti-EGFR therapy is supposed to be HER2 amplification, in the Italian study HERACLES, heavily pretreated patients with HER2-positive, EGFR inhibitor-refractory advanced CRC have been treated with the combination of lapatinib and trastuzumab.[42] As expected from the literature,[43] the screening failure for HER2-positive patients was impressively high. Eighteen patients were enrolled (2.8% of the patients screened), and an ORR of 33% was achieved. Patients with HER2 3+ CRC and with a gene copy number $\geq$20 had the highest chance to respond to the dual inhibition.

Besides the new therapies and new strategies, the 2015 Gastrointestinal Cancers Symposium challenged some old paradigms. A retrospective review of 145 patients with locally advanced rectal cancer who received standard neoadjuvant chemoradiation suggests that patients who obtained a clinical complete response can avoid surgery with little compromise in the overall outcomes.[44] After a median follow-up of 3.5 years, there were no significant differences in disease-specific parameters or OS between patients who had a clinical complete response to preoperative therapy and skipped surgery on the one hand and patients who underwent rectal resection with a pathologic complete response (pCR) on the other. The study highlighted that a nonoperative approach may obtain preservation of rectal function in more than three-fourths of the patients.

The optimal timing of surgical resection of rectal cancer after preoperative chemoradiation was investigated in a retrospective analysis of 6,805 patients in the National Cancer Database.[45] A significant relationship between time delay (TD) and pCR was demonstrated (P=0.0002). At TD $<$30 days, 4.0% of patients achieved pCR, while 9.3% of patients achieved pCR by 75 days. At TD $>$75 days, the rate of pCR decreased. However, TD of $>$60 days was associated with 20% greater risk of mortality (95% CI: 1.07–1.36). Direct correlation between pCR and survival does not seem very strong in rectal cancer.

Conclusion

In the era of targeted therapies, trastuzumab and ramucirumab are the only biologic therapy agents approved for patients with advanced gastroesophageal cancers, the first being limited for use in the 15% of patients with HER2-positive tumors. There is a need for novel agents to be offered to these patients. In this landscape, MET inhibitors fostered the debate, with discordant results: while onartuzumab and rilotumumab did not fulfill their promises, AMG 337 provided interesting results. After several years of intense clinical and translational research, sorafenib still remains the only available therapeutic option for patients with advanced HCC. However, novel prognostic markers and interesting treatment strategies might, in the near future, change the way we approach this highly deadly disease. Besides TH-302, other novel drugs have emerged against pancreatic cancers. MM-398, an investigational nanocompound consisting of the chemotherapeutic irinotecan encapsulated in a liposomal sphere, and PF-04136309, a novel orally available human chemokine receptor 2 antagonist with immunomodulating and antineoplastic properties, may provide new hope for patients with advanced disease when combined with standard chemotherapy. With the expansion of the process of knowledge acquisition on CRC biology and, correspondingly, of growth of complexity, famitinib and ramucirumab will provide new options to patients with advanced disease. Once again, many studies have been presented. Hopefully, the time needed to transfer these scientific advances to clinical practice will be shorter than ever.

Disclosure

The authors report no conflicts of interest in this work.

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