

Advances in the Management of GI Cancers:
Highlights from the 2010 Gastrointestinal Cancers Symposium

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Target Audience

The target audience for this program includes medical, surgical, and radiation oncologists, as well as allied oncology healthcare professionals who treat gastrointestinal cancers.

Learning Objectives

Upon completion of this educational activity, participants should be better able to:

- Describe the design and results of studies on treatment of GI cancers presented at the 2010 Gastrointestinal Cancers Symposium
- Interpret study results in light of current standard of care of GI cancers
- Outline recent information on risk factors for, prevention of, and management of serious treatment-related side effects in GI cancers
- Incorporate individual patient parameters and toxicity considerations in selection of treatment for GI cancers

Statement of Need

Advances in GI cancers have resulted from decades of well-designed clinical trials and new insights into the biology as well as shifts in epidemiology, increasing development of and access to new agents, and rapid advances in diagnostic and therapeutic technologies. The management of GI cancers in recent years has involved increasingly complex, combined-modality treatment approaches. Advances in treatment strategies have affected all the approaches used in GI cancers: radiation therapy, chemotherapy, targeted agents, and surgery and supports a best practices model of multidisciplinary team involvement. Numerous ongoing trials are assessing the benefits of these and other novel agents, and as such, it is imperative that physicians and allied healthcare professionals (including nurses, nutritionists, and pharmacists) treating patients with GI cancers be informed of the results of these trials to facilitate optimal management of GI cancers. This newsletter will highlight areas of new knowledge from the 2010 Gastrointestinal Cancers Symposium, a meeting specially designed for the education and presentation of new data in GI cancers.

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INTRODUCTION

Exciting presentations of new results, important updates of seminal trials, and expert perspectives were featured at the 2010 Gastrointestinal Cancers Symposium held in Orlando, Florida in January. The co-sponsors for the meeting were the American Gastroenterological Association Institute, the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology. This newsletter highlights treatment trials important for clinicians caring for patients with GI cancers. Complete abstracts are available at <http://www.asco.org/ASCOv2/Meetings/Abstracts>.

COLORECTAL CANCER

Peeters M, Price T, Hotko YS, et al. Randomized phase III study of panitumumab with FOLFIRI versus FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer: patient-reported outcomes. Abstract 282.

Siena S, Cassidy J, Tabernero J, et al. Randomized phase III study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as first-line treatment for metastatic colorectal cancer: PRIME trial. Abstract 283.

Two presentations updated or expanded the results of international randomized phase III studies with the humanized epidermal growth factor receptor (EGFR) monoclonal antibody panitumumab, administered in a dose of 6 mg/kg every 2 weeks. One (referred to as the PRIME trial) evaluated the drug in combination with FOLFOX4 in the first-line setting and the other utilized it with FOLFIRI in the second-line setting.

From August, 2006 to February, 2008, 1183 patients (60% *KRAS* wild-type [wt], 40% *KRAS* mutant) received treatment in the PRIME trial. The primary endpoint was progression-free survival (PFS) by blinded central radiology review, initially in the entire population but later amended to focus on the *KRAS* wt subset once the importance of this biomarker was reported.

This amendment occurred prior to completion of enrollment and any efficacy analysis. The results are shown in **Table 1**. Importantly, when panitumumab was added to FOLFOX4, a statistically significant improvement in PFS was seen in patients with *KRAS* wt tumors and a statistically significant detriment in PFS was seen in patients with *KRAS* mutated tumors. Corresponding trends were seen in overall survival (OS). A forest-plot illustrated that all subgroups had similar benefits except for patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 (n = 38), showing a trend toward worse survival when they received panitumumab (HR 1.99, 95% CI 0.96-4.15).

Table 1. Efficacy and selected toxicity results with panitumumab in untreated mCRC

	<i>KRAS</i> wild-type		<i>KRAS</i> mutant	
	P + FOLFOX	FOLFOX	P + FOLFOX	FOLFOX
n	325	331	221	219
Median PFS (mo)	9.6	8	7.3	8.8
HR (95% CI)	0.8 (0.66-0.97)		1.29 (1.04-1.64)	
P	0.02		0.02	
Median OS (mo)	23.9	19.7	15.5	19.3
HR (95% CI)	0.83 (0.67-1.02)		1.24 (0.90-1.57)	
P	0.07		0.07	
Grade 3/4 AE (%)				
Skin toxicity	38	2	30	1
Neutropenia	42	41	37	47
Diarrhea	18	9	20	10
Stomatitis	9	1	6	4
Hypomagnesemia	6	< 1	6	< 1

P = panitumumab

In the second-line treatment trial, 1186 patients were randomized between June, 2006 and March, 2008. There were co-primary endpoints (PFS and OS by *KRAS* mutation status) and a patient-reported outcome (PRO) assessment utilizing the EQ-5D

Health State Index (HSI) and the overall health rating (OHR) every 4 weeks until progression. The HSI assesses 5 dimensions on a 3-point scale: mobility, self-care, anxiety/depression, usual activities, and pain/discomfort. The OHR is a single visual analog scale for the current overall health-related quality of life. The PRO parameters were adjusted for baseline and randomization factors. The primary endpoint results are shown in **Table 2**. There was a statistically significant difference favoring panitumumab in the OHR area-under-the-curve analysis but no difference in the HSI. Adverse events were of similar type and magnitude as those reported in the first-line trial.

Table 2. Results of panitumumab in second-line treatment of mCRC

	KRAS wild-type		KRAS mutant	
	P + FOLFIRI	FOLFIRI	P + FOLFIRI	FOLFIRI
n	303	294	238	248
Median PFS (mo)	5.9	3.9	5.0	4.9
HR (95% CI) P	0.73 (0.59-0.90) 0.004		0.85 (0.68-1.06) 0.14	
Median OS (mo)	14.5	12.5	11.8	11.1
HR (95% CI) P	0.85 (0.70-1.04) 0.12		0.94 (0.76-1.15) 0.55	

P = panitumumab

Van Cutsem E, Lang I, Folprecht G, et al. Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer: the influence of KRAS and BRAF biomarkers on outcome: updated data from the CRYSTAL trial. Abstract 281.

The phase III CRYSTAL trial, published in the *New England Journal of Medicine* in April, 2009, showed that when cetuximab was added to FOLFIRI there was a statistically significant improvement in PFS compared to FOLFIRI alone in KRAS wt, previously untreated, metastatic

colorectal cancer (mCRC). An analysis with additional biomarker studies and longer follow-up was presented at the GI Cancers Symposium. KRAS and BRAF mutation status was determined with quantitative polymerase chain reaction (PCR) on available tumor tissue from randomized patients. BRAF, a serine-threonine kinase that is a downstream effector of KRAS, is occasionally mutated in colon cancers and has been suggested to be an additional determinant of cetuximab activity. It occurs exclusively in KRAS wt tumors. The updated presentation contained KRAS results for 89% of patients (twice as many as in the previous publication) and BRAF for almost all KRAS wt tumors. Wild-type KRAS was present in 56% and of those, 9% had BRAF mutation. The efficacy results by KRAS were confirmatory of previous findings (**Table 3**). The low sample size of patients with BRAF mutation prevents conclusions regarding the efficacy of cetuximab when added to FOLFIRI, but the biomarker does seem to indicate a poor prognosis.

Perspective

Dr J. Randolph Hecht was the discussant for the 3 trials described above. He pointed out that the 2 panitumumab trials are useful additions to the evidence base since there are relatively few trials of the drug in combination with chemotherapy.

Table 3. Results of CRYSTAL trial according to mutation status

	KRAS wt		KRAS mut		BRAF wt*		BRAF mut*	
	C+F	F	C+F	F	C+F	F	C+F	F
n	316	350	214	183	277	289	26	33
Best overall response (%)	57.3	39.7	31.3	36.1	61.0	42.6	19.2	15.2
P value	< 0.0001		0.3475		< 0.0001		0.9136	
Median PFS (mo)	9.9	8.4	7.4	7.7	10.9	8.8	8.0	5.6
Hazard ratio (95% CI) P value	0.70 (9.6-0.9) 0.0012		1.17 (0.9-1.5) 0.2661		0.697 (0.5-0.9) 0.0016		0.934 (0.4-2.1) 0.8656	
Median OS (mo)	23.5	20.0	16.2	16.7	25.1	21.6	14.1	10.3
Hazard ratio (95% CI) P value	0.80 (0.7-1.0) 0.0093		1.04 (0.8-1.3) 0.7551		0.83 (0.7-1.0) 0.0549		0.908 (0.5-1.6) 0.7440	

wt = wild-type, mut = mutation, C = cetuximab, F = FOLFIRI (infusional fluorouracil, leucovorin, irinotecan)

*BRAF assessed only in KRAS wild-type.

Confirmation of the importance of *KRAS* mutation in resistance to anti-EGFR antibodies, with these large studies using prospective assessment, has important clinical relevance. On the other hand, he mentioned the divergent (and relatively unexplained) results of the COIN trial, a large study of 729 patients, presented by Maughan and colleagues in the general poster session. In that study, patients received fluoropyrimidine and oxaliplatin, with or without cetuximab and the *KRAS* mutation patients achieved virtually identical PFS on Kaplan-Meier analysis as those with *KRAS* wt. The COIN was the only trial that used capecitabine in some patients, which may be relevant to the lack of association with *KRAS* status.

The most novel data reported in this session were *BRAF* data. Since mutation occurs with relatively low frequency and is observed exclusively with *KRAS* wt, Hecht proposed that investigators combine data on treatment of *BRAF* mutated patients in a meta-analysis to allow proper statistical analysis of the predictive nature of this biomarker. While *BRAF* is a readily available test in commercial laboratories and is clearly a marker of poor prognosis, he believes it is premature to use it for therapy decision making.

The need to accurately predict patients who will benefit from anti-EGFR therapy is especially critical since virtually all patients receiving such therapy experience some toxicity that can impact quality of life. The PROs reported by Peeters may indicate that benefits in properly selected patients outweigh the impact of toxicity, but the improvement indicated by the OHR (a single visual analog scale) in a setting where patients and caregivers are not blinded (and probably cannot be blinded due to the skin reaction) may not be reliable.

Hecht concluded that an important comparison that remains unanswered in the treatment of mCRC is that of anti-EGFR therapy vs anti-VEGF therapy in the *KRAS* wt population. The phase III PEAK and CALGB 80405 trials in the first-line setting and the SPIRITT and S0600 trials in second-line will help answer this. Effective therapy for *KRAS* mutated patients remains an unmet need.


Haller DG, Cassidy J, Tabernero, et al. Efficacy findings from a randomized phase III trial of capecitabine plus oxaliplatin versus bolus 5-FU/LV for stage III colon cancer (NO106968): no impact of age on disease-free interval. Abstract 284.

Previous studies have shown that the oral fluoropyrimidine, capecitabine, has similar efficacy in the adjuvant setting as bolus fluorouracil plus leucovorin (FU/LV). Current treatment guidelines recommend the addition of oxaliplatin for patients with stage III and high risk or intermediate risk stage II, but limited data are available on the combination of capecitabine and oxaliplatin. This trial randomized 1886 patients to this combination (XELOX) or a bolus FU/LV regimen (Mayo Clinic or Roswell Park, based on institutional preference). The primary endpoint was PFS. An analysis by age was incorporated in response to a report by McCleary et al at the 2009 ASCO Annual Meeting. Those investigators performed a meta-analysis of the ACCENT database, and found a trend for newer adjuvant regimens to produce worse outcomes than bolus FU/LV. The efficacy results of NO106968 are shown in **Table 4**. The OS results are premature at this time.

Table 4. Efficacy results and age analysis in NO106968 trial

	XELOX	Bolus FU/LV
3-yr DFS in all patients (%)	71	67
HR	0.80	
P	0.0045	
3-yr DFS in patients < 70 yr (%) n = 1477	72	69
HR	0.79	
95% CI	0.66-0.94	
3-yr DFS in patients ≥ 70 yr (%) n = 409	66	60
HR	0.87	
95% CI	0.63-1.18	

There were fewer treatment days and less dose intensity in the group ≥ 70 years. The older patients in the FU/LV arm received 6% fewer days of therapy and their dose intensity was 0.76 compared with 0.82 in the younger



group. In the XELOX arm, the older patients received approximately 18% fewer days of therapy and a dose intensity of approximately 0.6 compared with 0.78 in the younger group. Statistical analysis of these differences was not provided. Toxicity was not markedly different between the age groups.

The results of the NO106968 analysis appear to indicate that patients older than 70 years receive benefit from the use of XELOX rather than FU/LV since the hazard ratio for PFS is < 1.0, although the confidence interval is wide and crosses 1.0, preventing definitive conclusion.

Perspective

Dr Avery de Gramont provided his viewpoint on the presentation by Dr Haller. He began by reminding the audience that the evidence is clear that elderly patients with colorectal cancer benefit from chemotherapy in both the adjuvant and metastatic settings. The question is whether regimens that include drugs in addition to a fluoropyrimidine are of benefit in elderly patients with mCRC. This is a critical issue since more than 50% of patients diagnosed are over 70 years, although the population in most trials contains fewer than 20% from this age group. The ACCENT results from ASCO 2009 have resulted in changes in German treatment guidelines, the PETACC-8 trial design, and to some degree, clinical practice in the UK and US.

The ACCENT analysis included trials with stage 2 patients as well as stage 3: MOSAIC, NSABP C-07, CALGB 89803, PETACC 3, NSABP C-06, and X-ACT. These trials compared intravenous FU/LV to FOLFOX4, FLOX, IFL, FOLFIRI, uracil/tegafur, or capecitabine, respectively. A sub-group analysis combining these studies into oral, oxaliplatin, and irinotecan regimens showed that there was a detrimental effect on disease-free survival (DFS) and OS compared to FU/LV, although the confidence intervals, like in NO106986, crossed 1.0. Limitations in the ACCENT analysis include the relatively small number of patients (approximately 700), and that there were only 2 trials in each treatment subgroup, different fluoropyrimidine control regimens, and no data on toxicity, dose-intensity, and co-morbidities.

Dr de Gramont displayed unpublished data from the MOSAIC trial to put these results in perspective. Plots were shown where the DFS in patients older than 70 years was slightly higher with FOLFOX4 than FU/LV (HR 0.914, 95% CI 0.633-1.343) but there was no difference in OS. Proposed causes for this were that the elderly group who received FOLFOX4 had increased toxicity during treatment, were less likely to receive intensive post-relapse therapy (chemotherapy or surgery), and were more likely to experience non-colon cancer deaths. These observations could be explained by either patient-related or physician-related factors.

His conclusions were that for the elderly:

- Capecitabine alone, in stage 3 patients, might be a reasonable option
- XELOX or FOLFOX can still be considered for the DFS advantage
 - The AVANT trial is comparing these regimens in combination with bevacizumab
- OS may be improved with a more intensive management of relapse or second cancer
- Reduced duration of chemotherapy should be tested
 - The IDEA pooled analysis is evaluating this question

HEPATOCELLULAR CARCINOMA

Okita K, Imanaka K, Chida N, et al. Phase III study of sorafenib in patients in Japan and Korea with advanced hepatocellular carcinoma treated after transarterial chemoembolization (TACE). Abstract LBA 128.

Transarterial chemoembolization (TACE) has become a preferred approach to management of intermediate stage hepatocellular carcinoma (HCC). A clinical trial evaluating the efficacy of sorafenib in prolonging the time to progression (TTP) and preserving liver function was reported. Patients with unresectable HCC and Child-Pugh A disease with $\geq 25\%$ tumor necrosis or shrinkage after TACE (1 to 3 treatments) were randomized to sorafenib 400 mg bid or placebo (229

in each arm). There was no difference in the primary endpoint of TTP by central review (HR 0.87, 95% CI 0.70-1.09, $P = 0.25$). OS was similar in each arm. Median duration of treatment was 17 weeks in the sorafenib group, compared with 20 weeks in the placebo group. Adverse events are shown in **Table 5**. Treatment was discontinued due to adverse events in 45% of the sorafenib patients and 7% of the placebo patients.

Table 5. Adverse events in post-TACE HCC trial

	All grades (% of patients)		Grade 3/4 (% of patients)	
	Sorafenib	Placebo	Sorafenib	Placebo
HFSR	82	7	35	0
Alopecia	42	4	NR	NR
Rash/desquamation	43	16	NR	NR
Diarrhea	36	12	6	2
Hypertension	33	9	16	2

HFSR = hand/foot skin reaction

Raoul J, Sherman M, Nadel A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subgroup analysis of the SHARP trial by baseline transaminases/alpha-fetoprotein and bilirubin levels. Abstract 129.

Previously reported in the *New England Journal of Medicine* in 2008, the pivotal randomized, phase III, SHARP trial concluded that sorafenib was statistically significantly superior to placebo in terms of OS (median 10.7 months vs 7.9 months, respectively) in patients with Childs-Pugh A, advanced HCC. A subsequent exploratory analysis of the SHARP trial database was conducted to determine if indicators of liver function (alfa-fetoprotein [AFP] and transaminases) were associated with poorer outcomes or if sorafenib influenced bilirubin levels. There was no difference in disease control rate, TTP, or OS based on transaminases or AFP levels. Sorafenib produced a modest initial increase in bilirubin level that had returned to baseline by the end of treatment.

Sangro R, Carpanese L, Cianni R, et al. European multicenter evaluation of survival for patients with hepatocellular carcinoma treated by radioembolization (RE) with ⁹⁰Y-labelled resin microspheres. Abstract 130.

The prognosis of HCC patients who have received RE with ⁹⁰Y microspheres has not been studied in a large controlled trial. Eight European centers treated 252 consecutive patients with the agent from 2003 to 2009 and reported their observations. The population was relatively unfavorable in that 53% had bilobar disease, 16% had some degree of portal vein occlusion, and most had poor BCLC stage (50% stage B and 37% stage C). Almost all patients received a single treatment with the median activity of 1.5 GBq. The median survival was 14.5 months. CLIP score, bilirubin, number of nodules, and presence of extrahepatic disease (EHD) were strong indicators of prognosis (**Table 6**). Limited toxicity information is available due to the retrospective nature of this report.

Table 6. Relationship of clinical parameters and outcome after radioembolization

Parameter	Survival (mo)	P
CLIP score		
0	24.4 (9.6-NR)	< 0.001
1	20.8 (14.9-23.2)	
2	10.9 (8.6-15.3)	
3/4	7.6 (6.5-11.7)	
Child-Pugh class		
A	16.8 (13.8-20.8)	< 0.001
B	10.3 (7.4-12.6)	
C	2.4 (0.4-4.4)	
Number of nodules		
≤ 5	19.1 (14.9-23.7)	< 0.001
> 5	8.3 (7.2-11.4)	
Extrahepatic disease		
Positive	15.3 (12.4-19.4)	0.005
Negative	7.5 (4.3-14.9)	

Discussion

Dr Anthony El-Khoueiry from the University of Southern California discussed the HCC presentations. He proposed a number of reasons for the negative results in the study of post-TACE sorafenib. Most patients had only 1 TACE treatment (that may not have been “optimal” locoregional therapy based on average interventions in most TACE studies), the duration of sorafenib was rather short, and there was a high discontinuation rate due to adverse events. There was also considerable heterogeneity in the population in that the majority of patients had 3 lesions or less; yet up to 10 lesions were allowed, perhaps masking effects in some subgroups. A theoretical concern has been raised by recent research showing that patients who do not respond to local TACE therapy may have the highest levels of neoangiogenic activity such that delayed administration of a VEGF inhibitor like sorafenib may be suboptimal. Therefore, clinicians should await the results of ECOG 1208, which incorporates sorafenib or placebo prior to and during TACE (up to 4 courses in the absence of disease progression or unacceptable toxicity), before arriving at a conclusion on the role of sorafenib in this setting.

The information on ⁹⁰Yttrium therapy indicates that the agent can be considered in treatment of unresectable HCC, but comparisons between it, TACE and drug-eluting bead embolization have not been done. Whether any of these options is safer in patients with portal vein occlusion or severe liver disease would be valuable information. Regarding the subgroup analysis of the SHARP trial, Dr El-Khoueiry acknowledged that the safety and efficacy of sorafenib have been established in patients with Child-Pugh A cirrhosis, but cautioned that information remains lacking for Child-Pugh B patients.

PANCREATIC CARCINOMA

Crane CH, Varadhachary GR, Javle MM, et al. Multi-institutional phase II trial of induction cetuximab, gemcitabine, and oxaliplatin, followed by radiotherapy with concurrent capecitabine, and cetuximab, for locally advanced pancreatic adenocarcinoma (LAPC). Abstract 132.

This phase II trial enrolled 69 treatment-naïve patients with locally advanced pancreatic adenocarcinoma (LAPC) and ECOG PS 0 or 1. Gemcitabine (1000 mg/m²), oxaliplatin (100 mg/m²), and cetuximab (500 mg/m²) were administered every 2 weeks for 4 doses. Patients without progression were subsequently treated with 50.4 Gy to the local tumor and concurrent capecitabine (825 mg/m² on the days of radiation) and cetuximab (500 mg/m² every 2 weeks). Thereafter, gemcitabine and cetuximab were continued until progression. At a median follow-up is 12.5 months, the median, 1-year, 30-month actuarial OS are 19 months (95% CI 14.3-23.7), 66.7% (95% CI 60.2-73.2), and 18.4% (95% CI 10.4-26.4), respectively. Best radiographic response measured 6 weeks after completion of chemoradiotherapy is partial response in 19%, minor response in 17%, stable disease in 48%, and progressive disease in 15%. Four patients were able to undergo R0 resection. The worst acute toxicity during any part of therapy (grade 2/3, respectively) was gastrointestinal 30%/7%, fatigue 25%/2%, paresthesias 12%/2%, and acneiform rash 60%/2%. Grade 3/4 hematologic events occurred in 14%. Serious adverse events related to treatment were 5 episodes of cholangitis and 4 episodes of dehydration requiring admission. The authors concluded that the primary endpoint (1-year OS > 45%) was met and the regimen should be studied further.

GASTROINTESTINAL STROMAL CELL TUMORS

Blackstein ME, Conless CL, Ballman KV, et al. Risk assessment for tumor recurrence after surgical resection of localized primary gastrointestinal stromal tumor (GIST): North American Intergroup phase III trial ACOSOG 29001. Abstract 6.

This research team published the positive results of a phase III, randomized, double-blind, placebo-controlled trial of adjuvant imatinib for 1 year after gross resection of *KIT*-positive tumors at least 3 cm in size in the *Lancet* in 2009. The trial was stopped based on an interim analysis. Updated efficacy results and an analysis of pathologic data in relationship to recurrence were presented at the GI Cancers

Symposium. At a median follow-up of 20 months, 2-year DFS was 91% in the imatinib group and 74% in the placebo group. Multivariate analysis revealed several parameters that predicted recurrence: high mitotic rate scored in a central laboratory (HR 11.3, $P < 0.0001$), tumor size (HR 2.0, $P < 0.0001$), and small bowel location (HR 1.7, $P = 0.02$). Miettinen risk score was low in 45% of patients, moderate in 24%, and high in 31%. In the imatinib and placebo arms, respectively, 2-yr relapse-free survival was 98% vs 98% ($P = 0.92$) in low-risk patients, 98% vs 76% ($P = 0.05$) for moderate-risk patients, and 77% vs 41% for high-risk patients ($P < 0.0001$). It appears that mitotic index, size, and location are useful indicators that can be used to select for alternate approaches to adjuvant therapy or recurrence monitoring in the future.

ANAL CARCINOMA

Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US. GI Intergroup RTOG 98-11 phase III trial. Abstract 285.

This trial randomized patients to 2 cycles of FU/mitomycin concurrent with radiation therapy 45 to 59 Gy or induction chemotherapy with 2 cycles of FU/cisplatin followed by 2 cycles of the FU/cisplatin concurrent with radiation therapy 45 to 59 Gy. The primary endpoint was DFS. The initial publication in *JAMA* in 2008 reported no statistically significant difference in 5-year DFS between the 644 patients in the 2 treatment arms (60% vs 54%, respectively), although there was a significantly lower rate of colostomy for mitomycin-based regimen compared to the cisplatin-based regimen (10% vs 19%, $P = 0.02$). This secondary analysis found that colostomy failure was related to tumor (T) category and not the tumor-node (TN) category, while patients with 2 high-risk TN factors have higher relapse rates and poorer survival than those with one high-risk factor, as follows:

- Best prognosis T2-3/N0
- Intermediate prognosis T4/N0 and T2/N1-3
- Worst prognosis T3-4/N1-3

Significant challenges remain in improving outcomes for patients with anal carcinoma, but this analysis gives investigators direction in developing treatment strategies based on level of recurrence risk.


GASTRIC CARCINOMA

Sasako M, Sano T, Tsuburaya A, et al. Final results of a surgical, randomized controlled trial (JCOG9502): left thoracoabdominal (LT) approach compared with abdominal and transhiatal (AT) approach for cardia or subcardia cancer. Abstract 3.

Japanese investigators reported the final long-term survival results of this trial compared the left thoracoabdominal (LT) and abdominal and transhiatal (AT) surgical approaches. Initially published in 2006, eligibility included patients age 75 or younger with esophageal invasion of 3 cm or less, clinical stage T2-T4, and lack of distant metastases. Lymph node dissection was similar with each procedure and no adjuvant therapy was allowed. The primary endpoint was OS. Median follow-up time is now 7.7 years in the 167 randomized patients. The LT approach was associated with 3 post-operative deaths (compared with none in the AT approach) and produced greater morbidity, including deterioration in respiratory function (vital capacity and PaO₂). Median 5-year OS rates were 51% in the AT group and 37% in the LT group although the hazard ratios were not statistically significant. This study update confirms that the AT approach is preferred for advanced gastric adenocarcinoma with esophageal invasion ≤ 3 cm.

Winder T, Zhang W, Yang D, et al. Association of germline polymorphism in the CD44 gene with clinical outcome in localized gastric adenocarcinoma. Abstract 2.

CD44 is a transmembrane glycoprotein important in cell adhesion, migration, and lymphocyte activation. In gastric adenocarcinoma, CD44 has been associated with high rates of cell division, metastasis, and poorer prognosis. Investigators at a single institution analyzed blood or formalin-fixed paraffin-embedded tissue



samples from 104 patients diagnosed from 1992 to 2008 for germline variations. Those carrying a single nucleotide polymorphism with at least one G allele at rs187116 had a significantly shorter time to recurrence than those with A/A genotype in a multivariate analysis including after adjustment for chemotherapy, nodal status, and race (2.1 years vs 7.0 years, adjusted $P = 0.019$). CD44 polymorphism is a candidate for further prospective study and if validated, could play a role in selecting patients for post-operative therapy and may be a target for drug development.

LISTING OF SELECTED PRESENTATIONS OF FAVORABLE PHASE I TRIALS

Javle MM, Varadhachary GR, Bhosale P, et al. Phase I study of MK-0646, a humanized monoclonal antibody against IGF-1R in combination with gemcitabine or gemcitabine plus erlotinib for advanced previously untreated pancreatic cancer. Abstract 131.

Chang KJ, Senzer NN, Soetikno R, et al. Long-term survival analysis of multicenter clinical trial using endoscopy and endoscopic ultrasound-guided fine needle injection of antitumor agent (TNFerade Biologic [TNF]) in patients with locally advanced esophageal cancer. Abstract 45.

CONCLUSION

This annual multidisciplinary meeting continues to provide a forum for the dissemination of new research results and multi-disciplinary discussions across the entire spectrum of GI cancers. Furthermore, it remains an excellent opportunity for investigators in the earlier phases of their careers to interact with an international group of GI oncologists on a more personal level and to present their data in a welcoming environment. Increasingly, the scientific abstracts are focusing on therapy tailored to disease biology such as *KRAS* or *BRAF* mutations or germline genetic polymorphisms, or to clinical features such as age in colorectal cancer or clinical presentation in GIST. These advances, while sometimes limited in scope or representing small

incremental improvements, allow us to personalize therapy, optimize outcome, and minimize toxicity. The use of biomarkers to guide clinical decision making is a welcome revolution and challenges our traditional paradigms for development of drugs and treatments for optimal use of more invasive diagnostic studies. This annual symposium is a catalyst for new ideas, new directions, and new teamwork and can be expected to add value to the field for years to come.



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