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LBA4 A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08

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This 2-arm randomized prospective study was conducted to determine whether mFOLFOX6 (modified fluorouracil [5-FU], leucovorin, oxaliplatin) plus bevacizumab would prolong disease-free survival (DFS) compared to mFOLFOX6 alone. The study randomized 2,672 patients with stage II or III colon cancer between September 2004 and October 2006; patients were randomized to receive either mFOLFOX6 (5-FU: 400 mg/m² IV bolus [day 1], 2,400 mg/m² continuous infusion over 46 hrs [day 1 and 2] every 14 days x 12 cycles; oxaliplatin: 85 mg/m² IV [day 1]; leucovorin: 400 mg/m² IV [day 1]) or mFOLFOX6 (same regimen) plus bevacizumab (5 mg/kg IV every 2 weeks x 1 year). The primary study endpoint was DFS; DFS events were defined as first recurrence, second primary cancer, or death. Study findings demonstrated a median follow-up of 36 months for patients who were still alive. An initial benefit that declined over time was seen in patients treated with bevacizumab; the smoothed estimate of DFS hazard ratio (HR) suggested that bevacizumab significantly decreased the risk of a DFS event between 6 months and 1 year (HR, 0.89; 95% confidence interval [CI], 0.76–1.04; *P*=.15). The investigators concluded that the addition of bevacizumab to mFOLFOX6 did not produce

a statistically significant prolongation in DFS (Table 1); however, a transient benefit was observed during the 1-year interval that bevacizumab was administered.

LBA4505 ESPAC-3(v2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma

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Clinical trials studying adjuvant 5-FU/FA (ESPAC-1 trial) and gemcitabine (CONKO-001 trial) therapy compared with no chemotherapy have demonstrated an improved survival for patients with resected pancreatic cancer. The current study, ESPAC-3 (v2), compared 5-FU/FA and gemcitabine to determine if either adjuvant chemotherapy produced better survival. From July 2000 to January 2007, 1,088 patients from 16 countries with an R0/R1 resection for pancreatic ductal adenocarcinoma were randomized to receive either 5-FU/FA (n=551; FA: 20 mg/m² IV bolus injection followed 5-FU: 425 mg/m² IV bolus injection on days 1–5 every 28 days) or gemcitabine (n=537; 1,000 mg/m² IV infusion on day 1, 8, and 15 every 4 weeks) for 6 months. The primary study endpoint was overall survival (OS), and secondary endpoints included toxicity, progression-free survival (PFS), and quality of life. Median age was 63 years (range, 31–85 years), and 598 (55%) patients were male. The patients had a median tumor size of 30 mm (range, 20–350 mm); 384 (35%) had R1 resections; 777 (72%) were node positive; and 263 (25%) had poorly differentiated tumors. Patients in the intent-to-treat population with a minimum follow-up of 2 years were included in the final analysis after 753 (69%) patients had died. The remaining 335 patients had a median follow-up of 34.2 months (range, 27.1–43.4 months),

Table 1. Safety Results of NSABP C-08

Treatment	N	# Events	3-year DFS	P Value
mFF6	1,338	312	75.5	
mFF6+B	1,334	291	77.4	.15

which was similar in the 2 treatment groups. The median survival for patients treated with 5-FU/FA was 23 months (95% CI, 21.1–25 months), and 23.6 months (95% CI, 21.4–26.4 months) for patients treated with gemcitabine. The findings showed no major difference in the effect of treatment across treatment subgroups according to resection status ($P=.56$) and no significant variance in survival between adjuvant 5-FU/FA and gemcitabine.

LBA4509 Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC)

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HER2 overexpression has been reported in as many as 35% of stomach and gastroesophageal tumors. Trastuzumab, a monoclonal antibody against HER2 has been seen to confer a survival benefit when administered with chemotherapy in patients with HER2-positive early and metastatic cancer. This study (ToGA) was the first randomized, prospective, multicenter, phase III trial to evaluate the safety and efficacy of trastuzumab in HER2-positive gastric cancer. Enrolled patients had HER2-positive gastroesophageal and gastric adenocarcinoma (locally advanced, recurrent, or metastatic). A total of 594 patients were randomized 1:1 to receive trastuzumab plus chemotherapy (5-FU or capecitabine and cisplatin) every 3 weeks for 6 cycles or chemotherapy alone; trastuzumab was administered until the disease progressed. Study sites included Europe, Latin America, and Asia. The primary study endpoint was OS and secondary endpoints comprised overall response rate (ORR), PFS, time to progression, duration of response, and safety. An interim analysis was planned at 75% of deaths, with a median follow-up of 17.1 months. The investigators centrally tested tumors from 3,807 patients for HER2 status: 22.1% of tumors were HER2 positive. Baseline characteristics were similar in both arms. The results showed a significantly improved median OS in patients receiving trastuzumab plus chemotherapy compared to patients receiving chemotherapy alone (13.5 vs 11.1 months; HR, 0.74; 95% CI, 0.60–0.91; $P=.0048$). Patients in the trastuzumab plus chemotherapy arm had an ORR of 47.3% versus 34.5% in the chemotherapy alone group ($P=.0017$). Toxicity profiles were similar in both arms and no unexpected adverse events were noted when trastuzumab was added to chemotherapy. Additionally, there was no difference in symptomatic congestive heart failure between groups;

however, asymptomatic left ventricular ejection fraction decreases were observed in 4.6% of patients receiving trastuzumab and chemotherapy and in 1.1% of patients receiving chemotherapy alone. Study findings showed that the combination of trastuzumab and chemotherapy was superior to chemotherapy alone. The prolonged survival seen with this combination supports the notion that trastuzumab is an effective and well-tolerated treatment for HER2-positive gastric cancer.

4000 A quantitative multigene RT-PCR assay for prediction of recurrence in stage II colon cancer: Selection of the genes in four large studies and results of the independent, prospectively designed QUASAR validation study

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Various development studies have been performed to determine the genes that predict recurrence and 5-FU/leucovorin (LV) benefit (The National Surgical Adjuvant Breast and Bowel Project [NSABP] C-01/C-02, $n=270$; CCF, $n=765$; NSABP C-04, $n=308$; and NSABP C-06, $n=508$). This study, which was undertaken to determine the clinical utility of the prespecified assay, was a large, independent, prospective clinical validation study in stage II colon cancer patients from the QUASAR trial. Reverse transcriptase polymerase chain reaction (RT-PCR) was used to quantify gene expression in 30- μm , microdissected fixed paraffin-embedded primary colon cancer tissue. Endpoints including recurrence-free interval, DFS, and OS, were analyzed by Cox regression. The combined analysis of the 4 development studies ($n=1,851$; 761 candidate genes) found that 48 genes were strongly associated with recurrence risk and 66 genes predicted a 5-FU/LV benefit. A multivariate analysis established 7 prognostic genes, 6 predictive genes, and 5 reference genes, along with separate prognostic recurrence score (RS) and predictive treatment score algorithms. The QUASAR validation study collected tumor blocks, which were available for 68% of patients: 1,490 patients with blocks had stage II colon cancer and RT-PCR was useful in 1,436 eligible patients (711 with surgery and 725 with surgery and 5-FU/LV). Median follow-up in the QUASAR study was 6.6 years. In the primary analysis of patients post surgery, RS was used to determine DFS ($P=.01$), OS ($P=.04$), and recurrence risk, which increased monotonically with increased RS ($P=.004$). In multivariate analyses, RS remained prognostically significant independent of mismatch repair, T stage, nodes examined, grade, and lymphovascular invasion. Study findings revealed a significant

5FU/LV benefit ($P<.001$) and determined that treatment score was not an effective predictor of 5FU/LV benefit. RS was however seen to be a valid independent predictor of recurrence risk for stage II colon cancer patients following surgery.

4010 Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: Findings from the ACCENT Database

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Because previous studies have proposed that older and younger colon cancer patients receive similar therapeutic benefit from intravenous fluoropyrimidine (FU) adjuvant therapy, the investigators of this trial evaluated the impact of adjuvant therapy (combination and/or oral FU) on colon cancer recurrence and mortality in patients younger than 70 years and in patients 70 years or older. Data from the ACCENT database were col-

lected for 10,499 patients younger than 70 years and 2,170 patients 70 years or older from 6 phase III adjuvant trials that compared intravenous FU to combinations with irinotecan or oxaliplatin, or oral FU in stage II/III colon cancer. Study endpoints included OS, DFS, and time to recurrence (TTR). The study results identified 75% of patients with stage III disease, 74% of whom were less than 70 years and 77% who were 70 years or older. In patients receiving the experimental therapy, OS, DFS, and TTR were statistically significantly improved compared to those patients in the control arm (IV FU) among patients younger than 70 years, but not among those older than 70 years (Table 2). Furthermore, the relation between age and type of treatment was statistically significant for all study endpoints (OS, DFS, TTR; $P=.01$) regardless of whether the therapy was oxaliplatin-based, irinotecan-based, or oral FU. Deaths within 6 months of adjuvant treatment were not significantly different between the treatment groups. The analysis showed that patients over 70 years do not receive the same benefit from combination and/or oral FU as those who are younger than 70 years in terms of OS, DFS, and TTR.

Table 2. Safety Findings from ACCENT Database

Treatment Arm	Endpoint Hazard Ratio (95% Confidence Interval)			Deaths within 6 months, Experimental vs Control % (P -value)
	Overall Survival*	Disease-free Survival*	Time to Recurrence*	
Overall				
<70 years	0.84 (0.79–0.91)	0.85 (0.79–0.91)	0.85 (0.79–0.91)	0.89 vs 0.79 ($P=.6$)
≥70 years	1.13 (0.96–1.32)	1.11 (0.97–1.28)	1.13 (0.97–1.32)	2.71 vs 2.11 ($P=.4$)
Oxaliplatin-based				
<70 years	0.81 (0.71–0.93)	0.77 (0.68–0.86)	0.76 (0.67–0.86)	0.81 vs 0.81 ($P=1.0$)
≥70 years	1.18 (0.90–1.57)	1.04 (0.81–1.35)	0.93 (0.70–1.24)	2.57 vs 1.37 ($P=.3$)
Irinotecan-based				
<70 years	0.88 (0.78–1.01)	0.90 (0.80–1.00)	0.88 (0.79–0.98)	0.90 vs 0.43 ($P=.1$)
≥70 years	1.14 (0.88–1.47)	1.17 (0.93–1.48)	1.33 (1.02–1.73)	3.96 vs 2.43 ($P=.3$)
Oral Fluoropyrimidine				
<70 years	0.89 (0.78–1.02)	0.89 (0.79–1.01)	0.90 (0.79–1.02)	0.98 vs 1.25 ($P=.5$)
≥70 years	1.19 (0.90–1.57)	1.15 (0.92–1.45)	1.18 (0.91–1.53)	1.68 vs 2.50 ($P=.4$)

* Values > 1 favor control treatment