

Supplemental Table 1. Trials and treatment arms included in this analysis

Trial	Reference	Treatment Group	Treatment	Patients
NCCTG-78-48-52	Laurie, J. A., Moertel, C. G., Fleming, T. R., Wieand, H. S., Leigh, J. E., Rubin, J., ... Mailliard, J. (1989). Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. <i>Journal of Clinical Oncology</i> , 7(10), 1447–1456. doi: 10.1200/jco.1989.7.10.1447	5FU	5FU+LEV	121
NCCTG-87-46-51	Oconnell, M. J., Mailliard, J. A., Kahn, M. J., Macdonald, J. S., Haller, D. G., Mayer, R. J., & Wieand, H. S. (1997). Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. <i>Journal of Clinical Oncology</i> , 15(1), 246–250. doi: 10.1200/jco.1997.15.1.246	5FU	5FU+LV	53
INT-0035	Moertel, C. G., Fleming, T. R., MacDonald, J. S., Haller, D. G., Laurie, J. A., Goodman, P. J., ... Mailliard, J. A. (1990). Levamisole and Fluorouracil for Adjuvant Therapy of Resected Colon Carcinoma. <i>The New England Journal of Medicine</i> , 322(6), 352–358.	5FU	5FU+LEV	457
FFCD	International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. <i>Lancet</i> , 345, 939-944	5FU	5FU+LV	127
NCIC	International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. <i>Lancet</i> , 345, 939-944	5FU	5FU+LV	180
SIENA	Francini, G., Petrioli, R., Lorenzini, L., Mancini, S., Armenio, S., Tanzini, G., ... Lorenzi, M. (1994). Folinic Acid and 5-Fluorouracil as Adjuvant Chemotherapy in Colon	5FU	5FU+LV	118

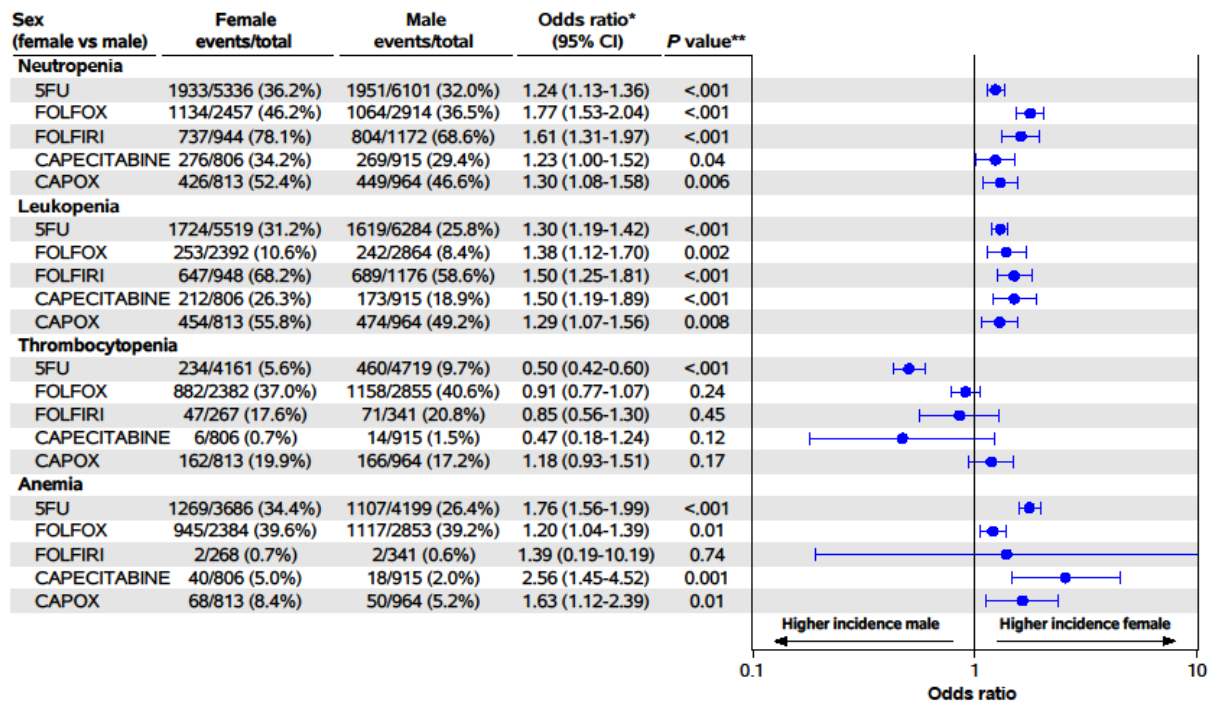
	Cancer. <i>Gastroenterology</i> , 106(4), 899–906.			
GIVIO	International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. <i>Lancet</i> , 345, 939-944	5FU	5FU+LV	376
NCCTG-89-46-51	O'Connell, M. J., Laurie, J. A., Kahn, M., Fitzgibbons, R. J., Erlichman, C., Sheperd, L., ... Figueredo, A. (1998). Prospectively Randomized Trial of Postoperative Adjuvant Chemotherapy in Patients With High-Risk Colon Cancer. <i>Journal of Clinical Oncology</i> , 16(1), 295–300.	5FU	5FU+LEV x 1yr	228
		5FU	5FU+LEV x 6 mos	230
		5FU	5FU+LEV+LV x 1yr	232
		5FU	5FU+LEV+LV x 6 mos	225
NCCTG-91-46-53	Oconnell, M. J., Sargent, D. J., Windschitl, H. E., Shepherd, L., Mahoney, M. R., Krook, J. E., ... Kugler, J. W. (2006). Randomized Clinical Trial of High-Dose Levamisole Combined with 5-Fluorouracil and Leucovorin as Surgical Adjuvant Therapy for High-Risk Colon Cancer. <i>Clinical Colorectal Cancer</i> , 6(2), 133–139. doi: 10.3816/cc.2006.n.030	5FU	High Dose LEV+5FU/CF	437
		5FU	Standard Dose LEV+5FU/CF	441
S9415	Poplin, E. A., Benedetti, J. K., Estes, N. C., Haller, D. G., Mayer, R. J., Goldberg, R. M., ... Macdonald, J. S. (2005). Phase III Southwest Oncology Group 9415/Intergroup 0153 Randomized Trial of Fluorouracil, Leucovorin, and Levamisole Versus Fluorouracil Continuous Infusion and Levamisole for Adjuvant Treatment of Stage III and High-Risk Stage II Colon Cancer. <i>Journal of Clinical Oncology</i> , 23(9), 1819–1825. doi: 10.1200/jco.2005.04.169	5FU	5FU/LV+LEV	632
		5FU	CI 5FU/LV	556
C02	Wolmark, N., Rockette, H., Wickerham, D. L., Fisher, B., Redmond, C., Fisher, E. R., ... Frazier, T. (1990). Adjuvant therapy of Dukes A, B, and C adenocarcinoma of the colon with portal-vein fluorouracil hepatic infusion: preliminary results of National Surgical Adjuvant Breast and Bowel Project Protocol C-02. <i>Journal of Clinical Oncology</i> , 8(9), 1466–1475. doi: 10.1200/jco.1990.8.9.1466	5FU	Surg+5-FU	342

C03	Wolmark, N., Rockette, H., Fisher, B., Wickerham, D. L., Redmond, C., Fisher, E. R., ... Jochimsen, P. (1993). The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. <i>Journal of Clinical Oncology</i> , 11(10), 1879–1887. doi: 10.1200/jco.1993.11.10.1879	5FU	5-FU+Leuc	519
		5FU	MOF	523
C04 (v 1)	Wolmark, N., Rockette, H., Mamounas, E., Jones, J., Wieand, S., Wickerham, D., ... Fisher, B. (1999). Clinical Trial to Assess the Relative Efficacy of Fluorouracil and Leucovorin, Fluorouracil and Levamisole, and Fluorouracil, Leucovorin, and Levamisole in Patients With Dukes B and C Carcinoma of the Colon: Results From National Surgical Adjuvant Breast and Bowel Project C-04. <i>Journal of Clinical Oncology</i> , 17(11), 3553–3559. doi: 10.1200/jco.1999.17.11.3553	5FU	5FU+LEV	693
		5FU	5FU+LV	693
		5FU	5FU+LV+LEV	697
C05	Wolmark, N., Bryant, J., Smith, R., Grem, J., Allegra, C., Hyams, D., ... Fisher, B. (1998). Adjuvant 5-Fluorouracil and Leucovorin With or Without Interferon Alfa-2a in Colon Carcinoma: National Surgical Adjuvant Breast and Bowel Project Protocol C-05. <i>JNCI Journal of the National Cancer Institute</i> , 90(23), 1810–1816. doi: 10.1093/jnci/90.23.1810	5FU	5FU+LV	1070
		5FU	5FU+LV+Interferon	1066
GERCOR	André, T., Colin, P., Louvet, C., Gamelin, E., Bouche, O., Achille, E., ... Gramont, A. D. (2003). Semimonthly Versus Monthly Regimen of Fluorouracil and Leucovorin Administered for 24 or 36 Weeks as Adjuvant Therapy in Stage II and III Colon Cancer: Results of a Randomized Trial. <i>Journal of Clinical Oncology</i> , 21(15), 2896–2903. doi: 10.1200/jco.2003.10.065	5FU	5FU+LV	439
		5FU	FUFOL	442
INT-0089 (v HDLV)	Haller, D. G., Catalano, P. J., Macdonald, J. S., O'Rourke, M. A., Frontiera, M. S., Jackson, D. V., & Mayer, R. J. (2005). Phase III Study of Fluorouracil,	5FU	HDLV	838
		5FU	LEV	829

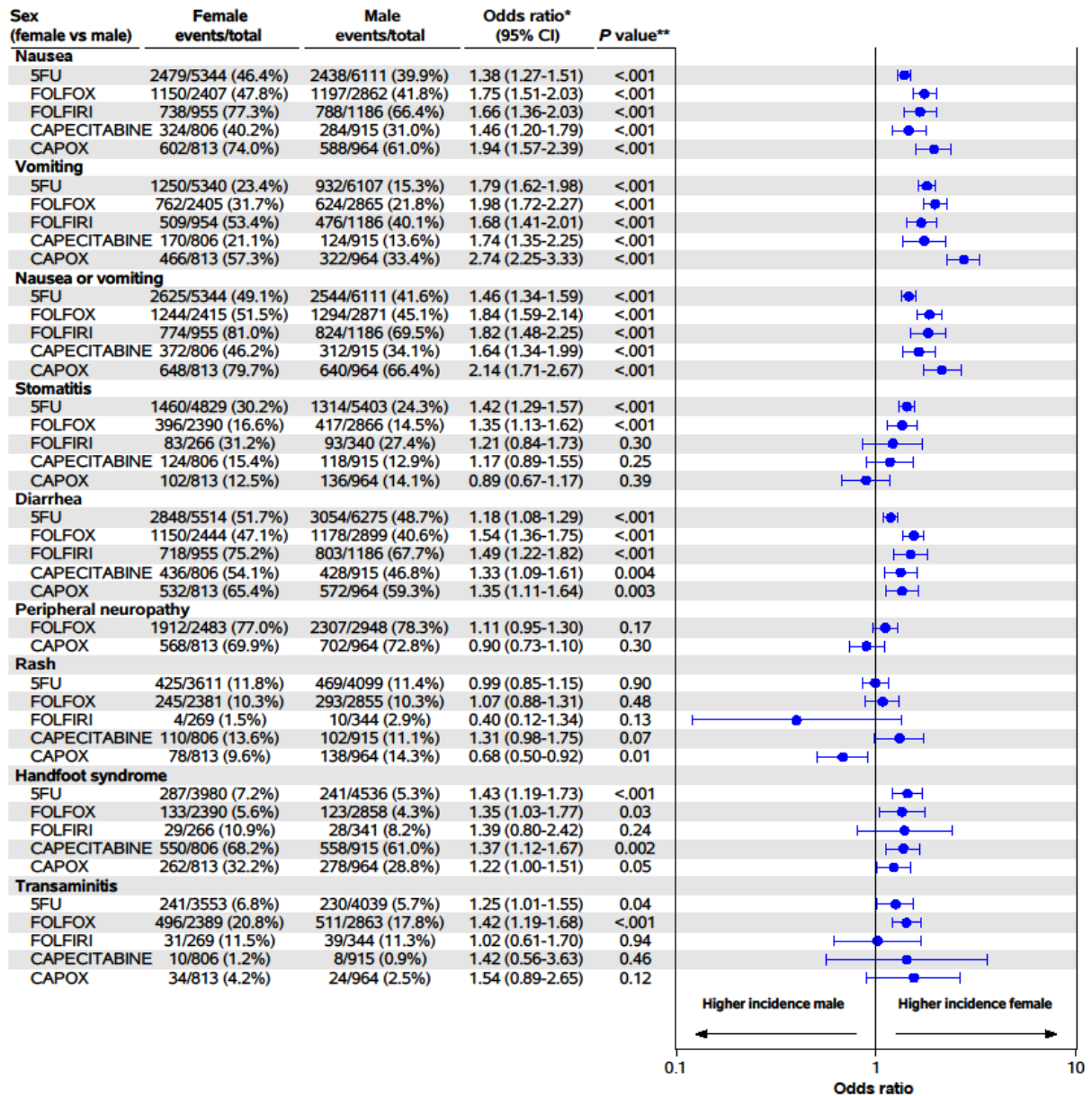
	Leucovorin, and Levamisole in High-Risk Stage II and III Colon Cancer: Final Report of Intergroup 0089. <i>Journal of Clinical Oncology</i> , 23(34), 8671–8678. doi: 10.1200/jco.2004.00.5686	5FU	LDLV	841
		5FU	LEV+LDLV	821
MOSAIC	André, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T., ... de Gramont, A. (2004). Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. <i>New England Journal of Medicine</i> , 350(23), 2343–2351. doi: 10.1056/nejmoa032709	5FU	LV5FU2	1095
		FOLFOX	LV5FU2+OXALIPLATIN	1105
XACT	Twelves, C., Wong, A., Nowacki, M., Abt, M., Burris, H., Carrato, A., ... Scheithauer, W. (2005). Capecitabine as Adjuvant Treatment for Stage III Colon Cancer. <i>The New England Journal of Medicine</i> , 352(26), 2696–2704.	5FU	5-FU + LEUCOVORIN	1868
		CAPECITABINE	CAPECITABINE	1914
C06	Lembersky, B. C., Wieand, H. S., Petrelli, N. J., Oconnell, M. J., Colangelo, L. H., Smith, R. E., ... Wolmark, N. (2006). Oral Uracil and Tegafur Plus Leucovorin Compared With Intravenous Fluorouracil and Leucovorin in Stage II and III Carcinoma of the Colon: Results From National Surgical Adjuvant Breast and Bowel Project Protocol C-06. <i>Journal of Clinical Oncology</i> , 24(13), 2059–2064. doi: 10.1200/jco.2005.04.7498	5FU	5-FU+Leuc	776
C07	Kuebler, J. P., Wieand, H. S., Oconnell, M. J., Smith, R. E., Colangelo, L. H., Yothers, G., ... Wolmark, N. (2007). Oxaliplatin Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for Stage II and III Colon Cancer: Results From NSABP C-07. <i>Journal of Clinical Oncology</i> , 25(16), 2198–2204. doi: 10.1200/jco.2006.08.2974	5FU	5-FU+Leuc	778
		FOLFOX	FLOX	773
C89803	Saltz, L. B., Niedzwiecki, D., Hollis, D., Goldberg, R. M., Hantel, A., Thomas, J. P., ... Mayer, R. J. (2007). Irinotecan Fluorouracil Plus Leucovorin Is Not	5FU	5FU/LV	620

	Superior to Fluorouracil Plus Leucovorin Alone As Adjuvant Treatment for Stage III Colon Cancer: Results of CALGB 89803. <i>Journal of Clinical Oncology</i> , 25(23), 3456–3461. doi: 10.1200/jco.2007.11.2144	FOLFIRI	CPT11/5FU/LV	630
PETACC3	Van Cutsem, E., Labianca, R., Bodoky, G., Barone, C., Aranda, E., Nordlinger, B., ... Cunningham, D. (2009). Randomized Phase III Trial Comparing Biweekly Infusional Fluorouracil/Leucovorin Alone or With Irinotecan in the Adjuvant Treatment of Stage III Colon Cancer: PETACC-3. <i>Journal of Clinical Oncology</i> , 27(19), 3117–3125. doi: 10.1200/jco.2008.21.6663	5FU	5FU/FA Alone	1605
		FOLFIRI	CPT-11+5FU/FA	1583
XELOXA (N016968)	Schmoll, H.-J., Tabernero, J., Maroun, J., De Braud, F., Price, T., Van Cutsem, E., ... Haller, D. G. (2015). Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the N016968 Randomized Controlled Phase III Trial. <i>Journal of Clinical Oncology</i> , 33(32), 3733–3740. doi: 10.1200/jco.2015.60.9107	5FU	5-FU/LV	1812
		CAPOX	XELOX	1864
C08	Allegra, C. J., Yothers, G., Oconnell, M. J., Sharif, S., Petrelli, N. J., Colangelo, L. H., ... Wolmark, N. (2011). Phase III Trial Assessing Bevacizumab in Stages II and III Carcinoma of the Colon: Results of NSABP Protocol C-08. <i>Journal of Clinical Oncology</i> , 29(1), 11–16. doi: 10.1200/jco.2010.30.0855	FOLFOX	mFOLFOX6	1317
PETACC8	Taieb, J., Tabernero, J., Mini, E., Subtil, F., Folprecht, G., Van Laethem, J.-L., ... Lepage, C. (2014). Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. <i>The Lancet Oncology</i> , 15(8), 862–873. doi: 10.1016/s1470-2045(14)70227-x	FOLFOX	FOLFOX	1263
N0147	Alberts, S., Sargent, D., Nair, S., Mahoney, M., Mooney, M., Thibodeau, S., ... Goldberg, R. (2012). Effect of Oxaliplatin, Fluorouracil, and Leucovorin	FOLFOX	FOLFOX	476

	With or Without Cetuximab on Survival Among Patients With Resected Stage III Colon Cancer. <i>Jama</i> , 307(13), 1383–1393. doi: 10.1001/jama.2012.385			
AVANT	De Gramont, A., Van Cutsem, E., Schmoll, H.-J., Tabernero, J., Clarke, S., Moore, M. J., ... Hoff, P. M. (2012). Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. <i>The Lancet Oncology</i> , 13(12), 1225–1233. doi: 10.1016/s1470-2045(12)70509-0	FOLFOX	FOLFOX-4	935



Supplemental Figure 1. Adjusted Odds Ratios (95% confidence intervals) for grade I-IV hematological toxicities (log base 10 scale). *Stratified by study and treatment arm, adjusted for age, stage grade, PS, and BMI; **Stratified Wald p-value; 5FU=Fluorouracil therapy, FOLFOX=Leucovorin + Fluorouracil + Oxaliplatin therapy, CAPOX=Capecitabine + Oxaliplatin therapy, CI=Confidence Interval, PS=Performance Status, BMI=Body Mass Index



Supplemental Figure 2. Adjusted Odds ratios (95% confidence intervals) for grade I-IV non-hematological toxicities (log base 10 scale). *Stratified by study and treatment arm, adjusted for age, stage grade, PS, and BMI; **Stratified Wald p-value; 5FU=Fluorouracil therapy, FOLFOX=Leucovorin + Fluorouracil + Oxaliplatin therapy, CAPOX=Capecitabine + Oxaliplatin therapy, CI=Confidence Interval, PS=Performance Status, BMI=Body Mass Index