

# BÖLÜM 14

## İlerlemiş kolorektal kanser kemoterapisinde tartışmalar

Çeviren: XXX  
XXX

### ANAHTAR NOKTALAR

- Tedavi edilmemiş metastatik kolorektal kanserde (mKRK) kombinasyon kemoterapisi (KT) standarttır. Ancak seçilmiş olgularda ardışık tedavi dikkate alınabilir.
- KRAS wild-tip hastaların tedavisinde biyolojik ajanların optimal bir sıralaması yoktur.
- Sınırlı KC metastatik hastalığında metastatektomi yaşam süresini uzatabilir ve olguların küçük bir kısmında kür sağlayabilir.
- Potansiyel hepato-toksisiteyi sınırlandırmak için konversiyon tedavisi 3-4 aya sınırlı olmalıdır.
- KT verilmeyen intervaller (CFI) mKRK'li bazı olgularda kabul edilebilir bir seçenektir.

### Giriş

ABD'de KRK ölümün 3. En sık [1]. Aşağı yukarı KRK'li olguların %50'sinde metastatic hastalık oluşur. Mevcut tedaviler yaşam süresini 24 ayın üstüne çıkarmıştır [2-18], ki bu da bu ajanların en etkilisini bulmada tartışma getirmiştir. Bu konuda KRAS wild-tip hastalıklı mKRK tedavisindeki bazı çelişkileri: ardışık mı kombinasyon mu, konversiyon tedavisini, CFI konularını irdelemektedir. Özellikle belirtilmedikçe 1. Basamak tedaviler kastedilmiştir.

**Olgu 2**

69 yaşında mKRK'li hasta 12 ay mFOLFOX6+Bev aldı, son 10 aydır parsiyel yanıtlı idi. Persisten grade 2 nöropati nedeniyle OX doz azaltımı gerkti. Halen günlük aktivitelerini sürdürmekte sorunu var.

2. Aşağıdakilerden hangi modifikasyonlar kabul edilebilirdir?

- A. 5-FU ve OX ve Bev en son dozlarda devam.
- B. OX kes, idame 5-FU ve Bev ile hastalık ilerlemesine kadar veya nörotoksisite düzeline kadar devam, OX düzeline OX yeniden verielbilir.
- C. KT'yi tam olarak kes, yakından takip et, hastalık ilerlemesi halinde KT başlamayı planla.
- D. OX dozunu 45 mg/m<sup>2</sup>'ye düşür ve tedaviye devam et.

**Kaynaklar**

- 1 Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010 Sep-Oct; 60(5): 277-300.
- 2 de Gramont A, Figuer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000 Aug; 18(16): 2938-47
- 3 Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004 Jan 1, 22(1): 23-30.
- 4 Saltz LB, Cox N Blake C, Rosen LS, Fernerbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer: the IRI-FLU Study Group. *N Engl J Med* 2000 Sep 28; 343(13): 905-14.
- 5 Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W Figuer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008 Apr 20; 26(12): 2013-19.
- 6 Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V Jeffery M, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 2007 Oct 20; 25(30): 4779-86.
- 7 Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. *J Clin Oncol* 2008 Feb 1, 26(4): 689-90.
- 8 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karapatakis P et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000 Mar 25; 355(9209): 1041-7

- 9 Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of paclitaxel plus irinotecan, fluorouracil, and oxaliplatin (FOLFIRI) versus FOLFIRI alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010 Nov 1, 28(31): 4697-705.
- 10 Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007 May 1, 25(13): 1670-6.
- 11 Fyfe GA, Hurwitz H, Fehrenbacher L, Cartwright T, Hainsworth J, Heim W et al. Bevacizumab plus irinotecan/5-FU / leucovorin for treatment of metastatic colorectal cancer: results in survival benefit in all pre-specified subgroups. *J Clin Oncol* 2004; 22( 14S).
- 12 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFIRI) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007 Apr 20; 25( 12) : 1539-44.
- 13 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004 Jun 3; 350(23): 2335-42.
- 14 Hurwitz H, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol* 2005 May 20; 23(15): 3502-8.
- 15 Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009 Apr 2; 360( 14): 1408-17
- 16 Bokemeyer C, Bondarenko I, Makhson A, Hartmann JT, Aparicio J, de Braud F, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009 Feb 10; 27 (5): 663-71.
- 17 Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011 Apr 18.
- 18 Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of paclitaxel plus irinotecan, fluorouracil, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010 Nov 1, 28(31): 4706-13.
- 19 Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, et al. Randomized trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998 Oct 31, 352(9138): 1407-12.
- 20 Cunningham D, Pyrhonen S, James RD, Pu nt CJ, Hickish TF, Heikkila R, et al. Randomized trial of irinotecan plus supportive care versus supportive care alone

- after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998 Oct 31, 352(9138): 1413-18.
- 21 Kim GP, Sargent DJ, Mahoney MR, Rowland KM, Jr, Philip PA, Mitchell E, et al. Phase III non-inferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. *J Clin Oncol* 2009 Jun 10; 27(17): 2848-54.
  - 22 Aranda E, Diaz-Rubio E, Cervantes A, Anton-Torres A, Carrato A, Massuti T, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with weekly high-dose 48-hour continuous-infusion fluorouracil for advanced colorectal cancer: a Spanish Cooperative Group for Gastrointestinal Tumor Therapy (TTD) study. *Ann Oncol* 1998 Jul; 9(7): 727-31.
  - 23 Jager E, Heike M, Bernhardt H, Kleino, Bernhardt G, Lautz D, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. *J Clin Oncol* 1996 Aug; 14(8): 2274-9.
  - 24 Buker TR, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Maillard JA, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *J Clin Oncol* 1994 Jan; 12(1): 14-20.
  - 25 de Gramont A, Bosser JF, Milane C, Rougier P, Bouche O, Etienne PL, et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997 Feb; 15(2): 808-15.
  - 26 Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989 Oct; 7(10): 1407-18.
  - 27 Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001 Apr 15; 19(8): 2282-92.
  - 28 Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001 Nov 1, 19(21): 4097-106.
  - 29 Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanaathan R, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil leucovorin: interim results of a phase III trial. *J Clin Oncol* 2003 Jun 1, 21(11): 2059-69.
  - 30 Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004 Apr 1, 22(7): 1209-14.

- 31 Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007 Jul 14; 370(9582): 143-52.
- 32 Koopman M, Antonini NF, Douma J, Wais J, Honkoop AH, Erdkamp FL, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007 Jul 14; 370(9582): 135-42.
- 33 Dy GK, Krook JE, Green EM, Sargent DJ, Delaunoy T, Morton RF, et al. Impact of complete response to chemotherapy on overall survival in advanced colorectal cancer: results from Intergroup N9741. *J Clin Oncol* 2007 Aug 10; 25(23): 3469-74.
- 34 Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004 Apr 1; 22(7): 1209-14.
- 35 Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, Wilson RH, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011 Jun 18; 377(9783): 2103-14.
- 36 Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pylhonen S, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: The NORDIC-VII Study. *J Clin Oncol* 20 May 2012; 30(15): 1755-62.
- 37 Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. *J Clin Oncol* 2008 Feb 1; 26(4): 689-90.
- 38 Van Cutsem E, Tabernero J, Lakomy R, Prausova J, Ruff P, Van Hazel G, et al. Intravenous (IV) aflibercept versus placebo in combination with irinotecan/5-FU (FOLFIRI) for second-line treatment of metastatic colorectal cancer (mCRC): results of a multinational phase III trial (EFC10262-VELOUR). *Ann Oncol* 2011; 22(5s).
- 39 Hurwitz HI, Yi J, Ince W, Novotny WF, Rosen O. The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-ras mutation status: analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer. *Oncologist* 2009 Jan; 14(1): 22-8.
- 40 Kemeny N. Management of liver metastases from colorectal cancer. *Oncology* 2006 Sep; 20(10): 1161-76, 1179; discussion 1179-80, 1185-6.
- 41 Alberts SR, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005 Dec 20; 23(36): 9243-9.
- 42 Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007 Oct 10; 25(29): 4575-80.

- 43 Adam R, Wichern DA, de Haas RJ, Ciaccio J, Levi F, Paul B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 2009 Apr 15; 27(15): 1829-35.
- 44 Masi G, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, et al. Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases. *Ann Surg* 2009 Mar; 249(3): 420-5.
- 45 Nordlinger B, Van Cutsem E, Rougier P, Iohne CH, Ychou M, Sobrero A, et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur J Cancer* 2007 Sep; 43(14): 2037-45.
- 46 Alberts SR, Horvath WL, Sternfeld WC, Goldberg RM, Mahoney MR, Dakhil SR, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005 Dec 20; 23(36): 9243-9.
- 47 Barone C, Nuzzo G, Cassano A, Basso M, Schinzari G, Giulante F, et al. Final analysis of colorectal cancer patients treated with irinotecan and 5-fluorouracil plus folinic acid neoadjuvant chemotherapy for unresectable liver metastases. *Br J Cancer* 2007 Oct 22; 97(8): 1035-9.
- 48 Ychou M, Viret F, Kramar A, Desseigne F, Mitry E, Guimbaud R, et al. Tritherapy with fluorouracil/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX): a Phase II study in colorectal cancer patients with non-resectable liver metastases. *Cancer Chemother Pharmacol* 2008 Jul; 62(2): 195-201.
- 49 Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D, et al. Resection of non resectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996 Oct; 224(4): 509-0; discussion 520-2.
- 50 Delaunoy T, Alberts SR, Sargent DJ, Green E, Goldberg RM, Krook J, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol* 2005 Mar; 16(3): 425-9.
- 51 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000 Aug; 18(16): 2938-47.
- 52 Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Randomized Phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008 Apr 20; 26(12): 2006-12.
- 53 Toung ND C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer: a GERCOR study. *J Clin Oncol* 2006 Jan 20; 24(3): 394-400.
- 54 Toung ND C, Andre T, Achille E, Lledo G, Flesch M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004 Jan 15; 22(2): 229-37.
- 55 Diaz-Rubio E, Gomez-España A, Massuti B, Sastre J, Abad A, Valladares M, et al. First line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic

- colorectal cancer: the phase III MACRO TTD study. *Oncologist* 2012 Jan 10; 17( 11): 1426-8.
- 56 Giacchetti S, Perpoill B, Zidani R, Le Bail N, Faggiuolo R, Focant C, et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000 Jan; 18(1): 136-47
- 57 Karoui M, Penna C, Anin-Hashem M, Mitry E, Benoist S, Franc B, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 2006 Jan; 243(1): 1-7
- 58 Aloia T, Sebag M, Plasse M, Karam V, Levi F, Giacchetti S, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol* 2006 Nov 1; 24 (31): 4983-90.
- 59 Rubbia-Brandt L, Audard V, Sartorelli P, Roth AD, Brezault C, Le Champentier M, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol* 2004 Mar; 15(3): 460-6.
- 60 Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM, et al. Chemotherapy regimen predicts steatosis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006 May 1; 24(13): 2065-72.
- 61 Hubert C, Sempoux C, Horsmans Y, Rahier J, Humblet Y, Machiels JP et al. Nodular regenerative hyperplasia: a deleterious consequence of chemotherapy for colorectal liver metastases? *Liver Int* 2007 Sep; 27 (7): 938-43.
- 62 Kooby DA, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS, et al. Impact of steatosis on perioperative outcome following hepatic resection. *J Gastrointest Surg* 2003 Dec; 7(8): 1034-44.
- 63 Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. *J Gastrointest Surg* 2007 Jul; 11(7): 860-8.
- 64 Hubert C, Fervai C, Sempoux C, Horsmans Y, Humblet Y, Machiels JP et al. Prevalence and clinical relevance of pathological hepatic changes occurring after neoadjuvant chemotherapy for colorectal liver metastases. *Surgery* 2010 Feb; 147(2): 185-94.
- 65 Nakano H, Oussoultzoglou E, Rosso E, Casnedi S, Chenard-Neu MP, Dufour P et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* 2008 Jan; 247(1): 118-24.
- 66 Scoggins CR, Campbell ML, Landry CS, Slomiany BA, Woodall CE, McMasters KM, et al. Preoperative chemotherapy does not increase morbidity or mortality of hepatic resection for colorectal cancer metastases. *Ann Surg Oncol* 2009 Jan; 16(1): 35-41.
- 67 Cucchetti A, Ercolani G, Cescon M, Di Gioia P, Peri E, Brandi G, et al. Safety of hepatic resection for colorectal metastases in the era of neo-adjuvant chemotherapy. *Br J Surg* 2011 Aug; 98(8) : 1147-54.
- 68 Choti MA. Chemotherapy-associated hepatotoxicity: do we need to be concerned? *Ann Surg Oncol* 2009 Sep; 16(9): 2391-4.
- 69 Welsh FK, Tilney HS, Tekkis PP, John TG, Rees M. Safe liver resection following chemotherapy for colorectal metastases is a matter of timing. *Br J Cancer* 2007 Apr 10; 96(7): 1037-42.

- 70 Kishi Y, Zorzi D, Contreras CM, Ma rn DM, Kopetz S, Ribero D, et al. Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. *Ann Surg Oncol* 2010 Nov; 17(11): 2870-6.
- 71 Grothey A, Sugrue E, Hedrick E, Purdie D, Yi J, Dong W et al. Association between exposure to bevacizumab (BY) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): Results from a large observational study (BRiTE). *J Clin Oncol* 2007; 25(18S).
- 72 Kesmodel SB, Ellis LM, Lin E, Chang GJ, Abdalla EK, Kopetz S, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. *J Clin Oncol* 2008 Nov 10; 26(32): 5254-60.
- 73 D'Angelica M, Kornprat P, Gonen M, Chung KY, Jarnagin WR, DeMatteo RP et al. Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. *Ann Surg Oncol* 2007 Feb; 14(2): 759-65.
- 74 Reddy SK, Morse MA, Hurwitz HI, Bendell JC, Gan TJ, Hill SE, et al. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. *J Am Coll Surg* 2008 Jan; 206(1): 96-106.
- 75 Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinnavar FF, Purdie OM, et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRiTE observational cohort study. *Oncologist* 2009 Sep; 14(9): 862-70.
- 76 Mughan TS, James RD, Kerr DJ, Lederman JA, Seymour MT, Topham C, et al. Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicentre randomised trial. *Lancet* 2003 Feb 8; 361(9356): 457-64.
- 77 Chibaudel B, Maindault-Goebel F, Lledo G, Mineur L, Andre T, Bennamoun M, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 2009 Dec 1, 27(34): 5727-33.
- 78 Adams RA, Meade AM, Seymour MT, Wilson RH, Madi A, Fisher D, et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet Oncol* 2011 July; 12(7): 642-53.

### ÇOKTAN SEÇMELİ SORULARIN CEVAPLARI

1. B, C, D
2. B, C