KOLOREKTAL KANSERLERDE ADJUVAN TEDAVİDE YENİLİKLER

Özgür TANRıVERDı

Muğla Sıtkı Koçman Üniversitesi

Tıp Fakültesi Tıbbi Onkoloji Bilim Dalı

GENÇLERLE ONKOLOJİYE BAKIŞ KONGRESİ-2018

17.02.2018- ANTALYA

SUNU PLANI VE HEDEFLER

- Kolorektal kanserler ile ilgili GENEL BİLGİLERDE ÖNEMLİ NOKTALAR
- Kolon kanserinde adjuvant tedavi- TARTIŞILAN YENİLİKLER
- Rektum kanserinde adjuvant tedavi- TARTIŞILAN YENİLİKLER

  - Hangi hastalara adjuvant tedavi verelim
  - Hangi rejim ile adjuvant tedavi
  - Adjuvant tedavinin süresi
  - Adjuvant tedaviye başlama zamanı
  - Özel hasta grupları ve geriatrik onkoloji

GENEL BİLGİLER

- Tüm dünyada ölüm nedenleri arasında ilk sıralarda yer alır.
- Önemli bir toplum sağlığı sorunudur, erkek ve kadınlarda en sık görülen 3.kanser
- Genetik ve edinsel multifaktöryel etyoloji kanserin önlenmesi için önemli bir engel teşkil eder.
- Erken tanı hayat kurtarır!
- Moleküler temelde kanser hücresini anlamak, kanserin klinik seyrini daha net anlamamıza neden olur
- Kanser sadece fiziksel sağlık sorunu değil, toplumsal ve bireysel psikolojik ve sosyal bir sorundur (kolostomi).

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KOLON KANSERİ

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Discussion

PATHOLOGIC STAGE[e]	ADJUVANT TREATMENT[b,r]
Tis; T1, N0, M0; T2, N0, M0; T3, N0, M0[k] (MSI-H or dMMR)	Observation
T3, N0, M0[k,l] (MSI-L or MSS and no high-risk features)	Observation or Consider capecitabine[n] or 5-FU/leucovorin[n]
T3, N0, M0 at high risk for systemic recurrence[l,m] or T4, N0, M0	Capecitabine[n,o] or 5-FU/leucovorin[n,o] or FOLFOX[n,o,p,q] or CAPEOX[n,o,p,q] or Observation
T1-3, N1 (Low-risk stage III)	Preferred: • CAPEOX (3 mo)[n,q] or • FOLFOX (3–6 mo)[n,q] (category 1 for 6 mo) or Other options include: Capecitabine (6 mo)[n] or 5-FU (6 mo)[n]
T4, N1-2; T Any, N2 (High-risk stage III)	Preferred: • CAPEOX (3–6 mo)[n,o,q] (category 1 for 6 mo) or • FOLFOX (6 mo)[n,o,q] (category 1) or Other options include: Capecitabine (6 mo)[n,o] or 5-FU (6 mo)[n,o]

→ See Surveillance (COL-8)

[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B).
[k] See Principles of Risk Assessment for Stage II Disease (COL-F).
[l] High-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.
[m] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.
[n] See Principles of Adjuvant Therapy (COL-G).
[o] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (COL-E).
[p] A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, et al. J Clin Oncol 2012; published online ahead of print on August 20, 2012.
[q] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.
[r] In patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 vs. 6 months of FOLFOX has not been proven. In patients staged as T4, N1-2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for disease-free survival, whereas non-inferiority of 3 vs. 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months vs. 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CapeOX). Shi Q, et al. J Clin Oncol 2017;35 (suppl):LBA1.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE[1,2,3]

- **Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.**
- **When determining if adjuvant therapy should be administered, the following should be taken into consideration:**
  - **Number of lymph nodes analyzed after surgery (<12)**
  - **Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins)**
  - **Assessment of other comorbidities and anticipated life expectancy.**
- **The benefit of adjuvant chemotherapy does not improve survival by more than 5%.**
- **Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing (see COL-B 4 of 5)**

[1]Benson III AB, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;16:3408-3419.
[2]Figueredo A, Charette ML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the cancer care ontario program in evidence-based care's gastrointestinal cancer disease site group. J Clin Oncol 2004;16:3395-3407.
[3]Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797-1806.

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KOLON KANSERİ

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PRINCIPLES OF ADJUVANT THERAPY (1 OF 2)

- **FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.[1,2] Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer.**
- **Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.[3]**
- **A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.[4] FOLFOX is reasonable for stage II patients with multiple high-risk factors and is not indicated for good- or average-risk patients with stage II colon cancer.**
- **A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.[4]**
- **In patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 versus 6 months of FOLFOX has not been proven. In patients staged as T4, N1-2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for disease-free survival, whereas non-inferiority of 3 versus 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months versus 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CapeOX).[5]**

See Principles of Adjuvant Therapy - Chemotherapy Regimens and References on COL-G 2 of 2

[1]Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.
[2]Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trail. J Clin Oncol 2009;27:3109-16. Epub 2009 May 18.
[3]Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352(26):2696-704.
[4]Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol 2012;30:3353-3360.
[5]Shi Q, Sobrero AF, Shields AF, et al. Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): The IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration [abstract]. J Clin Oncol 2017;35 (suppl):LBA1.

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PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES (2 of 2)

mFOLFOX 6
Oxaliplatin 85 mg/m² IV, day 1*
Leucovorin 400 mg/m² IV, day 1**
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion.
Repeat every 2 weeks.[1,2,3]

Capecitabine[4]
Capecitabine 1000–1250‡ mg/m² twice daily days 1–14 every 3 weeks x 24 weeks.

CAPEOX[5]
Oxaliplatin 130 mg/m² IV* day 1
Capecitabine 1000‡ mg/m² twice daily days 1–14 every 3 weeks x 24 weeks.

5-FU/leucovorin
- **Leucovorin 500 mg/m² given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m² given bolus 1 hour after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles.[6]**
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[7]**
  Leucovorin 400 mg/m² IV day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks.**

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

[1]Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351.
[2]Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12177775.
[3]Maindrault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Annals of Oncology 2000;11:1477-1483.
[4]Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696-2704.
[5]Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. J Clin Oncol 2007;25:102-109. Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer. J Clin Oncol 2011;29:1465-1471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21383294.
[6]Haller DG, Catalano PJ, Macdonald JS Mayer RJ. Phase III study of fluorouracil, leucovorin and levamisole in high risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005:23:8671-8678.
[7]Andre T, Louvet C, Maindrault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. Eur J Cancer 1999;35(9):1343-7.

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Fluoropyrimidines ± Oxaliplatin Stage III

	HR for DFS	P value	DFS Δ (%)	HR for OS	P value	OS Δ (%)
MOSAIC *(FOLFOX)*	0.78 CI, 0.65-0.93 @ 5 year	0.005	Δ 7.5% 58.9% vs 66.4% @ 5 year	0.80 CI, 0.65-0.97 @ 6 year	0.023	Δ 4.2% 68.7% vs 72.9% @ 6 year
NSABP C-07 *(FLOX)*	0.78 CI, 0.68-0.90 @ 5 year	0.0007	Δ 6.6 % 57.8% vs 64.4% @ 5 year	0.85 CI, 0.72-1.00 @ 5 year	0.052	Δ 2.7% 73.8% vs 76.5% @ 5 year
XELOXA *(XELOX)*	0.80 CI, 0.69-0.93 @ 5 year	0.004	Δ 5 % 62% vs 67% @ 3 year	0.83 CI, 0.70-0.99 @ 5 year	0.04	Δ 3.0% 74% vs. 77% (@ 5y)
X-ACT **FU/FA bolus vs. Capecitabine**	**0.87** CI, 0.75-1.00 @ 3y	0.0528	**Δ 3.6%** 60.6% vs. 64.2% @ 3y	**0.84** **CI: 0.69–1.01** **@3y**	**p=0.07**	**Δ 3.7%** **77.6% vs. 81.3%** **@3y**

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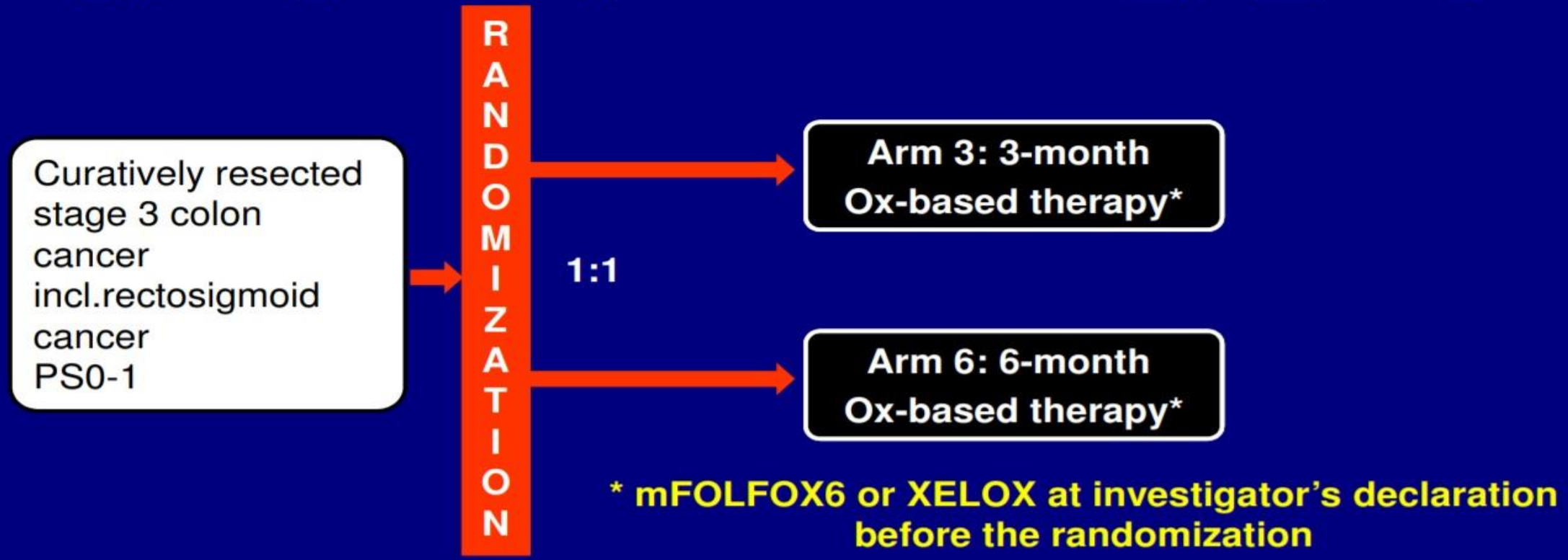
ACHIEVE Trial Design

Adjuvant Chemotherapy for colon cancer with HIgh EVidencE



- Primary endpoint: Relapse-free survival defined as time to colon cancer recurrence or death from any cause.

International Duration Evaluation of Adjuvant Chemotherapy (IDEA) of adjuvant therapy with FOLFOX or XELOX 3 vs. 6 months in stage III colon cnacer

Trial site	Trial	Group	Planned accrual
UK, Australia, New Zealand Denmark, Spain, Sweden,	SCOT	CACTUS, OCTO	4000
Italy	TOSCA	GISCAD	2500
France	IDEA	GERCOR, PRODIDGE	2000
US	80702	CALGB/SWOG	2500
Greece	HORG	HORG	1000
Japan	ACHIEVE	JFMC	1200
Total	6 trials	16 groups	>10.500

Statistical design of non-inferiority

- **2 sided 95% CI HR < 1.2**
- **DFS difference 2.7% @ 3 years**

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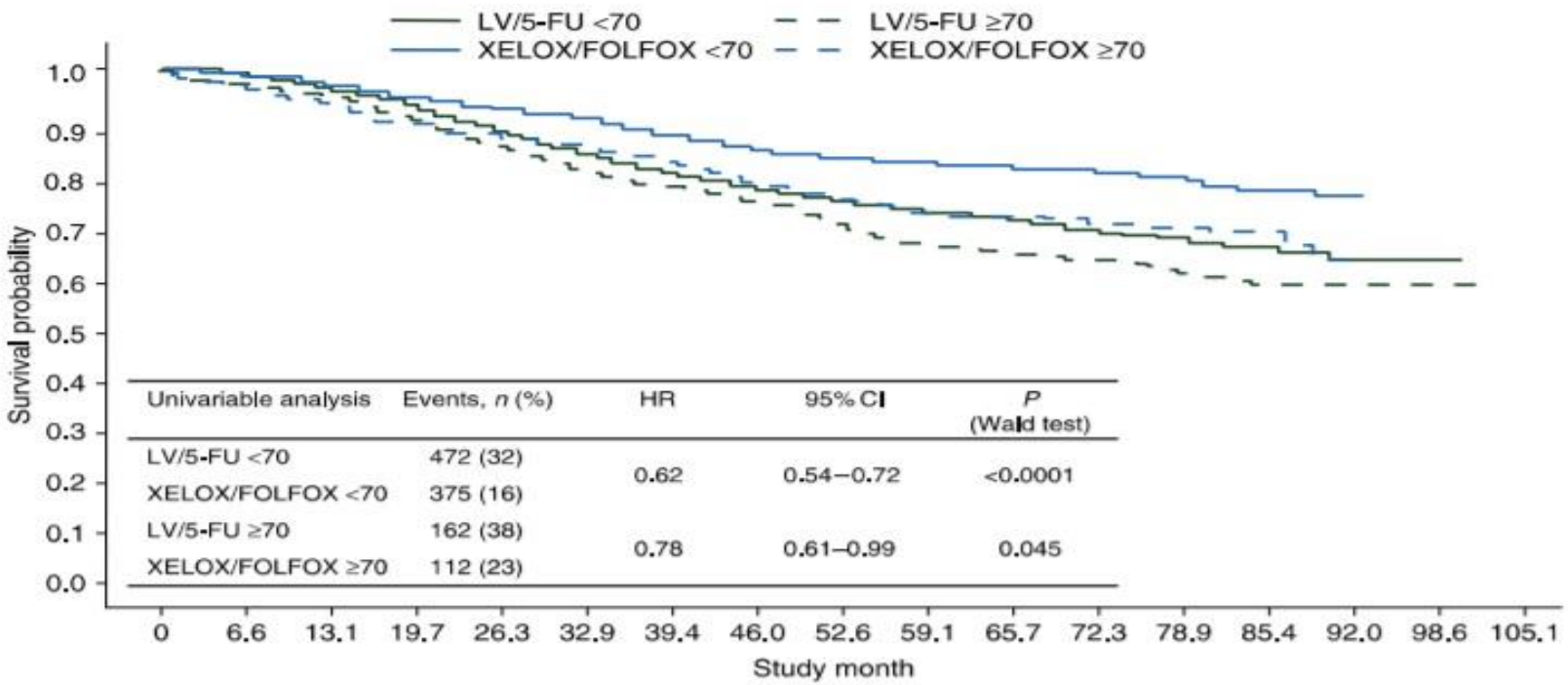
Pooled analysis of individual patient data (NSABP C-08, XELOXA, X-ACT, and AVANT) survival for age groups

B



Univariable analysis	Events, *n* (%)	HR	95% CI	*P* (Wald test)
LV/5-FU <70	472 (32)	0.62	0.54–0.72	<0.0001
XELOX/FOLFOX <70	375 (16)			
LV/5-FU ≥70	162 (38)	0.78	0.61–0.99	0.045
XELOX/FOLFOX ≥70	112 (23)			

Number at risk

LV/5-FU <70	1497	1454	1402	1350	1280	1207	1156	1106	1050	1012	931	781	581	201	38	4	0
LV/5-FU ≥70	424	407	398	379	358	334	321	307	284	267	245	198	142	56	13	1	0
XELOX/FOLFOX <70	2418	2329	2267	2197	2098	1848	1426	1070	879	638	541	526	437	135	3	0	0
XELOX/FOLFOX ≥70	480	450	431	414	399	344	274	208	173	130	117	110	88	35	0	0	0

Haller et al. Ann Oncol 2015

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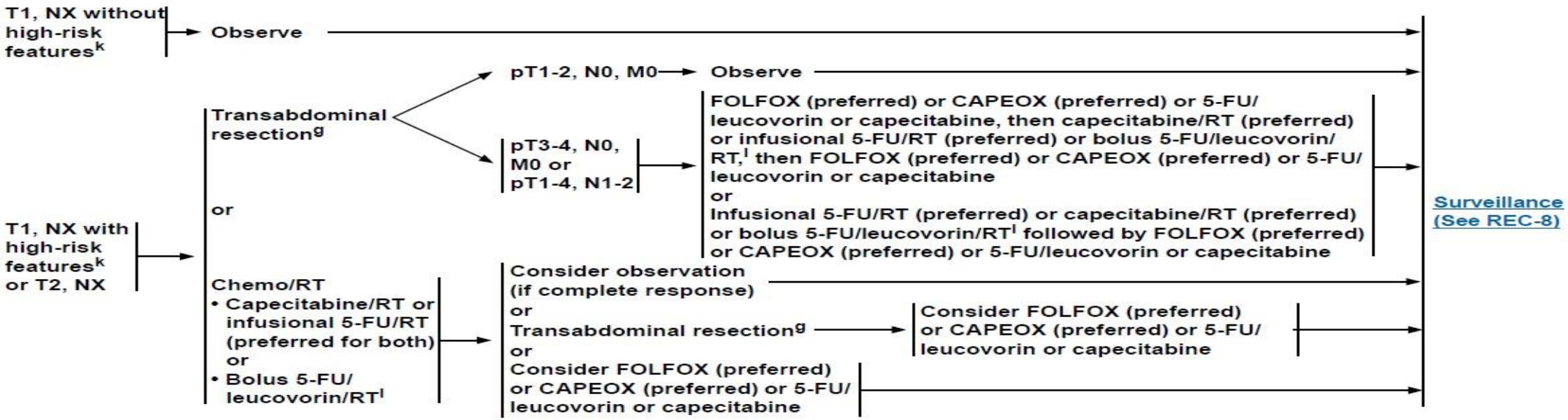

[g] See Principles of Surgery (REC-B).
[k] High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.
[l] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[m] See Principles of Adjuvant Therapy (REC-C).
[n] See Principles of Radiation Therapy (REC-D).
[o] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
[p] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

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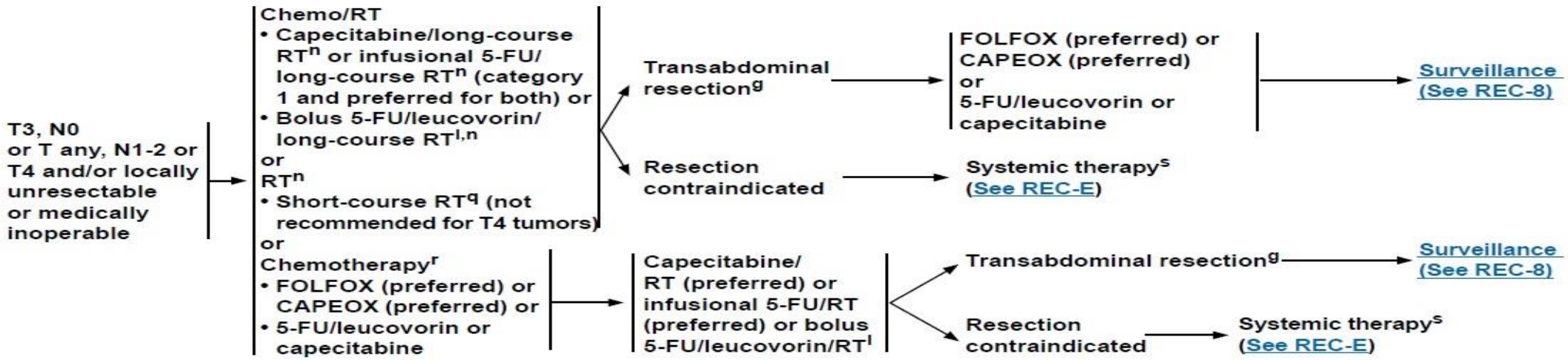

[g] See Principles of Surgery (REC-B).
[l] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[m] See Principles of Adjuvant Therapy (REC-C).
[n] See Principles of Radiation Therapy (REC-D).
[o] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
[q] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[r] Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.
Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.
[s] FOLFOXIRI is not recommended in this setting.

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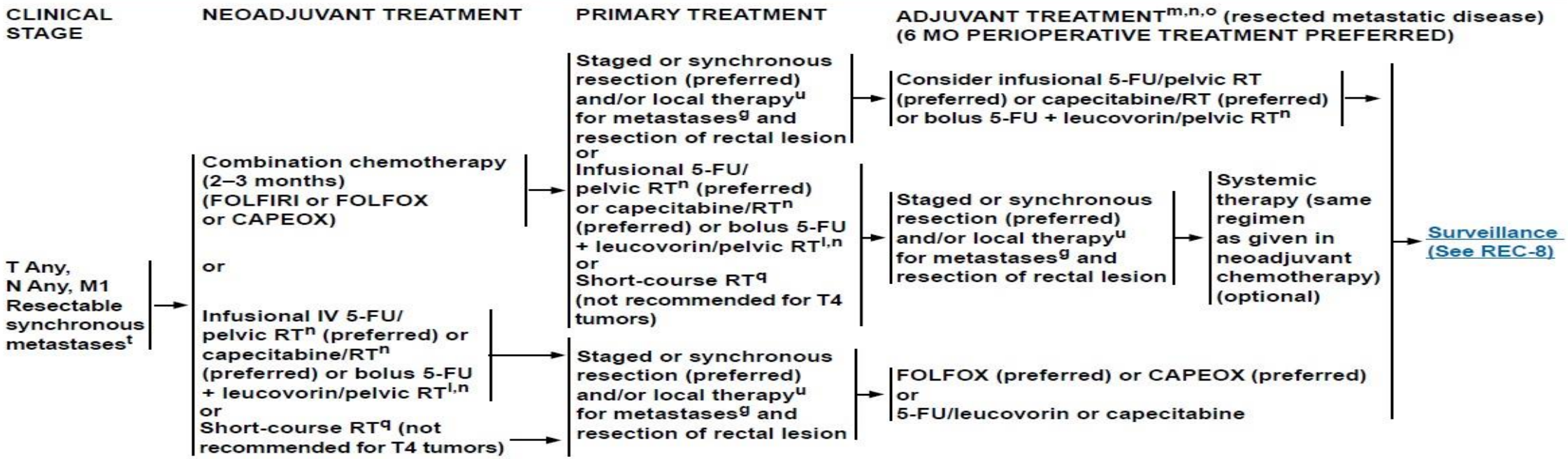

[g] See Principles of Surgery (REC-B).
[l] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[m] See Principles of Adjuvant Therapy (REC-C).
[n] See Principles of Radiation Therapy (REC-D).
[o] Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.
[q] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[t] Determination of tumor gene status for RAS and BRAF (individually or as part of next-generation sequencing [NGS] panel). Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[u] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-B and REC-D).

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PRINCIPLES OF ADJUVANT THERAPY (1 of 2)

Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. A total of approximately 6 months of perioperative treatment is preferred.

Postoperative Adjuvant Chemotherapy:

- **mFOLFOX 6[1,2,3]**
  Oxaliplatin 85 mg/m² IV, day 1,* leucovorin 400 mg/m² IV day 1, 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.**
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)[4]**
  Leucovorin 400 mg/m² IV day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.
- **Capecitabine[5]**
  Capecitabine# 1000–1250 mg/m² twice daily days 1–14 every 3 weeks to a total of 6 months perioperative therapy.
- **CAPEOX[6,7]**
  Oxaliplatin 130 mg/m² day 1.* Capecitabine# 1000 mg/m² twice daily days 1–14 every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.
- **5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8-week cycle. Repeat every 8 weeks to a total of 6 months perioperative therapy.[8]**

Dosing Schedules for Concurrent Chemotherapy/RT:

- **XRT + continuous infusion 5-FU[9]**
  5-FU 225 mg/m² over 24 hours 5 or 7 days/week during XRT
- **XRT + Capecitabine[11,12]**
  Capecitabine# 825 mg/m² twice daily 5 d/wk + XRT x 5 weeks
- **XRT + 5-FU/leucovorin[10‡]**
  5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during week 1 and 5 of XRT

See footnotes on REC-C 2 of 2

*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
**Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
‡Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
#The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

KOLOREKTAL KANSERLERDE ADJUVANT İMMUNOTERAPİ

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Table 2

Future and ongoing/recently completed trials of immunotherapy in colorectal cancer

Trial identifier	Sponsor/collaborator	Title	Phase
Vaccines			
NCT01952730	Massachusetts General Hospital	A pilot safety study of vaccination with autologous, lethally irradiated colorectal cancer cells engineered by adenoviral mediated gene transfer to secrete human granulocyte-macrophage stimulating factor	I
NCT01461148	Oryx GmbH & Co. KG	Phase I/IIa study of immunization with frameshift peptides administered with Montanide® ISA-51 VG in patients with advanced MSI-H colorectal cancer	I/IIa
NCT01376505	Ohio State University Comprehensive Cancer Center	Phase I active immunotherapy trial with a combination of two chimeric (trastuzumab-like and pertuzumab-like) human epidermal growth factor receptor 2 (HER-2) B cell peptide vaccine emulsified in ISA 720 and nor-MDP adjuvant in patients with advanced solid tumors	I
NCT01734564	Universidad de Navarra	Phase II study with hiltonol and dendritic cells in solid tumors	II
NCT01348256	Universidad de Navarra	Randomized phase II study with dendritic cell immunotherapy in patients with resected hepatic metastasis of colorectal carcinoma	II
NCT01380600	Jennerex Biotherapeutics	A phase Ib dose escalation study of JX-594 (thymidine kinase-inactivated vaccinia virus plus GM-CSF) administered by biweekly (every 2 weeks) intravenous infusion in patients with metastatic, refractory colorectal carcinoma	Ib

Adoptive cell therapy			
NCT02202928	Jingzhou Central Hospital	Phase II study of autologous tumor lysate-pulsed DC-CIK cell in colorectal cancer after surgery	II
Checkpoint inhibitors-CTLA4			
NCT00313794	AstraZeneca	Phase II, single arm study of ticilimumab in patients with refractory metastatic adenocarcinoma of the colon or rectum	II
NCT00378482	AstraZeneca	A rollover protocol for patients who received CP-675,206 in other protocols	II
Checkpoint inhibitors-PD1			
NCT02013804	MedImmune LLC	A phase I, multicenter, open-label study to evaluate the safety, tolerability, and pharmacokinetics of MEDI0680 (AMP-514) in subjects with advanced malignancies	I
NCT02404441	Novartis Pharmaceuticals	Open label multicenter phase I/II study of the safety and efficacy of PDR001 administered to patients with advanced malignancies	I/II
NCT02460198	Merck Sharp & Dohme Corp.	A phase II study of pembrolizumab (MK-3475) as monotherapy in subjects with previously treated locally advanced unresectable or metastatic (stage IV) mismatched repair deficient or microsatellite instability-high colorectal carcinoma (KEYNOTE-164)	II
NCT01375842	Genentech, Inc.	A phase I, open label, dose escalation study of the safety and pharmacokinetics of MPDL3280A administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies	I
Checkpoint other			
NCT01943461	Merck KGaA	A phase I trial to investigate the tolerability, safety, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in Japanese subjects with metastatic or locally advanced solid tumors, with expansion part in Asian subjects with gastric cancer	I
NCT01772004	EMD Serono	A phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications	I
NCT01115790	Eli Lilly and Company	A phase I study of LY2606368 in patients with advanced cancer	I

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