JOIN trial: treatment outcome and recovery status of peripheral sensory neuropathy during a 3-year follow-up in patients receiving modified FOLFOX6 as adjuvant treatment for stage II/III colon cancer

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Abstract
Purpose Adjuvant FOLFOX therapy is an established standard-of-care for resected colon cancer. Peripheral sensory neuropathy (PSN) is regarded as the major toxicity issue related to FOLFOX therapy. There have been a few reports on the recovery status from PSN thereafter. JOIN trial investigated the tolerability and efficacy of adjuvant modified FOLFOX6 (mFOLFOX6) in Japanese patients with stage II/III colon cancer.

Methods Twelve cycles of mFOLFOX6 were given to patients with stage II/III curatively resected colon cancer. Treatment outcomes, including disease-free survival (DFS), relapse-free survival (RFS), overall survival (OS), and recovery status of PSN during 3-year follow-up, were investigated.

Results Of the 882 patients enrolled from 2010 to 2012, 864 were eligible for the efficacy analyses. Three-year DFS, RFS, and OS were favorable in 92.1, 92.8, and 97.4% of stage II patients; 76.4, 77.9, and 93.8% of stage IIIA/B; and 61.6, 62.7, and 85.9% of stage IIIC, respectively. The cumulative incidence of PSN during treatment was 47.8% in grade 1 (G1), 30.3% in G2, and 5.8% in G3. For those with G3 PSN during treatment, there was gradual recovery in 1.1% of patients at 12 months after enrollment, 0.5% at 24 months, and 0.2% at 36 months. However, G1 or G2 residual PSN after 3 years was observed in 21.0% (18.7%, G1; 2.3%, G2).

Conclusions Adjuvant mFOLFOX6 therapy was effective and well tolerated in patients with stage II/III colon cancer. Most patients recovered from G3 PSN related to oxaliplatin, but approximately 20% of patients had G1 or G2 PSN at 3-year follow-up.

Keywords Modified FOLFOX6 · Long-term peripheral sensory neuropathy · Oxaliplatin · Colon cancer · Efficacy

Introduction
Six months of adjuvant oxaliplatin-based 5-fluorouracil (5-FU), leucovorin and oxaliplatin (FOLFOX) chemotherapy following surgery is the standard care for patients with stage III colon cancer as well as for patients with high-risk stage II colon cancer who have risk factors for recurrence that are associated with a relatively poor prognosis, such as T4 status, poorly differentiated histology, vascular invasion, ileus, < 12 lymph nodes examined, and neural invasion, as recommended by several treatment guidelines [1–3].

FOLFOX4 regimen has proven efficacy in the adjuvant treatment of resected stage II and stage III colon cancers, as demonstrated by the pivotal MOSAIC [4, 5] and MACSCOT [6] trials conducted in Western and Asian patient populations, respectively. More recently, FOLFOX4 has frequently been substituted by the modified FOLFOX6 (mFOLFOX6) regimen in the adjuvant setting [7, 8], which is easier to administer, and mFOLFOX6 has been shown to be tolerable in the adjuvant treatment of Japanese
patients with resected stage II and stage III colon cancer in the JOIN (JFMC41-1001-C2) trial [9].

Many patients, however, develop peripheral sensory neuropathy (PSN) by the standard 6 months, 12 cycles of mFOLFOX6 administration, leading to treatment discontinuations [10–14]. PSN can be troublesome in daily life and problems usually persist long after treatment has finished. In the key trials of adjuvant oxaliplatin-based therapy, the incidences of grade ≥ 3 PSN due to FOLFOX4 therapy during treatment were 12.4% and 5.7% for the MOSAIC and Asian MASCOT trials, respectively [4–6]. In the adjuvant US NSABP C-08 trial [7] and Japanese JOIN trial [9] in which patients received the mFOLFOX6 regimen, the incidences of grade ≥ 3 PSN at the end of the studies were 14.4% and 5.8%, respectively. During a 3-year follow-up in patients receiving FOLFOX4 in the MOSAIC trial [5], the recovery status of PSN for any grade and grade 3 PSNs was reported as having a frequency of 18.1 and 0.6%, respectively. No trial has revealed the PSN recovery rate from mFOLFOX6, particularly in Asian patients. In addition, 6 months of FOLFOX treatment even in the post-IDEA collaboration era is a standard adjuvant treatment in patients with curatively resected stage II/III colon cancer [3]. The results of the JOIN trial for safety during the treatment course and the treatment compliance have been reported elsewhere [9].

Here, we report the treatment outcomes including disease-free survival (DFS), relapse-free survival (RFS), overall survival (OS), and recovery rate from PSN during a 3-year follow-up.

**Endpoints**

The primary endpoints were the incidence of PSN persisting for ≥ 8 days that interfered with activities of daily living and with an incidence of ≥ grade 3 allergic reactions/anaphylaxis (AR). Secondary endpoints were DFS, RFS, OS, time to treatment failure, adverse events (AEs), comparison of PSN between patients with or without receiving prophylactic therapy, recovery status of PSN during the 3-year follow-up period, the treatment completion rate, the relative dose intensity (RDI), and the number of lymph-node metastases and number of dissected lymph nodes in relation to the prognosis. DFS was defined as the time from enrollment to relapse, secondary primary colorectal cancer, or death, whichever occurred first. RFS was defined as the time from enrollment to relapse, or death, whichever occurred first. OS was measured from the time of enrollment until death from any cause.

AEs were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. However, PSN was evaluated by following the NCI-CTC Version 1.0, 2.0 and CTCAE Version 3.0.

**Statistical analysis**

Descriptive statistics were calculated as the number of patients and percentage for categorical baseline characteristics and mean with a range for continuous baseline characteristics. Three-year DFS, RFS, and OS rates were estimated using the Kaplan–Meier method. Greenwood’s formula was applied for calculation of the 95% confidence interval (95% CI) of the 3-year DFS, RFS, and OS. The multivariate Cox proportional hazard model was applied to evaluate the prognostic value of patient baseline characteristics for DFS, RFS, and OS. Covariates were selected using the stepwise method with an inclusion criterion of \( p < 0.20 \). The proportion of recovery status of PSN during the 3-year follow-up period was calculated by the number of PSN in the total efficacy population at each follow-up. All statistical analyses were performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA).

**Results**

**Patient population and baseline characteristics**

Between November 2010 and March 2012, 882 patients were enrolled at 198 institutions. Among these 882 patients, 11 were ineligible, as previously reported [9]. Of the remaining 871 eligible patients, 864 patients (98.0%) for whom
the treatment status was fixed with a median follow-up of 3 years as of October 30, 2015 via an electronic data capture system (Viedoc®, PCG Solutions, Uppsala, Sweden) with central monitoring were included in the efficacy analysis (Fig. 1). The characteristics of these patients are shown in Table 1. Baseline patient characteristics were as follows: median age, 64 years; male, 53.8%; PS 0, 93.8%; stage II/IIIA/IIIB/IIIC by TNM Classification, 7th edition, 18.5%/7.3%/52.5%/21.6%; and lymph nodes examined, <12/≥12/unknown: 17.2/82.5/0.2%, respectively.

**Treatment outcome**

Three-year DFS, RFS, and OS in the overall efficacy population were 76.1% (95% CI 73.0–78.8), 77.3% (95% CI 74.3–80.0), and 92.7% (95% CI 90.7–94.3), respectively (Fig. 2). Favorable 3-year DFS, RFS, and OS were 92.1, 92.8, and 97.4% in stage II patients, while these were 76.4, 77.9, and 93.8% in stage IIIA/B; and 61.6, 62.7, and 85.9% in stage IIIC, respectively (Fig. 3). The main recurrent sites were liver (7.6%), lung (7.3%), and lymph nodes (5.2%). In multivariate Cox regression analysis, tumor histology, venous invasion, and lymph-node metastatic ratio were statistically significant prognostic factors for DFS, RFS, and OS (Table 2), while the tumor location was not significant, although OS in left-sided primary tumors was better than that in right-sided ones with statistical non-significance (Supplementary Fig. 1).

**Recovery status of PSN**

The cumulative incidence of PSN during treatment was 47.8% grade 1, 30.3% grade 2, and 5.8% grade 3, respectively (Fig. 4). Grade 3 PSN appeared to gradually recover from 5.8% to 1.1%, 0.5%, and 0.2% at 12 months, 24 months, and 36 months after enrollment, respectively. However, grade 1 or grade 2 PSNs after 3-year follow-up were observed in 21.0% of patients (18.7% in grade 1 and 2.3% in grade 2). The transition from each grade of PSN during study treatment (from grade 1, grade 2, and grade 3) is shown in Supplementary Fig. 2.

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**Table 1** Patient characteristics

| n (%) | 864 |
|-------|-----|
| Male/female | 465/399 (53.8/46.2) |
| Median age (range) | 64 (21–83) |
| PS: 0/1 | 810/54 |
| Stage (TNM 7th): II/IIIA/IIIB/IIIC | 100/34/26/63/45/187 |
| II/A/IIIB/IIIC | (11.6/3.9/3.0/7.3/52.5/21.6) |
| Number of lymph nodes examined | 2/149/713 |
| Unknown/1–11/≥12 | 0.2/17.2/82.5 |
| Number of positive lymph nodes | 160/424/280 |
| 0/1–3/≥4 | (18.5/49.1/32.4) |

*TNM classification of malignant tumors, 7th edition
**Discussion**

The JOIN trial results confirm the efficacy and safety of adjuvant mFOLFOX6 in over 800 patients with stage II/III curatively resected colon cancer among approximately 200 community hospitals in Japan. Approximately 6% of Asian patients only showed grade 3 or higher PSN in the JOIN and MASCOT, while 12–14% patients did in the Western trials such as MOSAIC and NSABP C-08 [5–9].

The PSN during treatment was the highest and gradually recovered during the 3-year follow-up period. In addition, it was confirmed that approximately 20% of patients had grade 1 or grade 2 PSN from the 3-year PSN follow-up, which is consistent with that of FOLFOX4 [5]. PSN caused by oxaliplatin, either FOLFOX4 or mFOLFOX6, is a common issue worldwide. However, the remaining PSN may be influenced by factors other than oxaliplatin. In the NSABP C-07 trial [15] comparing weekly bolus fluorouracil and leucovorin (FL) therapy with or without oxaliplatin, the PSN for some patients (less than 5%) remained in the FL group at 12 months of follow-up, suggesting that the PSN may occur due to factors other than oxaliplatin.

Three-year DFS and OS in the JOIN trial were 76.1 and 92.7%, respectively. Stratified by stage, 3-year DFS and OS were 92.1 and 97.4% in stage II, 76.4 and 93.8% in stage IIIA/B, 61.6, and 85.9% in stage IIIC, respectively. Three-year DFS in other recent clinical trials conducted in Japan for stage II/III or stage III colon cancer were reported to range from 70.0 to 86.2%, while those in 3-year OS were reported to range from 92.7 to 98.0%, which is consistent with those in the JOIN trial (Supplementary Table) [16–22].

Based on the results of Japanese clinical trials including the JOIN trial, the survival rate of patients with stage II/III colon cancer appeared to be relatively higher in Japan than in Western countries (Supplementary Table) [16–22]. This difference might be largely due to the lower percentage of patients with <12 nodes examined as well as the Japanese D3 lymph-node dissection procedure, given that the number of lymph nodes examined after surgical resection was shown to correlate with survival [23]. In fact, the percentage of patients with <12 nodes examined in Japanese trials...
in patients with stage II and III colon cancer such as JOIN, SACURA, and ACTS-CC trials was substantially lower than that in the NSABP C-07 trial, which enrolled subjects during the same period (17–26% vs. 41%, respectively). However, recently, a comparison of Japanese D3 lymph-node dissection and European complete mesocolic excision (CME) with central vascular ligation has been reported [24], and favorable outcomes of CME compared with conventional Western-style colon resection have also been reported from Western countries [25]. These findings imply that the gap in the survival of patients with stage II/III colon cancer between Japan and Western countries is closing, suggesting that Japanese outcomes might be applicable to the West. Considering the recent improved survival rate of patients with stage II/III colon cancer worldwide, we should reconsider the relatively high oxaliplatin-associated toxicity which could be weighed against the expectation of lower absolute treatment benefit in patients with a low risk of recurrence.

Recent IDEA collaboration reported 3 months adjuvant chemotherapy significantly reduced the rate of any grade PSN, compared with 6 months, without compromising efficacy in patients with low-risk stage III colon cancer [26, 27]. In addition, the ACHIEVE trial, the part of IDEA collaboration, reported the incidence of any grade PSN lasting for 3 years was significantly lower for CAPOX (capecitabine plus oxaliplatin) than mFOLFOX6, suggesting that 3 months of CAPOX therapy may be the most appropriate option in low-risk patients [28], although ACHIEVE results need to be interpreted within the IDEA combined analysis as well as in terms of the reproducibility of the results across all trials. Therefore, 6 months of FOLFOX treatment even in the post-IDEA collaboration era is a standard adjuvant treatment in patients with curatively resected stage II/III colon cancer [3]. As the efficacy and safety of 6-month adjuvant mFOLFOX6 in Japanese patients with stage II/III colon cancer was confirmed in the JOIN trial, we moved forward to conduct two-phase three trials called the ACHIEVE trial for stage III and the ACHIEVE-2 trial for high-risk stage II [29, 30], which led to the first Japanese participation in the IDEA Collaboration [26, 27].

**Fig. 3** Kaplan–Meier curves for **a** DFS, **b** RFS and **c** OS in the overall population stratified by stage in the TNM Classification of Malignant Tumors, 7th edition. **DFS** disease-free survival, **RFS** relapse-free survival, **OS** overall survival, 95% CI 95% confidence interval
Table 2  Multivariate analysis of risk factors for DFS, RFS and OS

| Risk factor                | DFS          | RFS          | OS           |
|----------------------------|--------------|--------------|--------------|
|                            | HR\(^a\)     | 95% CI\(^b\) | P            | HR           | 95% CI        | P            | HR           | 95% CI        | P            |
| **T**                      |              |              |              |              |              |              |              |              |              |
| SM, MP, SS, A              | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        |
| SE, SI, AI                 | 1.386        | 1.041–1.845  | 0.0255       | 1.441        | 1.073–1.937  | 0.0152       | 1.406        | 0.878–2.251  | 0.1556       |
| **Histology**              |              |              |              |              |              |              |              |              |              |
| Pap, tub                   | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        |
| Por, muc, sig              | 1.570        | 1.028–2.398  | 0.0367       | 1.569        | 1.017–2.419  | 0.0416       | 2.860        | 1.619–5.051  | 0.0003       |
| **N**                     |              |              |              |              |              |              |              |              |              |
| N0                         | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        |
| N1                         | 1.793        | 0.784–4.100  | 0.1663       | 1.375        | 0.522–3.618  | 0.5194       | 1.395        | 0.348–5.592  | 0.6380       |
| N2, N3                     | 1.624        | 0.658–4.008  | 0.2924       | 1.309        | 0.464–3.693  | 0.6104       | 1.412        | 0.306–6.525  | 0.6587       |
| **v**                     |              |              |              |              |              |              |              |              |              |
| v0                         | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        |
| v1, v2, v3                 | 1.347        | 0.954–1.903  | 0.0907       | 1.472        | 1.017–2.129  | 0.0402       | 1.957        | 1.032–3.777  | 0.0398       |
| LN ratio (%)               |              |              |              |              |              |              |              |              |              |
| 1–4                        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        | 1.000        |
| 5–11                       | 1.469        | 0.719–3.001  | 0.2918       | 2.011        | 0.855–4.732  | 0.1094       | 1.326        | 0.382–4.607  | 0.6572       |
| 12–22                      | 1.920        | 0.938–3.930  | 0.0742       | 2.741        | 1.165–6.444  | 0.0208       | 1.563        | 0.446–5.483  | 0.4854       |
| 22 <                       | 2.924        | 1.380–6.198  | 0.0051       | 3.930        | 1.619–9.539  | 0.0025       | 2.838        | 0.762–10.56  | 0.1199       |
| **Tumor location**         |              |              |              |              |              |              |              |              |              |
| Right-sided                |              |              |              |              |              |              |              |              |              |
| Left-sided                 |              |              |              |              |              |              |              |              | 1.000        |

\(^a\)Hazard ratio
\(^b\)Confidence interval
\(^c\)Japanese classification of colorectal carcinoma 7th ed

Fig. 4 Recovery status of PSN during follow-up periods. PSN peripheral sensory neuropathy, \(\text{trt}\) treatment

Recovery of PSN during follow-up periods
Conclusion

Six-month adjuvant mFOLFOX6 in patients with stage II/III colon cancer is effective and safe. Most patients successfully recovered from grade 3 PSN related to oxaliplatin, but approximately 20% of patients had grade 1 or grade 2 PSN at the 3-year follow-up.

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Compliance with ethical standards

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Ethical approval The institutional review board at each study center approved the protocol, and the study was conducted by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC), a non-commercial organization for investigator-initiated cancer trials, in accordance with the principles expressed in the Declaration of Helsinki. All patients provided written informed consent prior to enrolment. This study is registered with UMIN Clinical Trial Registry (Trial Identifier UMIN0000044443).

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References

1. Labianca R, Nordlinger B, Beretta GD et al (2013) Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):vi64–vi72
2. Watanabe T, Muro K, Ajioka Y et al (2017) Japanese society for cancer of the colon and rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 23:1
3. NCCN guidelines for patients: colon cancer version 4 (2018) www.nccn.org. Accessed 5 Nov 2018
4. Andre T, Boni C, Mounedji-Boudiaf L et al (2004) Oxaliplat, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343–2351
5. Andre T, Boni C, Navarro M et al (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27:3109–3116
6. Lee P-H, Park Y-S, Ji J-F, Fu Y-T, Ratanatharathorn V (2009) Safety and tolerability of FOLFOX4 in the adjuvant treatment of colon cancer in Asian patients: the MASCOT study. Asia-Pac J Clin Oncol 5:101–110
7. Allegra CJ, Yothers G, O’Connell MJ et al (2009) Initial safety report of NSABP C-08: a randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer. J Clin Oncol 27:3385–3390
8. Allegra CJ, Yothers G, O’Connell MJ et al (2011) Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 29:11–16
9. Kotaka M, Yoshino T, Oba K et al (2015) Initial safety report on the tolerability of modified FOLFOX6 as adjuvant therapy in patients with curatively resected stage II or III colon cancer (JFMC41-1001-C2: JOIN trial). Cancer Chemother Pharmacol 76:75–84
10. Kidwell KM, Yothers G, Ganz PA et al (2012) Long-term neurotoxic effects of oxaliplatin added to fluorouracil and leucovorin
as adjuvant therapy for colon cancer: results from National Surgical Adjuvant Bowel Project trials C-07 and LTS-01. Cancer 118:5614–5622.

11. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Pol-Franse LV (2013) Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: results from the population-based PROFILES registry. J Clin Oncol 31:2699–2707.

12. Pachman DR, Qin R, Seissler DK et al (2015) Clinical course of oxaliplatin-induced neuropathy: results from the randomized phase III trial N08CB (alliance). J Clin Oncol 33:3416–3422.

13. Pietrangeli A, Leandro M, Terzoli E, Jandolo B, Garufi C (2006) Persistence of high-dose oxaliplatin-induced neuropathy at long-term follow-up. Eur J Neurol 13:16–16.

14. Toftbøgen C, Donovan KA, Morgan MA, Shibata D, Yeh Y (2013) Oxaliplatin-induced peripheral neuropathy’s effects on health-related quality of life of colorectal cancer survivors. Support Care Cancer 21:3307–3313.

15. Land SR, Kopec JA, Cencini RS, Ganz PA, Wieand HS, Colangelo LH, Murphy K, Kuebler JP, Seay TE, Needles BM, Bearden JD 3rd, Colman LK, Lanier KS, Pajon ER Jr, Cella D, Smith RE, O’Connell MJ, Costantino JP, Wolmark N (2007) Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: NSABP C-07. J Clin Oncol 25(16):2205–2211 (Epub 2007 Apr 30).

16. Kotani D, Kuboki Y, Yoshino T (2016) Adjuvant chemotherapy for colon cancer: guidelines and clinical trials in Japan. Curr Colorectal Cancer Rep 12:289–295.

17. Kondo K, Sadahiro S, Tsuchiyi T, Sasaki K, Katsumata K, Nishimura G, Kakeji Y, Baba H, Kodaira S, Saji S (2012) Phase III trial of treatment duration for oral uracil and tegafur/leucovorin adjuvant chemotherapy for patients with stage IIIB/III colon cancer: results of JFMC33-0502. ESMO 2012 Abstract #552P.

18. Yamaguchi S, Kunieda Y, Sato T, Naomoto Y, Kobayashi M, Ogata Y, Furuhata T, Takii Y, Kusunoki M, Machida Y, Koda K, Okuno K, Ohno M, Mishima H, Sadahiro S, Hamada C, Sakamoto J, Saji S, Tomita N (2016) Phase III trial of 24 weeks vs. 48 weeks capcitabine adjuvant chemotherapy for patients with stage III colon cancer: final results of JFMC/37-0801. ESMO 2016 Abstract #469PD.

19. Yoshihisa M, Ishiguro M, Ikejiri K, Mochizuki I, Nakamuro Y, Kimura S, Takagane A, Endo T, Shinozaki H, Takii Y, Mochizuki H, Katase K, Kanesaka S, Takahashi K, Watanabe T, Watanabe M, Boku N, Tomita N, Nakatani E, Sugihara K (2014) ACTS-CC study group. S-1 as adjuvant chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). Ann Oncol 25(9):1743–1749.

20. Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, Ohue M, Sato T, Naomoto Y, Yamaguchi S, Akaike M, Mishima H, Kubo Y, Nakamura K, Fukuda H, Moriya Y (2014) Randomised phase III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous fluorouracil and levofofinolate in patients with stage III colorectal cancer who have undergone Japanese D2/D3 lymph node dissection: final results of JCOG0205. Eur J Cancer 50(13):2231–2240. https://doi.org/10.1016/j.ejca.2014.05.025 (Epub 2014 Jun 21).

21. Hamaguchi T, Shimada Y, Mizusawa J, Kinugasa Y, Kanemitsu Y, Ohue M, Fujii S, Takiguchi N, Yatsuka T, Takii Y, Ojima H, Masuko H, Kubo Y, Mishima H, Yamaguchi T, Bando H, Sato T, Kato T, Nakamura K, Fukuda H, Moriya Y (2018) Cepacetinib versus S-1 as adjuvant chemotherapy for patients with stage III colorectal cancer (JCOG0910): an open-label, non-inferiority, randomised, phase 3, multicentre trial. Lancet Gastroenterol Hepatol 3(1):47–56.

22. Kajiwara Y, Ishiguro M, Teramukai S, Matsuda C, Fuji S, Kinugasa Y, Nakamoto Y, Takata M, Sakamoto Y, Kurachi K, Maeda A, Komori K, Tomita N, Shimada Y, Takahashi K, Kotake K, Watanabe M, Mochizuki H, Sugihara K, SAGURA Study Group (2018) A randomized phase III trial of 1-year adjuvant chemotherapy with oral tegafur-uracil (UFT) vs surgery alone in stage II colon cancer: SAGURA trial. Eur J Cancer 96:54 (ASCO2016 Abstract #3617).

23. Chang GJ, Rodriguez-Bigas MA (2007) Lymph node evaluation and survival after curative resection of colon cancer: systematic review. J Natl Cancer Inst 99(6):433–441.

24. Nicholas PW, Kobayashi H, Takahashi K et al (2012) Understanding optimal colorectal surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol 30(15):1763–1769.

25. Bertelsen CA, Neuenusschaffer AU, Jansen JE et al (2015) Disease-free survival after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. Lancet Oncol 16(2):161–168.

26. Andre T, Iveson T, Labianca R et al (2013) The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration: prospective combined analysis of phase III trials investigating duration of adjuvant therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 versus 6 months) regimen for patients with stage III Colon Cancer: trial design and current status. Curr Colorectal Cancer Rep 9:261–269.

27. Grotch A, Sobrobo AF, Shields AF et al (2018) Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med 378(13):1177–1188.

28. Takeuchi S, Yoshino T, Yamanaka T et al (2018) Long-term effect of peripheral sensory neuropathy (PSN) of 3 or 6 months oxaliplatin-based adjuvant chemotherapy for stage III colon cancer: ACHIEVE as part of the IDEA collaboration. Age 70:70 (WCGC Abstract #O-028).

29. Yoshino T, Watanabe T, Mori M, et al (2014) Two phase III studies comparing 6 months of either mFOLFOX6 or XELOX with 3 months of the same regimen as adjuvant chemotherapy in patients with completely resected stage III colon cancer (ACHIEVE) or high-risk stage II colon cancer (ACHIEVE-2). ASCO 2014 Abstract #TPS 3655.

30. Yoshino T, Yamanaka T, Kotaka M, et al (2017) Efficacy of 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer (CC): Results from phase III ACHIEVE trial as part of the International Duration Evaluation of Adjuvant therapy (IDEA) collaboration. ESMO 2017 Abstract #LBA 24.
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