**C**omparative economics **of a 12-gene assay for predicting risk of recurrence in stage II colon cancer**

# *PharmacoEconomics*

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# Costs of adverse events with chemotherapy

An analysis of claims from the Thomson Reuters Healthcare MarketScan® Commercial Claims and Encounters, and Medicare Supplemental and Coordination of Benefits databases reported costs related to AE prevention and/or treatment for patients receiving aCT treatment for colorectal cancer, stratified by the aCT regimen received (Supplemental Table 1) [[1](#_ENREF_1)]. Complications specific to aCT considered in this analysis included anemia, alopecia, asthenia, constipation, cough, dehydration, dermatitis, diarrhea, esophagitis, fever, gastritis, headache, infection, insomnia, mucositis, nausea and vomiting, neutropenia, night sweats, weight loss, and complications of vascular access devices (central line infection, central line thrombosis, pneumothorax, and secondary thrombocytopenia).Instances of aCT complications were identified using diagnosis codes or treatments specific to these conditions during aCT treatment episodes (time periods defined by aCT claims). The amount reimbursed for adjudicated claims were used to estimate the total costs.

Supplemental Table 1 Adverse event prevention and treatment costs [[1](#_ENREF_1)]

|  |  |  |  |
| --- | --- | --- | --- |
| **Chemotherapy** | **N** | **Mean monthly cost per patient a** | **Mean total cost of AEs b** |
| **Reported a** | **Present c** |
| Capecitabine | 1,317 | US$568 | US$3,135 | US$4,237 |
| 5-FU/LV | 2,840 | US$1,177 | US$6,496 | US$8,779 |
| FOLFOX | 2,250 | US$2,515 | US$13,882 | US$18,758 |
| *Adverse events considered in the claims analysis included anemia, alopecia, asthenia, constipation, cough, dehydration, dermatitis, diarrhea, esophagitis, fever, gastritis, headache, infection, insomnia, mucositis, nausea and vomiting, neutropenia, night sweats, weight loss, and complications of vascular access devices (central line infection, central line thrombosis, pneumothorax, and secondary thrombocytopenia).* |
| *Abbreviations: AEs, adverse events; US$, United States Dollar; 5-FU/LV, 5-fluorouracil and leucovorin; FOLFOX, 5-FU/LV and oxaliplatin.* |
| *a Costs reported in 2005 United States Dollars.* |
| *b Treatment duration is 24 weeks (5.52 months).* |
| *c Inflated to 2014 United States Dollars using consumer price index reported by the Bureau of Labor Statistics [*[*2*](#_ENREF_2)*].* |
| *Source: Chu et al. Cancer 2009 [*[*1*](#_ENREF_1)*].* |

Large, phase III, randomized clinical trials of FOLFOX versus 5-FU/LV aCT for stage II and III colon cancer were used to identify other AEs associated with aCT treatment that were not among those sought and reported in the claims analysis by Chu et al. [[3](#_ENREF_3), [1](#_ENREF_1), [4](#_ENREF_4)]. The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial documented peripheral sensory neuropathy (PSN) adverse events during treatment with either aCT regimen, and at follow-up visits up to four years after treatment with FOLFOX. The incidence and severity of these AEs is reported in Supplemental Table 2.

Supplemental Table 2 Adverse event incidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time** | **Adverse event** | **Grade** | **Fluoropyrimidine monotherapy** | **FOLFOX** |
| During treatment a |  |  |  |  |
| NSABP C-07 randomized clinical trial (n=2,409) [[4](#_ENREF_4)] |  |  |  |
|  | Fatal toxicity b | Fatal | 1.1% | 1.3% |
|  | Any b | 4 or 5 | 9.9% | 11.8% |
|  | Diarrhea b | 3 | 32.4% | 38.1% |
|  | Nausea/vomiting b | 3 | 18.9% | 27.7% |
| MOSAIC randomized clinical trial (n=2,246) [[3](#_ENREF_3)] |  |  |  |
|  | Peripheral sensory neuropathy | 3 | 0.2% | 12.5% |
|  |  | 2 |  | 31.4% |
|  |  | 1 |  | 48.1% |
| Months after end of treatment [[3](#_ENREF_3)] |  |  |  |
| MOSAIC randomized clinical trial (n=2,246)  |  |  |  |
| 0.92 | Peripheral sensory neuropathy | 3 |  | 5.1% |
|  |  | 2 |  | 15.8% |
|  |  | 1 |  | 40.2% |
|  |  |  |  |  |
| 6 | Peripheral sensory neuropathy | 3 |  | 1.5% |
|  |  | 2 |  | 7.6% |
|  |  | 1 |  | 32.3% |
|  |  |  |  |  |
| 12 | Peripheral sensory neuropathy | 3 |  | 1.3% |
|  |  | 2 |  | 4.6% |
|  |  | 1 |  | 24.1% |
|  |  |  |  |  |
| 18 | Peripheral sensory neuropathy | 3 |  | 0.7% |
|  |  | 2 |  | 3.5% |
|  |  | 1 |  | 19.9% |
|  |  |  |  |  |
| 24 | Peripheral sensory neuropathy | 3 |  | 0.6% |
|  |  | 2 |  | 3.4% |
|  |  | 1 |  | 16.7% |
|  |  |  |  |  |
| 36 | Peripheral sensory neuropathy | 3 |  | 0.6% |
|  |  | 2 |  | 2.2% |
|  |  | 1 |  | 15.3% |
|  |  |  |  |  |
| 48 | Peripheral sensory neuropathy | 3 |  | 0.7% |
|  |  | 2 |  | 2.8% |
|   |   | 1 |  | 11.9% |
| *Abbreviations: FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; NSABP, National Surgical Adjuvant Breast and Bowel Project; MOSAIC, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer.* |
| *a Treatment duration is 24 weeks (5.52 months).*  |
| *b These rates were not used the adverse event cost-assessment to avoid double counting with the claims analysis described in Supplemental Table 1. Rates of neurosensory adverse events reported in the NSABP C-07 study were not considered to avoid double-counting with the peripheral sensory neuropathy rates reported in the MOSAIC study.* |
| *Sources: Yothers et al. J Clin Oncol 2011 [*[*4*](#_ENREF_4)*]; Andre et al. J Clin Oncol 2009 [*[*3*](#_ENREF_3)*].* |

The additional costs for treatment of aCT-related PSN were computed separately using values in published literature. An evaluation of PSN treatment costs using patient-control methods reported costs were US$3,542 (2014 United States Dollars) in the first 6 months following diagnosis and US$3,244 in the following 12 months [[5](#_ENREF_5)]. The cost of treating PSN was weighted by the probability of this AE occurring with each type of aCT (fluoropyrimidine monotherapy [capecitabine or 5-FU/LV] or FOLFOX), then added to the claims analysis data to estimate the average cost of adverse events with different chemotherapies to derive the total costs attributed to aCT-related AEs (Supplemental Table 3).

Supplemental Table 3 Average costs of aCT-related adverse events per patient treated

|  |  |
| --- | --- |
| **Adverse events** | **Chemotherapy regimens** |
| **Fluoropyrimidine monotherapy a** | **FOLFOX** |
| **Capecitabine** | **5-FU/LV** |
| Claims analysis [[1](#_ENREF_1)]  | US$4,237 | US$8,779 | US$18,758 |
| Peripheral sensory neuropathy [[3](#_ENREF_3), [5](#_ENREF_5)] | US$0 | US$7 | US$6,072 |
| Total | US$4,237 | US$8,786 | US$24,830 |
| Average | US$6,511 |
| Assumed 95% compliance | US$6,186 | US$23,589 |
| *Abbreviations: aCT, adjuvant chemotherapy; 5-FU/LV, 5-fluorouracil and leucovorin; FOLFOX, 5-FU/LV and oxaliplatin; US$, United States Dollar.* |
| *a Fluoropyrimidine monotherapy is 50% capecitabine aCT, and 50% 5-FU/LV aCT [*[*6*](#_ENREF_6)*].* |

# Quality of life

Health utilities data were extracted from published literature. The PubMed and Tufts CEA registry databases were searched for articles published between 1966 and August 2012. Recent data was preferred to better reflect current practice patterns. Health utility estimates related to colon cancer remission (0.87) and metastasis (0.42) were from a published US study that used time-trade-off methods [[7](#_ENREF_7)].

The effect of aCT on quality of life was derived from a time-trade-off survey study by investigators in Australia of 100 patients with stage II or III colon cancer who had completed 5-FU/LV (79%), FOLFOX (17%), or other (4%) aCT within the previous 3 to 60 months [[8](#_ENREF_8)]. In that study, patients were asked about the duration of survival benefit beyond 5 years and 15 years required to make adjuvant chemotherapy worthwhile (Supplemental Table 4). For this analysis, the responses reported by the time-trade-off study were averaged, weighted by the proportions of patients in the Mayo Clinic Cancer Research Consortium decision impact study who had life-expectancies without chemotherapy less than and greater than 10 years (27% and 73%, respectively). Based on these responses, the mean duration of additional survival necessary to make aCT worthwhile to patients was approximately 14.2 months. Given that the estimate of utility during remission is 0.87, this translates to 12.4 quality-adjusted months, or 1.0 quality-adjusted life-years (QALYs).

Supplemental Table 4 Survival benefit for which patients judged aCT worthwhile

|  |  |  |  |
| --- | --- | --- | --- |
| **Additional survival a** | **Total patients judging aCT worthwhile** | **Marginal change** | **Weighted required survival (months)** |
| **Beyond 5 years a** | **Beyond 15 years a** | **Weighted average b** |
| 1 day | 46% | 50% | 49% | 49% | 0.016 |
| 1 month | 51% | 52% | 52% | 3% | 0.028 |
| 3 months | 65% | 61% | 62% | 10% | 0.310 |
| 6 months | 70% | 68% | 69% | 6% | 0.388 |
| 9 months | 85% | 84% | 84% | 16% | 1.416 |
| 1 year | 88% | 86% | 87% | 2% | 0.272 |
| 18 months | 90% | 88% | 89% | 2% | 0.360 |
| 2 years | 92% | 90% | 91% | 2% | 0.480 |
| 3 years | 97% | 93% | 94% | 4% | 1.274 |
| 5 years | 97% | 93% | 94% | 0% | 0.000 |
| 7 years | 98% | 94% | 95% | 1% | 0.840 |
| 10 years | 98% | 94% | 95% | 0% | 0.000 |
| 15 years | 99% | 95% | 96% | 1% | 1.800 |
| 15 years+1 day c |  |  | 100% | 4% | 7.061 |
|  |  |  |  |  |  |
| Mean survival benefit required to make aCT worthwhile (months) | 14.245 |
|  | Utility without recurrence or chemotherapy | 0.87 |
|  | Quality-adjusted survival required (months) | 12.394 |
| *a Extracted from Blinman et al.* Eur J Cancer *2010 [*[*8*](#_ENREF_8)*].* |
| *b Average weighted by the proportions of patients in the MCCRC decision impact study whose life expectancy without chemotherapy was projected to be less than 10 years (27%) or greater than 10 years (73%) [*[*9*](#_ENREF_9)*].* |
| *c Survey questions only went up to 15 years additional survival.* |
| *Abbreviations: aCT, adjuvant chemotherapy; MCCRC, Mayo Clinic Cancer Research Consortium.* |

## Regimen-specific decrements with chemotherapy

The utility of aCT has not been reported separately for different regimens (fluoropyrimidine monotherapy [5-FU/LV or capecitabine] versus FOLFOX). Therefore, the difference between the quality-of-life decrements associated with fluoropyrimidine monotherapy compared to FOLFOX aCT treatment was calculated based on the disutilities of specific AEs observed with 5-FU/LV or FOLFOX in randomized clinical trials (Supplemental Table 2 and Supplemental Table 5) [[10](#_ENREF_10), [3](#_ENREF_3), [7](#_ENREF_7), [11](#_ENREF_11), [12](#_ENREF_12), [4](#_ENREF_4)]. In the literature search for (dis)utility values associated with AEs, time trade-off studies were preferred in order to be consistent with the methods of the data sources used for quality of life with remission, metastasis, and treatment with any aCT. These studies were not always available, so AE disutilities were also extracted from qualitative interviews, assumptions made in other published CEAs, and studies using standard gamble methods.

Supplemental Table 5 Disutilities of adverse events

|  |  |  |
| --- | --- | --- |
| **Adverse event** | **Disutility** | **Data source / country** |
| Mild neuropathy | 0.02 | [[7](#_ENREF_7)] / US |
| Moderate neuropathy | 0.12 | [[7](#_ENREF_7)] / US |
| Severe neuropathy | 0.19 | [[7](#_ENREF_7)] / US |
| Nausea/vomiting | 0.32 | [[12](#_ENREF_12)] / US |
| Severe diarrhea | 0.19 | [[11](#_ENREF_11)] / Australia |
| Hospitalization a | 0.44 | [[10](#_ENREF_10)] / US |
| *a 50% reduction in utility of remission has been used in previously published cost-effectiveness analyses [*[*10*](#_ENREF_10)*]. This was applied to grade 4 or 5 adverse events (assumed to require hospitalization) reported in the NSABP C-07 trial.* |

The disutilities associated with aCT-related AEs (Supplemental Table 5), were applied to the AE incidence rates reported among patients treated with 5-FU/LV and FOLFOX in the MOSAIC trial and in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial (Supplemental Table 2) [[10](#_ENREF_10), [3](#_ENREF_3), [7](#_ENREF_7), [11](#_ENREF_11), [12](#_ENREF_12), [4](#_ENREF_4)]. The difference in quality-of-life decrements with the two aCT regimens was calculated as 0.09 QALYs including AEs occurring up to four years following aCT treatment (the extent of follow-up reported by the MOSAIC study).

To interpret this data in the context of the results of the survey of aCT-treated patients by Blinman et al., the quality-of-life decrements with chronic PSN were weighted by the proportion of patients who had reached that follow-up time point (Supplemental Table 6). For example, the decrement in quality-of-life related to PSN that does not remit 1.5 years after aCT was weighted by the proportion of patients surveyed by Blinman et al. who completed aCT between 1 to 2 years prior to the time-trade-off survey. Using this method, the difference in quality-of-life decrement between the regimens was estimated to be 0.08 QALYs [[3](#_ENREF_3), [7](#_ENREF_7), [8](#_ENREF_8), [11](#_ENREF_11), [12](#_ENREF_12), [4](#_ENREF_4)].

Supplemental Table 6 Time since completion of aCT among patients in the Blinman et al. time-trade-off survey population [[8](#_ENREF_8)]

|  |  |
| --- | --- |
| **Years** | **Patients** |
| **Number** | **Percent** |
| < 1 | 20 | 20% |
| 1 to < 2 | 23 | 23% |
| 2 to < 3 | 29 | 29% |
| ≥ 3 | 28 | 28% |
| All | 100 | 100% |
| *Abbreviation: aCT, adjuvant chemotherapy.* |
| *Source: Blinman et al. Eur J Cancer 2010 [*[*8*](#_ENREF_8)*].* |

These data were used to calculate quality-of-life decrements with fluoropyrimidine monotherapy or FOLFOX aCT using the following equations. Specifically, Equation 1 and Equation 2 were used to estimate the quality-of-life decrement with fluoropyrimidine monotherapy, and Equation 3 was used to find the quality-of-life decrement with FOLFOX.

Equation 1

$$\left(Quality of life decrement with any aCT\right)= \left(Patients receiving fluoropyrimidine monotherapy, \%\right)×\left(Fluoropyrimidine monotherapy decrement\right)+\left(Patients receiving FOLFOX, \%\right)×(FOLFOX decrement\_{Blinman})$$

Equation 2

$$\left(FOLFOX decrement\_{Blinman}\right)=\left(Fluoropyrimidine monotherapy decrement\right)+(Difference between regimens\_{Blinman})$$

Equation 3

$$\left(FOLFOX decrement\_{4-year}\right)=\left(Fluoropyrimidine monotherapy decrement\right)+(Difference between regimens\_{4-year})$$

The “*Blinman*” subscript indicates that chronic PSN-related quality-of-life decrements were weighted by the years since aCT completion among the patients in the Blinman study population described in Supplemental Table 6 [[8](#_ENREF_8)]. The “*4-year*” subscript indicates that chronic PSN-related quality-of-life decrements were for all 4-years of follow-up as reported in the MOSAIC randomized clinical trial [[3](#_ENREF_3)]. Using Equation 1 and Equation 2, the *fluoropyrimidine monotherapy decrement* was 1.0 QALYs. Using Equation 3, the *FOLFOX decrement4-year* was 1.1 QALYs.

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