

Supplemental online content for:

## Treatment and Survival Among Patients With Colorectal Cancer in Sub-Saharan Africa: A Multicentric Population-Based Follow-Up Study

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**eFigure 1:** Patient Flowchart and Description of Cohorts

**eFigure 2:** Overall Survival of Traced Patients

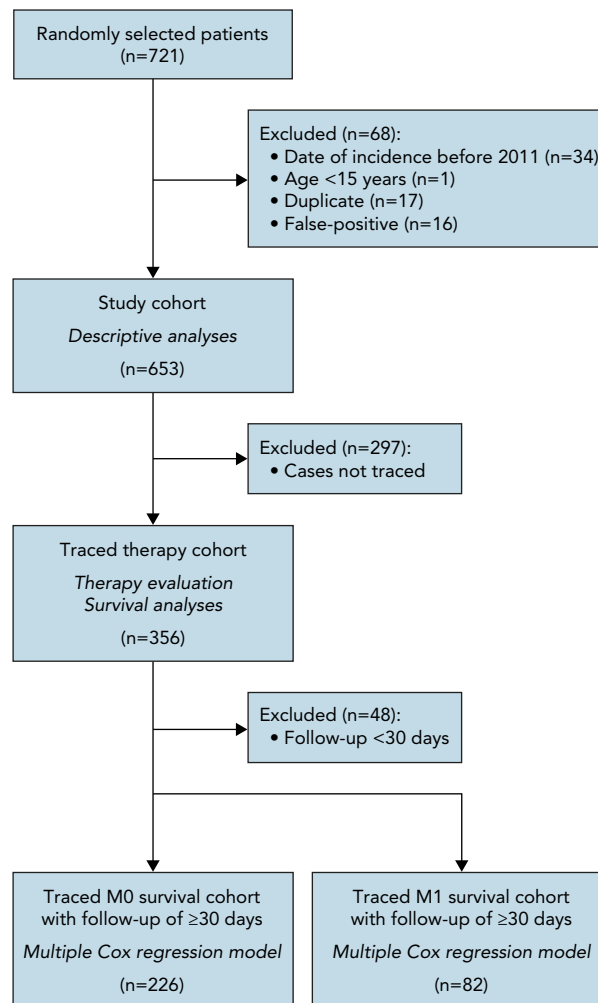
**eFigure 3:** Kaplan-Meier Curve Showing Overall Survival According to Disease Stage

**eTable 1:** Data From Cancer Registries in Sub-Saharan Africa

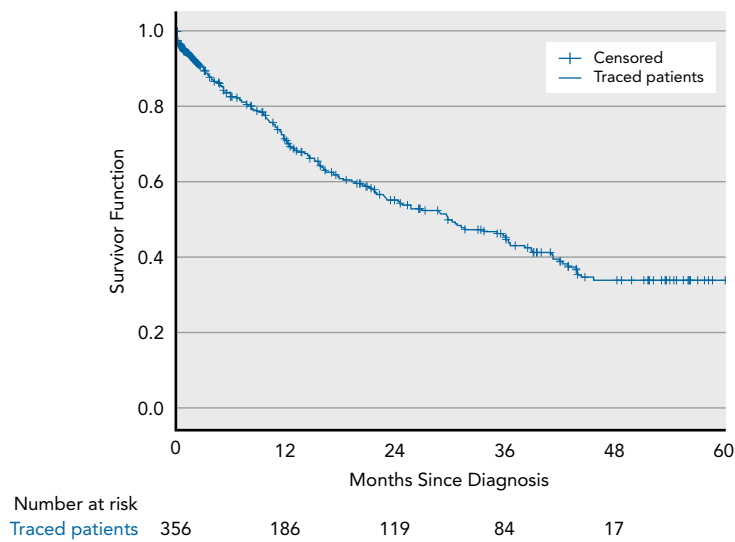
**eTable 2:** Simplified NCCN Harmonized Guidelines Concordance Scheme for Resectable Colon and Rectal Cancers

**eTable 3:** Empirical Evidence for Simplified Guideline Evaluation Scheme for Colon and Rectal Cancer

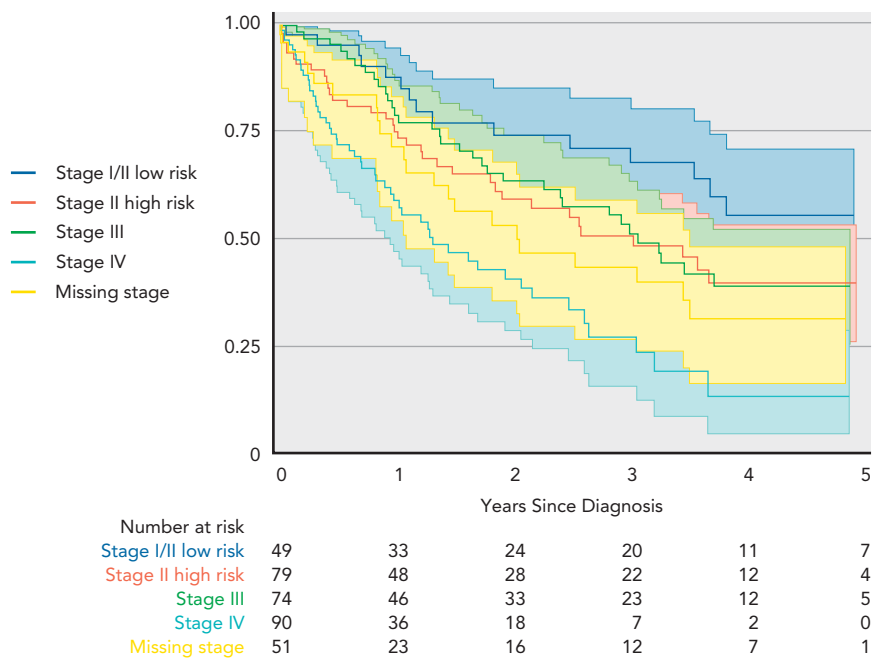
**eTable 4:** Multivariable Cox Regression Analysis in the Traced Cohort With Follow-Up  $\geq 30$  Days and M1 Disease



**eFigure 1.** Patient flowchart and description of cohorts.



**eFigure 2.** Overall survival of traced patients.



**eFigure 3.** Kaplan-Meier curve showing overall survival, with 95% confidence intervals, according to disease stage.

**eTable 1. Data From Cancer Registries in Sub-Saharan Africa**

|             | Registry    | Diagnosis Years | Population of Registry Area <sup>a</sup><br>n | Randomly Selected Cases<br>n | Sampling Fraction<br>% | Exclusions <sup>b</sup><br>n (%) <sup>c</sup> |
|-------------|-------------|-----------------|---|------------------------------|------------------------|---|
| Total, N    |             |                 | 21,518,198                                    | 721                          |                        | 68  |
| Ivory Coast | Abidjan     | 2011–2013       | 4,402,949                                     | 80                           | 50.8                   | 12 (15.0)                                     |
| Ethiopia    | Addis Ababa | 2011–2014       | 3,050,000                                     | 85                           | 15.5                   | 3 (3.5)                                       |
| Mali        | Bamako      | 2011–2014       | 1,810,366                                     | 100                          | 26.9                   | 2 (2.0)                                       |
| Congo       | Brazzaville | 2011–2013       | 1,549,693                                     | 58                           | 100                    | 0 (0)   |
| Zimbabwe    | Bulawayo    | 2012–2014       | 653,000                                       | 60                           | 63.2                   | 3 (5.0)                                       |
| Benin       | Cotonou     | 2013–2014       | 678,874                                       | 22                           | 100                    | 5 (22.7)                                      |
| Kenya       | Eldoret     | 2011–2014       | 894,179                                       | 91                           | 100                    | 33 (36.3)                                     |
| Uganda      | Kampala     | 2011–2013       | 2,010,000                                     | 60                           | 39.5                   | 3 (5.0)                                       |
| Mozambique  | Maputo      | 2014–2015       | 1,225,868                                     | 25                           | 100                    | 1 (4.0)                                       |
| Kenya       | Nairobi     | 2011–2013       | 3,138,369                                     | 60                           | 16.3                   | 2 (3.3)                                       |
| Namibia     | Nationwide  | 2012–2015       | 2,104,900                                     | 80                           | 21.1                   | 4 (5.0)                                       |

<sup>a</sup>From Parkin DM, Ferlay J, Jemal A, et al, eds. Cancer in Sub-Saharan Africa. International Agency for Research on Cancer; 2018.

<sup>b</sup>Cases were excluded due to false diagnosis at registration, incidence before 2011 or after 2015, or double registration.

<sup>c</sup>Percentage of randomly selected cases.

**eTable 2. Simplified NCCN Harmonized Guidelines Concordance Scheme for Resectable Colon and Rectal Cancers**

|                                    | Standard of Care   | Minor Deviation  | Major Deviation   | No Cancer-Directed Therapy   |
|------------------------------------|--|--|---|--|
| <b>Colon cancer</b>                |  |  |   |  |
| Stage I/II<br>low risk             | Colectomy with en bloc removal of regional lymph nodes (lymph nodes >11)<br><i>no (neo-)adjuvant treatment<sup>a</sup></i>   | Colectomy with en bloc removal of regional lymph nodes (lymph nodes 1–11)<br><i>Irrespective of adjuvant treatment</i>   | Colectomy without removal of lymph nodes (no lymph nodes reported)<br><i>Irrespective of adjuvant treatment</i>                           |  |
| Stage II<br>high risk <sup>b</sup> | Radical surgical resection with en bloc removal of regional lymph nodes (lymph nodes >11)<br>±<br><i>Adjuvant chemotherapy: 3–6 months 5-FU/LV or 8 cycles capecitabine</i>  |  |   | No surgery or colostomy/laparotomy only<br><i>Irrespective of adjuvant treatment</i> |
| Stage III                          | Radical surgical resection with en bloc removal of regional lymph nodes (lymph nodes >11)<br>+<br><i>CapeOx for at least 3 months or mFOLFOX or capecitabine or 5-FU/LV for at least 3–6 months</i>  | Radical surgical resection (number of lymph nodes removed 1–11) and <i>any other complete<sup>c,d</sup> chemotherapy protocol</i> or<br>Radical surgical resection (lymph nodes >11) and <i>Incomplete<sup>c,d</sup> chemotherapy and/or no adjuvant treatment</i> | Inadequate surgical resection (no lymph node removal) and/or<br><i>Incomplete<sup>c,d</sup> chemotherapy and/or no adjuvant treatment</i> |  |
| <b>Rectal cancer</b>               |  |  |   |  |
| Stage I                            | Transanal local excision or transabdominal (abdominoperineal or low anterior) resection and TME, no RCT  | Surgical resection with incomplete TME (number of lymph nodes removed 1–11)  | Inadequate surgical resection without TME (no lymphadenectomy reported)   |  |
| Stage II/III                       | Neoadjuvant RCT <sup>e</sup> : Capecitabine/RT or 5-FU/RT or FL/RT or chemotherapy only (12–16 weeks)<br><br>Transabdominal resection and TME (lymph nodes ≥12)<br><br>(optional:) Adjuvant chemotherapy: FOLFOX or CapeOx or FL or capecitabine (6 months of perioperative treatment preferred) | Neoadjuvant RCT with other agents then capecitabine/5-FU or incomplete RCT and/or<br>Surgical resection with incomplete TME (number of lymph nodes removed 1–11)   | No neoadjuvant RCT and/or<br>Inadequate surgical resection without TME (no lymphadenectomy reported)                                      | No surgery or colostomy/laparotomy only; irrespective of RCT                         |

Abbreviations: CapeOx, capecitabine/oxaliplatin; FL, 5-FU/leucovorin; FOLFOX, leucovorin/5-FU/oxaliplatin; LV, leucovorin; RCT, radiochemotherapy; RT, radiotherapy; SSA, Sub-Saharan Africa; TME, total mesorectal excision.

<sup>a</sup>Due to presumable understaging, adjuvant treatment in stage I/II was not considered as treatment deviation but as adequate therapy.

<sup>b</sup>High-risk factors: <12/<10 lymph nodes removed, tumor perforation, high-grade tumor, mucinous adenocarcinoma or signet ring cell carcinoma, emergency surgery, lymphatic/vascular invasion, bowel obstruction, positive resection margins.

<sup>c</sup>Chemotherapy was considered “complete” if patient received ≥85% of planned regimen.

<sup>d</sup>The final survival analysis was based on initiation of treatment rather than completeness to allow assessment of concordance with NCCN Harmonized Guidelines for SSA.

<sup>e</sup>RT was considered “received” if patient received ≥20 Gy and/or at least 4 RT sessions.

**eTable 3. Empirical Evidence for Simplified Guideline Evaluation Scheme for Colon and Rectal Cancer**

| <b>Colon cancer</b>   |  |                                       |  |   |
|---|--|---------------------------------------|--|---|
| <b>Resectable cancer – stage I–III</b>  |  |                                       |  |   |
| <b>Radical resection is the most relevant therapeutic modality. Prognosis is dependent on the number of lymph nodes examined</b>  |  |                                       |  |   |
| Chang et al   | Lymph node evaluation and survival after curative resection of colon cancer: systematic review   | J Natl Cancer Inst<br>2007;99:433–441 | <b>Stage II</b><br>>20 negative lymph nodes examined vs <11                                | Higher absolute <b>5-y OS</b> : 14%   |
| Le Voyer et al  | Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of Intergroup trial INT-0089  | J Clin Oncol<br>2003;21:2912–2919     | <b>Stage IIIa</b><br>>40 lymph nodes examined vs <11                                       | Higher absolute <b>5-y OS</b> : 23%   |
| <b>Stage II</b>   |  |                                       |  |   |
| <b>In high-risk situation (T4, bowel obstruction or perforation, emergency surgery) adjuvant chemotherapy can be of advantage</b> |  |                                       |  |   |
| QUASAR Collaborative Group  | Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomized study  | Lancet<br>2007;370:2020–2029          | <b>Stage II</b><br>Adjuvant chemotherapy with fluorouracil and folinic acid vs observation | Absolute improvement in <b>OS</b> : 3.6% (95% CI, 1.0–6.0)<br><b>RR of recurrence</b> : 0.78 (95% CI, 0.67–0.91; <i>P</i> = .001) |
| <b>Stage III</b>  |  |                                       |  |   |
| <b>In N+ situation, adjuvant chemotherapy with FOLFOX, XELOX, or similar scheme is indicated</b>                                  |  |                                       |  |   |
| Gill 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<br>2004;22:1797–1806     | <b>Stage IIIa</b><br>Surgery alone vs surgery + adjuvant chemotherapy                      | <b>DFS</b> : HR, 0.605<br><b>OS</b> : HR, 0.662   |
| André et al   | 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<br>2009;27:3109–3116     | <b>Stage III</b><br>LV5FU2 vs FOLFOX4 regimen  | Improvement in <b>DFS</b> : 7.5% (HR, 0.78; 95% CI, 0.65–0.93; <i>P</i> = .005)   |
| Schmoll et al   | Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial | J Clin Oncol<br>2015;33:3733–3740     | <b>Stage III</b><br>XELOX vs FU/FA   | <b>7-y DFS</b> : HR, 0.80; (95% CI, 0.69–0.93; <i>P</i> = .004)<br><b>7-y OS</b> : HR, 0.82 (95% CI, 0.7–0.99; <i>P</i> = .04)    |

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| <b>eTable 3. Empirical Evidence for Simplified Guideline Evaluation Scheme for Colon and Rectal Cancer (cont.)</b>                    |  |                                  |  |  |
|---|--|----------------------------------|--|--|
| <b>Rectal cancer</b>  |  |                                  |  |  |
| <b>Stage I</b><br><b>Preoperative treatment is not associated with improved OS</b>  |  |                                  |  |  |
| van Gijn et al  | Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomized controlled TME trial            | Lancet Oncol 2011;12:575–582     | <b>Stage I</b><br>RT + TME vs TME only   | <b>OS: 1.17</b> (95% CI, 0.86–1.59)  |
| <b>Stage I–III</b><br><b>Total anatomic dissection is crucial</b>   |  |                                  |  |  |
| Bokey et al   | Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: role of total anatomic dissection  | Br J Surg 1999;86:1164–1170      | Independent predictive factors for local recurrence: total anatomic dissection of the rectum | <b>HR, 2.0; P=.01</b>  |
| <b>Stage II/III (cT3/4 or N+)</b><br><b>Tumors of middle or lower rectum should be treated with preoperative RCT or short-time RT</b> |  |                                  |  |  |
| Colorectal Cancer Collaborative Group   | Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomized trials   | Lancet 2001;358:1291–1304        | Preoperative RCT vs surgery alone  | <b>5-y local recurrence:</b> 12.5% vs 22.2%  |
| Fiorica et al   | Can chemotherapy concomitantly delivered with radiotherapy improve survival of patients with resectable rectal cancer? A meta-analysis of literature data                        | Cancer Treat Rev 2010;36:539–549 | Preoperative RCT vs preoperative RT alone  | <b>RR of 5-y local recurrence:</b> 1.05 (95% CI, 1.01–1.10)<br>But: 5-y OS: RR, 0.94 (95% CI, 0.94–1.09) |
| <b>Stage I–III</b><br><b>TME is surgical standard in rectal cancer</b>  |  |                                  |  |  |
| Havenga et al   | Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1,411 patients | Eur J Surg Oncol 1999;25:368–374 | TME vs “conventional surgery”  | <b>5-y OS:</b> 62%–75% vs 42%–44%<br><b>Local recurrence:</b> 4%–9% vs 32%–35%                           |

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RCT, radiochemotherapy; RR, relative risk; RT, radiotherapy; TME, total mesorectal excision.

**eTable 4. Multivariable Cox Regression Analysis in the Traced Cohort With Follow-Up  $\geq 30$  Days and M1 Disease**

|                         | Traced Cohort<br>(n=81)<br>(46 total events) | HR (95% CI)          | P Value <sup>a</sup> |
|-------------------------|--|----------------------|----------------------|
| Age                     |  |                      |                      |
| <60 y                   | 54   | Ref                  |                      |
| $\geq 60$ y             | 28   | 1.22 (0.6–2.5)       | .58                  |
| ECOG performance status |  |                      |                      |
| I–II                    | 14   | Ref                  |                      |
| III–IV                  | 33   | 1.35 (0.5–3.6)       | .54                  |
| Unknown                 | 35   | 0.80 (0.3–2.0)       | .65                  |
| Surgery use             |  |                      |                      |
| Yes                     | 45   | Ref                  |                      |
| No/Unknown              | 37   | <b>2.1 (1.1–4.0)</b> | <b>.02</b>           |
| Chemotherapy use        |  |                      |                      |
| Yes                     | 49   | Ref                  |                      |
| No/Unknown              | 33   | 0.73 (0.4–1.5)       | 1.48                 |
| Radiotherapy use        |  |                      |                      |
| Yes                     | 18   | Ref                  |                      |
| No/Unknown              | 64   | 2.06 (0.9–4.7)       | .09                  |

<sup>a</sup>Bold indicates statistically significant P value.