

Supplementary Online Content

Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol*. Published online January 10, 2019. doi:10.1001/jamaoncol.2018.5896

eFigure 1. Swimmer Plot of Local Regrowth Patients

eFigure 2. Overall Survival (OS), Disease-Free Survival (DFS) and Disease-Specific Survival (DSS) At 5 Years in the Pathologic Complete Response (pCR) Cohort

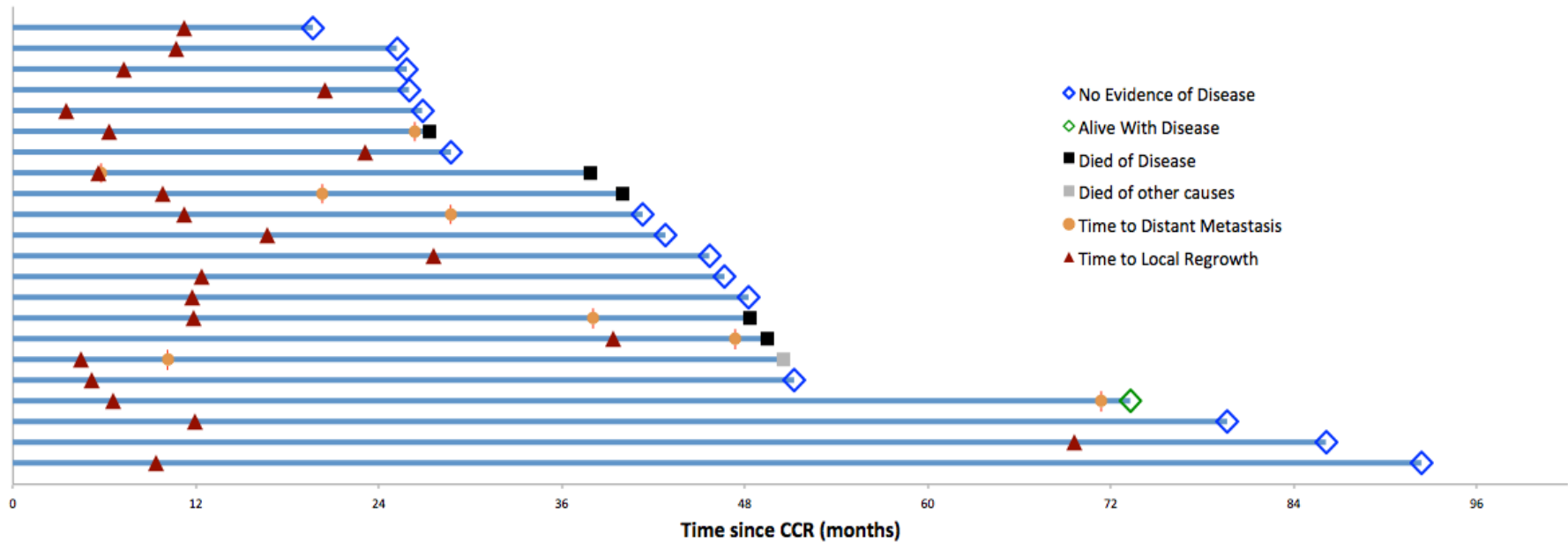
eFigure 3. Five-Year Survival in the WW Cohort in Relation to Treatment Received

eFigure 4. Five-Year Overall Survival in the WW Cohort in Relation to MRI Staging

eTable. Comparison With Previous Watch-And-Wait Studies

This supplementary material has been provided by the authors to give readers additional information about their work.

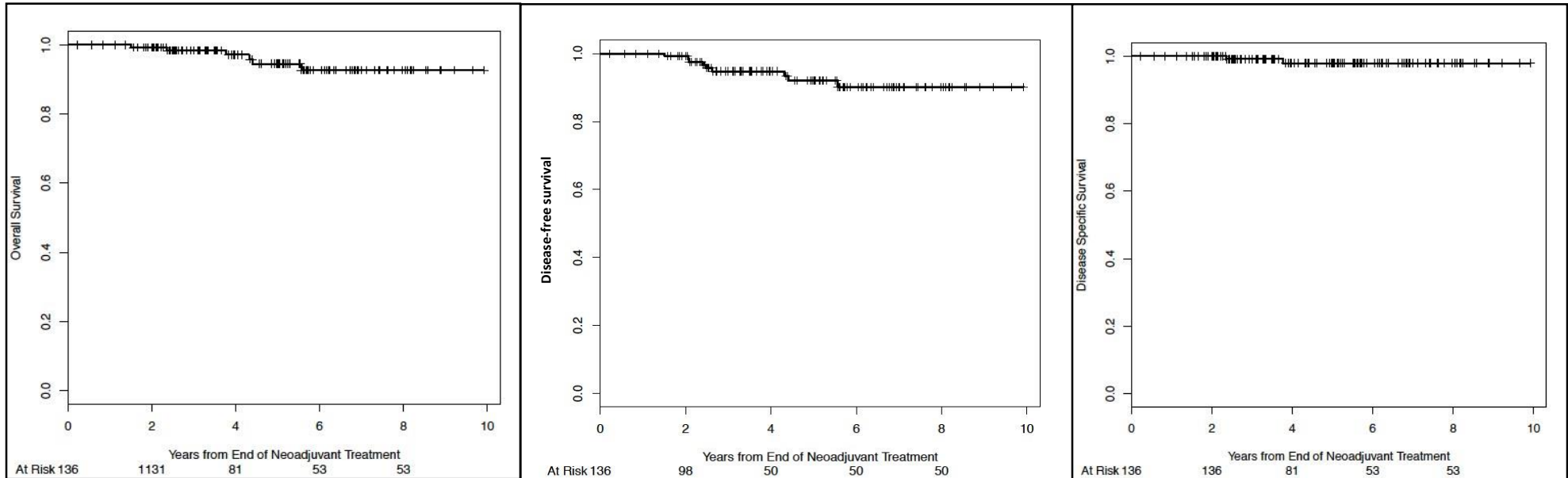
Patients with Local Regrowth



eFigure 1. Swimmer Plot of Local Regrowth Patients

Swimmer plot depicting the clinical course of patients from the watch and wait group who had a local regrowth. Patients are plotted in order by length of follow-up from declaration of clinical complete response (cCR). The majority of patients were found to have a local regrowth in the first 12 months (72%) from the date of cCR with a median time of 11.2 months. 15 patients remain free of disease (68%), one is alive with disease, five died of disease and one died of other causes. Patients who developed distant metastasis are denoted by an orange circle, and the one patient with distant metastasis and no current evidence of disease after metastasectomy is also denoted by an orange circle with the open blue diamond.

Pathologic Complete Response Cohort



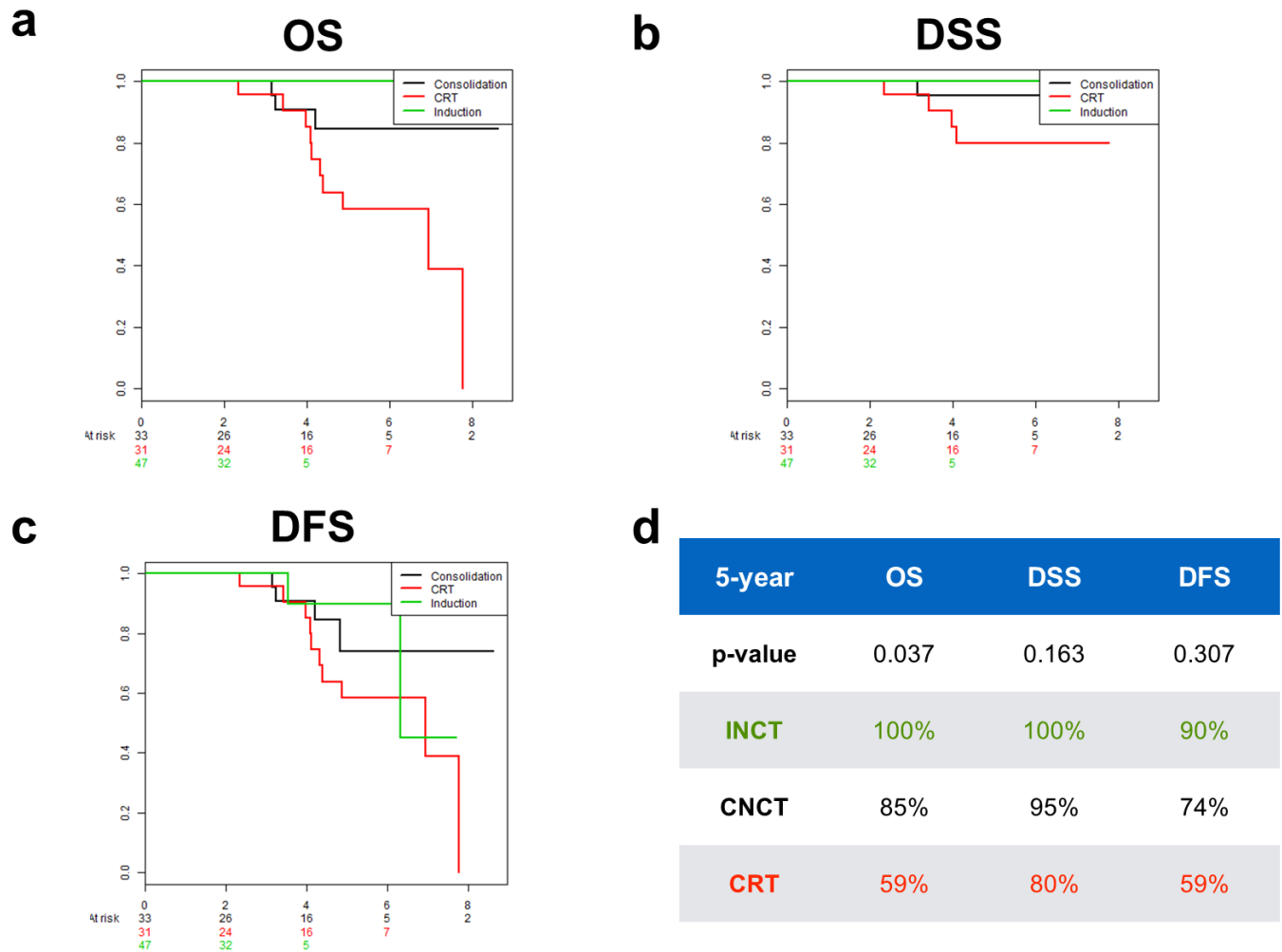
a. Overall Survival

b. Disease-free survival

c. Disease-specific survival

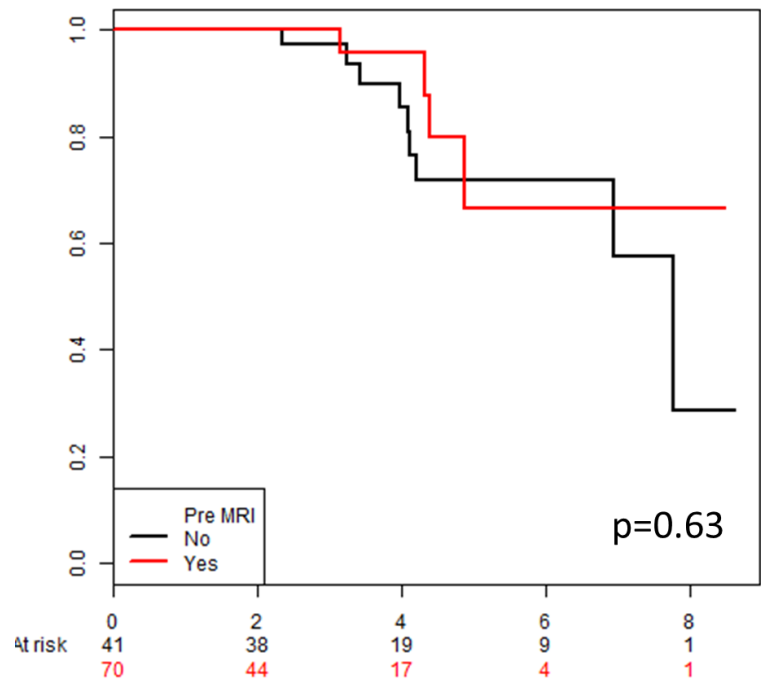
eFigure 2. Overall Survival (OS), Disease-Free Survival (DFS) and Disease-Specific Survival (DSS) at 5 Years in the Pathologic Complete Response (pCR) Cohort

a) OS was 94% (95% CI 90%–99%); b) DFS was 92% (95% CI 87%–98%); and c) DSS was 98% (95% CI 95%–100%) in the pCR group. Survival was measured from the end of NAT. DFS events included loco-regional recurrence, distant recurrence, and death from any cause.



eFigure 3. Five-Year Survival in the WW Cohort in Relation to Treatment Received

Patients received (i) induction chemotherapy followed by chemoradiotherapy (INCT), (ii) chemoradiotherapy followed by consolidation chemotherapy (CNCT), or (iii) chemoradiotherapy only (CRT). p-values were calculated using the log-rank test.



eFigure 4. Five-Year Overall Survival in the WW Cohort in Relation to MRI Staging
 Patients were grouped by whether pretreatment staging of their disease involved MRI.

eTable. Comparison with Previous Watch-and-Wait (WW) Studies								
Study	N	Follow-up Months (Range)	cCR (n%)	LR (n%)	Salvage (%) (Details and other notes if available)	DM	DFS	OS
Habr-Gama A 2004 PMID: 15383798	265	Mean 57.3 (12-156)	71/265 (26.8)	2/71 (3%)	97% (69/71) - 2 TAE/SBRT **100% (69/69)	3/71 (4.2%) - 3 systemic CTX	92% (5Y)	100% (5Y)
Habr-Gama A 2014 PMID: 24495589	183	Median 60 (12-233)	90/183 (49%)	28/90 (31%)	93%* (26/28) - 25 R0 TME - 1 SBRT - 2 no salvage **84% (22/26) - 4 palliative procedures	8/90 (8.9%) -1 curative liver rsxn -7 systemic CTX	68% (5Y)	91% (5Y)
Maas M 2011 PMID: 22067400	192	Mean 25 (+/- 19)	21/192 (11%)	1/21 (4.8%)	1/ 21 (4.8%) - 1 TAE	0/21 (0%)	89% (2y)	100% (2Y)
Martens MH 2016 PMID: 27509881	100	Median 41.1 (12-120)	61/100 (61%)	15/100 (15%)	87%* (13/15) 13 R0 TME - 8 APR - 5 LAR - 2 LR: -1 SBRT to lung/Papillon to regrowth tumor -1 palliative CTX	5/100 (5%) - 4 lung (OR, CTX & RT) - 1 peritoneum (POD)	81% (3Y)	97% (3Y)

Appelt A 2016 PMID: 26156652	51	Median 24 (15-31)	40/51 (78%)	9/40 (23%)	*100% (9/9) 9 R0 TME - 9 APR **100% (9/9)	3/40 (8%) - 3 lung rxns	70% (2Y)	100% (2Y)
Renehan A 2016 PMID: 26705854	259 (+98 WW ONLY via registry)	Median 33 (19-43)	129 / 259 (50%) (31 +98 registry)	44/129 (34%)	*68% (30/44) 30 R0 TME <u>(Others:</u> - 1 R1 resection - 5 Papillon - 5 Palliative CTX/other - 1 APR + Liver (LR+DM) - 2 chemo only (LR + DM))	7/129 (6%) - 3 liver rxns - 1 inguinal rxns - 3 systemic CTX	NR	96% (3Y)
Van der Valk MJM 2018 PMID: 29976470	880	Median 39.6 (95% CI 37.2%- 43.2%)	-	213/667 (24%) - 2-year rate 25%	*Only 148 of 213 with data - 46 TAE - then 13 TME (included below in TME count) - 115 TME - 101 R0 88% - 7 R1 (6%) - 7 R status unknown (6%)	71/809 (8%) - No treatment details	NR	85% (5Y) -88% if no regrowth - 75% if regrowth
Smith JJ 2018 <i>JAMA Oncol.</i> PMID: pending	249	Median 43 (IQR 27-43)	113/1070 (11%)	22/113 (19.5%)	100%* (22/22) 2 TAE	9/113 (8%) - 5 systemic	75% (5Y)	73% (5Y)

	-113 WW (eTable data is focused on WW group) -136 pCR	- WW median 33 months - pCR median 55 months			20 R0 TME - 9 LAR - 11 APR **91% (20/22) - 2 eventual pelvic recurrences - 1 small bowel bowel bypass -1 palliative CTX	CTX - 1 lung rsxn (no local regrowth) - 1 lung stable on CTX - 1 liver SBRT - 1 supportive care only			
cCR = clinical complete response LR = local regrowth DM = distant metastasis rate DFS = disease-free survival rate OS = overall survival pCR = pathologic complete response					*Salvage surgery performed **Long-term pelvic control (if reported) - not reported	CTX = chemotherapy resxn = resection OR = operating room RT = radiation therapy POD = progression of disease			
Y = year; R0 = margin negative resection; R1 = microscopic margins positive; TAE = transanal excision; SBRT = stereotactic body radiation therapy; IQR = interquartile range									
<u>Additional notes on local regrowth vs. no local regrowth and metastasis rates in PMID 29976470 and in our current paper:</u> Van der Valk MJM et al. <i>Lancet</i> 2018: Local regrowth metastasis rate = 18% vs. No local regrowth metastasis rate = 5% Smith et al. <i>JAMA Oncol.</i> 2018: Local regrowth metastasis rate = 36% vs. No local regrowth metastasis rate = 1%									