Supplementary Table 1 Treatment schedules and important findings of clinical trials

Trials (patients, period)	Treatment arms	Details of radiotherapy and chemotherapy[1]	Results[2] (primary endpoint, arm A vs B [vs C])
TOTAL NEOADJUVANT TREATMENT TRIALS			
POLISH II[1, 2] Phase III (541, 2008–2014) NCT00833131	A. CRT (5-FU+LV #2, oxaliplatin #5) → S (→ CT) B. SCRT → FOLFOX4 #3 → S (→ CT) Surgery was performed 10-11 weeks from beginning of RT and at least 4 weeks from the last dose of 5-FU or the last dose of RT. The decision on delivering adjuvant chemotherapy was left to the discretion of treating physicians.	RT Dose: 50.4 Gy in 28 fractions (group A) 25 Gy in 5 fractions (group B) CT During CRT: two 5-day cycles of **5-FU** 325 mg/m^2/day and LV 20mg/m^2/day in bolus during the 1st and 5th weeks of RT. **Oxaliplatin** 50 mg/m^2 once a week 5 times during 1, 8, 15, 22 and 29 days of radiation (since 2012, the decision about delivery of oxaliplatin was left to the discretion of the local institution).	R0: 71% vs 77% (ns) pCR: 12% vs 16% (ns) 8y OS: 49% vs 49% (ns) 8y DFS: 41% vs 43% (ns) cLF: 32% vs 35% (ns) cDM: 34% vs 36% (ns) Gr 3+ late toxicities 9% vs 11% (ns)
FOWARC[3] Phase III (495, 2010–2015) NCT01211210	A. CRT (de Gramont #5) → TME → de Gramont #7 B. CRT (mFOLFOX6 #5) → TME → mFOLFOX6 #7 C. mFOLFOX6 #4–6 → TME → mFOLFOX6 #6–8 RT was given during the 2nd to 4th cycles of the de Gramont or mFOLFOX6 regimen in group A and B. In group C, the addition of RT before or after surgery was considered at physician discretion (mainly for patients with mesorectal fascia involvement/positive circumferential resection margin and T4 disease).	RT Dose: 46–50.4 Gy in 23–28 fractions (group A/B) Technique: 3-field or 4-field box technique to the primary tumor and to mesorectal, presacral, and internal iliac lymph nodes. CT group A: de Gramont (LV 400 mg/m^2 IV, followed by 5-FU 400 mg/m^2 IV bolus and 5-FU 2.4 g/m^2 by 48-h continuous IV every 14 days) group B/C: **mFOLFOX6** (de Gramont regimen + oxaliplatin 85 mg/m^2 IV on day 1 of each chemotherapy cycle, every 14 days)	pCR: 14.0% vs 27.5% vs 6.5% 3y DFS: 72.9%vs 77.2% vs 73.5% (ns) 3y LF: 8.0% vs 7.0%vs 8.3% (ns) 3y OS: 91.3% vs 89.1% vs 90.7% (ns)
RAPIDO[4, 5]	A. CRT (cape) → TME → CAPOX #9 or FOLFOX4	RT	**pCR: 14% vs 28% (*)**

Phase III (920, 2011–2016) NCT01558921	#12 B. SCRT → CAPOX #6 or FOLFOX4 #9 → TME Surgery was performed 6–10 weeks after the last RT fraction (group A) or 2–4 weeks after completion of CT (group B).	Dose: 50–50.4 Gy in 25–28 fractions (± boost 1.8- 2 Gy x 2-4) for group A, 25 Gy in 5 fractions (± boost 2 Gy x 2-3) for group B Technique: 3D-CRT. CTV included the entire mesorectum with the primary tumor and relevant regional lymph nodes. An additional boost dose was optional CT During CRT: **capecitabine** (825 mg/m^2 twice daily on all days of RT, including weekends) Neoadjuvant or adjuvant: **CAPOX** or **FOLFOX4**	3y OS: 88.8% vs 89.1% (ns) **3y DRTF: 30.4% vs 23.7% (*)** **3y DM: 26.8% vs 20.0% (*)** 3y LF: 6.0% vs 8.3% (ns)
PRODIGE23[6] Phase III (461, 2012–2017) NCT01804790	A. CRT (cape) → TME → mFOLFOX6 #12 or cape B. FOLFIRINOX #6 → CRT (cape) → TME → mFOLFOX6 #6 or cape Surgery was performed 6–8 weeks after CRT.	RT Dose: 50 Gy in 25 fractions (group A/B) Technique: 3D-CRT. CTV included the entire mesorectum with the primary tumor and relevant regional lymph nodes. An additional boost dose was optional. CT (neoadjuvant and adjuvant) Induction: **FOLFIRINOX** During CRT: **capecitabine** (800 mg/m^2 twice daily on the days of RT) Adjuvant: **mFOLFOX6** or **capecitabine** (1250 mg/m^2 twice daily on days 1–14 every 21 days) for 6 months in group A and 3 months in group B.	**pCR: 12% vs 28% (*)** 3y OS: 88% vs 91% (ns) 3y CSS: 89% vs 92% (ns) **3y DFS: 69% vs 76% (*)** **3y DMFS: 72% vs 79% (*)** LF: 5.7% vs 4.3% (ns)
STELLAR[7] Phase III (599, 2015–2018) NCT02533271	A. CRT (cape) → TME → CAPOX #6 B. SCRT → CAPOX #4 → TME → CAPOX #6 Surgery was performed 6-8 weeks after preoperative treatment. The protocol allowed for a watch-and-wait strategy if patients achieved cCR, requested organ preservation, or refused radical surgery (nonoperative management).	RT Dose: 50.4 Gy in 28 fractions (group A) 25 Gy in 5 fractions (group B) Technique: IMRT. CTV included the primary tumor, regional lymph nodes, and pelvic regions at risk according to consensus reached by the Radiation Therapy Oncology Group[8] and Roels[9]. CT During CRT: **capecitabine** (825 mg/m^2 twice a day on the	**pCR: 11.8% vs 16.6% (*)** **3y OS: 75.1% vs 86.5% (*)** 3y DFS: 62.3% vs 64.5% (ns) 3y LF: 11.1% vs 8.4% (ns) 3y DM: 24.7% vs 22.8% (ns)

		days of RT) Consolidation or adjuvant: **CAPOX (**group A/B)	
CAO/ARO/AIO-12[10, 11] Phase II (311, 2015–2018) NCT02363374	A. FOLFOX #3 → CRT (5-FU+oxaliplatin) → TME B. CRT (5-FU+oxaliplatin) → FOLFOX #3→ TME Surgery was performed approximately day 123 after initiation of TNT. Adjuvant chemotherapy after TME was not recommended.	RT Dose: 50.4 Gy in 28 fractions (group A/B) Technique: IMRT to the primary tumor and to mesorectal, presacral, and internal iliac lymph nodes CT During CRT: **5-FU** (250mg/m^2 continuous IV on days 1 to 14 and days 22 to 35) and **oxaliplatin** (50 mg/m^2 on days 1, 8, 22, and 29) Induction or consolidation: **FOLFOX (**oxaliplatin 100 mg/m^2 IV, followed by LV 400mg/m^2 IV, followed by 5-FU 2 400 mg/m^2 continuous IV over 46 h every 14 days)	**pCR: 17% vs 25% (*)** 3y DFS: 73% vs 73% (ns) 3y cLF: 6% vs 5 % (ns) 3y cDM: 18% 16% (ns)
OPRA[12, 13] Phase II (324, 2014–2020) NCT02008656	A. mFOLFOX6 #8 or CAPOX #5→ CRT → WW or TME B. CRT → mFOLFOX6 #8 or CAPOX #5 → WW or TME Restaging was performed within 8 (±4) weeks after TNT. Patients with clinical complete response or near complete response were offered participation in a standardized WW protocol. Organ preservation, defined as TME-free survival measured in the intention-to-treat population, was the secondary endpoint.	RT Dose: 56 Gy in 28 fractions (45 Gy to the pelvis, with an integrated boost to the primary tumor and involved nodes of 50 Gy, followed by a 6 Gy boost to the primary tumor and involved nodes) for group A/B Technique: IMRT or 3D-CRT to deliver 45 Gy in 1.8 Gy over 25 fractions to regional pelvic nodes (including inguinal nodes for primary tumors involving the anus) CT During CRT: **5-FU** (225 mg/m^2/d continuous IV) or **capecitabine** (825 mg/m^2 twice a day) Induction or consolidation: **mFOLFOX6** or **CAPOX**	3y DFS: 76% vs 76% (ns) 3y LF: 6% vs 6% (ns) 3y DMFS: 84% vs 82% (ns) OS (ns) **Regrowth during WW: 40% vs 27% (*)** **3y TME-free survival: 41% vs 53% (*)**
Tang *et al*[14] Phase II RCT (224, 2020-2022) ongoing NCT04543695	A. CRT → TME → CAPOX #6 B. CRT → CAPOX #6 → TME or WW C. CAPOX #6 → CRT → TME or WW	RT Dose: 50 Gy in 25 fractions CT During CRT: **capecitabine** (825 mg/m^2 twice a day) Induction or consolidation: **CAPOX**	(preliminary) yp0-II: 77.1% vs 84.2% vs 57.1% pCR+sustained cCR: 22.9% vs 42.1% vs 28.6%
CAO/ARO/AIO-18.1[15]	A. SCRT → CAPOX #6 or mFOLFOX6 #8 → WW	RT	

Phase III ongoing NCT04246684	or TME B. CRT (5-FU+oxaliplatin) → CAPOX #4 or mFOLFOX6 #6 → WW or TME Restaging at week 22–24 (2–4 weeks after the last dose of CT), then WW for cCR or TME for non-cCR	Dose: 25 Gy in 5 fractions (group A) 54 Gy in 30 fractions (group B) CT During CRT: **5-FU** (250mg/m^2 continuous IV on days 1 to 14 and days 22 to 35) and **oxaliplatin** (50 mg/m^2 on days 1, 8, 22, and 29)	
NEOADJUVANT TRIALS USING IMMUNE CHECKPOINT INHIBITORS			
VOLTAGE-A[16] Phase I/II NCT02948348 (39, 2017–2019)	CRT (cape) → Nivolumab #5 → TME (→ mFOLFOX6/CAPOX) Surgery was performed within 14 weeks after the end of CRT (98 days from the day following the last day of CRT). For patients with favorable postoperative conditions, a maximum of 6 months on adjuvant mFOLFOX6 or CAPOX was recommended, at the investigator's discretion.	RT Dose: 50.4 Gy in 28 fractions (45 Gy/25 fractions to the pelvic cavity and 5.4 Gy/3 fractions boost to the primary lesion) CT During CRT: **capecitabine** (825 mg/m^2 twice a day on the days of RT) ICI **Nivolumab** 240 mg every 2 weeks, starting within 14 days of completion of CRT	pCR - 30% (MSS) vs 60% (MSI-H) - 75% (PD-L1 ≥1%) vs 17% (<1%) - 78% (CD8/eTreg ≥2.5) vs 13% (<2.5)
AVANA[17] Phase II NCT03854799 (101, 2019–2020)	CRT (cape) + Avelumab #6 → TME Surgery was performed 8–10 weeks after the end of CRT.	RT Dose: 50.4 Gy in 28 fractions CT During CRT: **capecitabine** (825 mg/m^2 twice a day on the days of RT)) ICI **Avelumab** 10 mg/kg every 2 weeks, starting on day 1 of CRT	pCR 23% major pathologic response 61.5%
R-IMMUNE[18] Phase Ib/II NCT03127007 (26, ongoing)	CRT (5-FU) + Atezolizumab #4 → S Surgery is planned at week 15.	RT Dose: 45–50 Gy in 25 fractions CT During CRT: IV protracted 5-FU given at 225mg/m^2 over 24h 5 days/week for 5 weeks	pCR 24%

		ICI Atezolizumab 1200 mg on day 1 of week 3, 6, 9 and 12	
NRG-GI002[19] Phase II randomized NCT02921256 (185, 2018–2019)	A. mFOLFOX6 #6 → CRT (cape) → TME B. mFOLFOX6 #6 → CRT (cape) + Pembrolizumab #6 → TME Surgery was performed 8–12 weeks after the last dose of RT.	RT Dose: 50.4 Gy in 28 fractions (45 Gy in 25 fractions for 5weeks plus a 5.4 Gy boost in 3 fractions) CT During CRT: **capecitabine** (825 mg/m^2 twice a day on the days of RT)) ICI **Pembrolizumab** 200mg every 3 weeks, starting on day 1 of CRT	NAR score: 14.08 vs 11.53 (ns) cCR: 13.6% vs 13.9% (ns) pCR: 29.4% vs 31.9% (ns) SSS: 71.0% vs 59.4% (ns)
AVERECTAL[20-22] Phase II (44, 2018–2020) NCT03503630	SCRT → mFOLFOX6 + Avelumab #6 → TME Surgery was performed 3–4 weeks after the last cycle of mFOLFOX-6 & avelumab.	RT Dose: 25 Gy in 5 fractions Technique: IMRT or 3D-CRT. CTV includes GTV with 0.5 cm extension and all perirectal, presacral, and internal iliac lymph nodes all the way up to the sacral promontory CT & ICI **mFOLFOX6** 30 min after **avelumab** 10 mg/kg every 2 weeks, starting one week after SCRT	pCR 37.5% major pathologic response 67.5%
Lin *et al*[23] Phase II (27, 2019-2020) NCT04231552	SCRT → CAPOX + Camrelizumab #2 → TME Surgery was performed after 1 week of the last dose of CT.	RT Dose: 25 Gy in 5 fractions CT & ICI **CAPOX** plus **Camrelizumab** (200mg on day 1 of each cycle), starting 1 week after SCRT, every 3 weeks	pCR 48.1% - pMMR 46.2% (12/26) - dMMR 100% (1/1)
TORCH[24, 25] Phase II randomized ongoing NCT04518280	A. SCRT → CAPOX + toripalimab #6 → TME or WW B. CAPOX + toripalimab #2 → SCRT → CAPOX + toripalimab #4 → TME or WW Surgery was performed 2–4 weeks after the end of	RT Dose: 25 Gy in 5 fractions Technique: IMRT CT & ICI **CAPOX** and **toripalimab** (240 mg) every 3 weeks	(preliminary) cCR+pCR: 81.3% (13/16 MSS patients) - group A (n=7) : cCR 1, pCR 4, near pCR 1 - group B (n=9): cCR 4, pCR 4

	the whole neoadjuvant treatment		
Cercek *et al*[26] Phase II ongoing NCT04165772	Dostarlimab #9 → if cCR → WW if residual+ → CRT → WW (cCR) or TME (residual+)	RT Dose: 50.4 Gy in 28 fractions CT During CRT: **capecitabine** (825 mg/m^2 twice a day) or **5-FU** (if patient is unable to tolerate oral medication) ICI **Dostarlimab** 500mg IV every 3 weeks	(preliminary) cCR 100% (12/12) - All are under active surveillance without progression or recurrence during 6 to 25 months.
PRIME-RT[27] Phase II randomized ongoing NCT04621370	A. (SCRT → mFOLFOX6 #6) + durvalumab #4 → S or WW B. (CRT → mFOLFOX6 #4) + durvalumab #4 → S or WW Assessment of response at approximately 16–18 weeks after day 1 of RT. If the patient is proceeding to surgery, this will be performed at approximately 18–20 weeks after day 1 of RT where possible.	RT Dose: 25 Gy in 5 fractions (group A) 50 Gy in 25 fractions (group B) 50 Gy to the primary tumor and 45 Gy to the elective pelvic nodes Technique: IMRT CT During CRT: **capecitabine** (825 mg/m^2 twice a day on the days of RT) ICI **Durvalumab** (1500 mg IV) starts in the week prior to day 1 of (C)RT, and continues every 4 weeks until completion of FOLFOX.	
EA2201[28] Phase II ongoing NCT04751370	Ipilimumab/Nivolumab #2 → SCRT → Ipilimumab/Nivolumab #2 → TME SCRT starts least 2 weeks but no longer than 6 weeks after completion of cycle 2 of nivolumab and ipilimumab. Surgery was performed 8–12 weeks after completion of 4th cycle of nivolumab and ipilimumab.	RT Dose: 25 Gy in 5 fractions ICI **Nivolumab** IV over 30 minutes and **ipilimumab** IV over 90 minutes on day every 28 days for 2 cycles	
Qiu[29] Phase Ib ongoing	SCRT + Sintilimab #3 → TME or WW Sintilimab starts on day 1 of SCRT.	RT Dose: 25 Gy in 5 fractions Technique: IMRT	

NCT04636008	Surgery was performed 6–8 weeks after RT	ICI **Sintilimab** 200 mg IV every 2 weeks

[1]The schedules of chemotherapy regimens are as follows:

CAPOX (capecitabine 1000 mg/m² orally twice daily on days 1–14, oxaliplatin 130 mg/m² IV on day 1, every 21 days)

FOLFOX4 (oxaliplatin 85 mg/m² IV on day 1, leucovorin 200 mg/m² IV on days 1 and 2, followed by 5-FU 400 mg/m² IV bolus and 5-FU 600 mg/m² IV for 22 h on days 1 and 2, every 14 days)

mFOLFOX6 (oxaliplatin 85 mg/m^2 IV, followed by LV 400 mg/m^2 IV, followed by 5-FU 400 mg/m^2 IV bolus, followed by 5-FU 2400 mg/m^2 continuous IV over 46-48 h every 14 days)

FOLFIRINOX (oxaliplatin 85 mg/m² and LV 400 mg/m² IV, followed by irinotecan 180 mg/m² IV, and fluorouracil 2400 mg/m² continuous IV over 46 h every 14 days)

[2]* denotes statistically significant result.

3D-CRT: 3-dimensional conformal radiotherapy; 5-FU: 5-fluorouracil; cape: capecitabine; cCR: clinical complete response; cDM: cumulative distant metastasis; cLF: cumulative local fa ilure; CRT: chemoradiotherapy; CSS: cancer-specific survival; CT: chemotherapy; CTV: clinical target volume; DFS: disease-free survival; DM: distant metastasis; DMFS: distant metas tasis-free survival; dMMR: deficient mismatch repair; DRTF: Disease-related treatment failure; GTV: gross tumor volume; ICI: immune checkpoint inhibitor; IMRT: Intensity-modulat ed radiotherapy; LF: local failure; LV: leucovorin; MSI-H: high microsatellite instability; MSS: microsatellite stable; NAR: neoadjuvant rectal; ns: not significant; OS: overall survival; pCR: pathologic complete response; PD-L1: programmed death-ligand 1; pMMR: proficient mismatch repair; RT: radiotherapy ; S: surgery; SCRT: short-course radiotherapy; TME: t otal mesorectal excision; TNT: total neoadjuvant treatment; WW: watch-and-wait.

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