Appendix II: Clinical trials that intensify neoadjuvant chemoradiotherapy for LARC.

Intensified strategies	Study and Trial number	Source	Phase/Total patients	Group	pCR or cCR rate	Toxicity
TNT modality	German CAO/ARO/AIO-12 NCT02363374	Fokas et al., J Clin Oncol 2019	II 306	Group A: 3 cycles of FOLFOX + LCCRT+TME Group B: LCCRT + 3 cycles of FOLFOX + TME	pCR rate: Induction chemotherapy group was 17% , consolidation chemotherapy group was 25%	Grade 3 or 4 toxicity was lower in group B (37% v 27%)
	TIMING NCT00335816	Garcia-Aguilar et al., Lancet Oncol 2015	II 259	Group1: LCCRT+TME(6 weeks post LCCRT) Experimental group: LCCRT + TME with intervals to add 2 (Group 2), 4 (Group 3), 6 (Group 4) cycles of mFOLFOX6	pCR rate was 18% with CRT alone, while 2, 4 and 6 rounds of consolidation FOLFOX following CRT increased the pCR rate to 25%, 30% and 38%, respectively	In group 2, two (3%) of 67 patients had grade 3 adverse events and one (1%) had a grade 4 adverse event; in group 3, 12 (18%) of 67 patients had grade 3 adverse events; in group 4, 18 (28%) of 65 patients had grade 3 adverse events and five (8%) had grade 4 adverse events

TNT modality	OPRA NCT02008656	Thompson et al., J Clin Oncol 2022; Int J Radiat Oncol Biol Phys 2024	II 324	INCT group: Induction neoadjuvant chemotherapy + CRT CNCT group : CRT + consolidation neoadjuvant chemotherapy Control group : CRT + TME	cCR rate: Induction chemotherapy group was 43%, consolidation chemotherapy group was 58%	No difference in adverse events was observed between groups.
	PRODIGE 23 NCT01804790	Conroy et al., Lancet Oncol 2021	III 461	LCCRT + TME + postoperative adjuvant chemotherapy versus neoadjuvant modified mFolfirinox regimen 6 cycles + LCCRT + TME + postoperative adjuvant chemotherapy	pCR rate: the induction chemotherapy group with the addition of the mFolfirinox regimen was higher (11.7 vs 27.5%; p <0.001)	During the entire treatment period, serious adverse events occurred in 63 (27%) of 231 participants in the neoadjuvant chemotherapy group and 50 (22%) of 230 patients in the standard-of-care group (p =0.167)
Enhanced chemotherapy intensity	NSABP R-04 NCT00058474	J. O'Connel et al., J Clin Oncol 2014	III 1608	During preoperative concurrent radiotherapy and chemotherapy: 5-fluorouracil ± oxaliplatin with capecitabine ± oxaliplatin	There is no benefit from adding oxaliplatin	Patients treated with oxaliplatin experienced significantly more grade 3 or 4 diarrhea (p < 0.001)

Enhanced chemotherapy intensity	STAR 01 NA	Aschele et al., J Clin Oncol，2011	III 294	Control group: 5-Fu during preoperative radiotherapy + TME + postoperative adjuvant chemotherapy ; experimental group: 5-Fu and oxaliplatin during preoperative radiotherapy + TME + postoperative adjuvant chemotherapy	There is no benefit from adding oxaliplatin	Oxaliplatin can be safely added to standard 5-FU-based CRT with an increased frequency and severity of acute toxicity but without major unexpected adverse events
	ACCORD 12 NCT002133-39	Pierre Gérard et al., J Clin Oncol 2012	III 598	Control group: preoperative radiotherapy with capecitabine + TME; experimental group: preoperative radiotherapy with capecitabine and oxaliplatin + TME	There is no benefit from adding oxaliplatin	There were no significant differences between the groups in terms of bowel continence, erectile dysfunction, and social life disturbance
	PETACC-6 NCT00766155	Schmoll et al., J Clin Oncol.2021	III 1094	Control group：preoperative radiotherapy with capecitabine+ TME + capecitabine；experimental group: preoperative radiotherapy with capecitabine and CAPOX + TME + CAPOX	There is no benefit of pCR rate from adding oxaliplatin	Pre-operative grade 3/4 toxicity occurred in 15.1% of patients in the control group, compared to 36.7% in the experimental group

Enhanced chemotherapy intensity	CAO / ARO /AIO-04 NCT00349076	Rödel et al., Lancet Oncol 2012	III 1236	Control group: 5-Fu during preoperative radiotherapy + TME + four cycles of 5-Fu; experimental group: 5-Fu and oxaliplatin during preoperative radiotherapy + TME + eight cycles of FOLFOX4 regimen	pCR rate: oxaliplatin arm was 17% and control group was 13% (p =0.031). **Note: Oxaliplatin was administered four times with a one-week interruption during the five-week period, allowing patients a rest period of approximately two weeks**	Experimental group has a higher incidence of grade 3-4 diarrhoea (12%) and grade 3-4 nausea or vomiting (4%) compared to control group (8% and 1% respectively)
	FOWARC NCT01211210	Wang et al., J Clin Oncol 2016	III 475	Three intervention groups: 5-Fu + radiotherapy, mFOLFOX6 + radiotherapy, and mFOLFOX6 alone	In the fluorouracil-radiotherapy, mFOLFOX6-radiotherapy and mFOLFOX6 groups, the rates of pathological complete response (pCR) were 14.0%, 27.5% and 6.6%, respectively. **Note: In contrast to the four aforementioned studies, this study administered an oxaliplatin dose of 85 mg/m2 and implemented a 2-week cycle regimen**	The group treated with mFOLFOX6 alone exhibited lower toxicity and fewer postoperative complications

Enhanced chemotherapy intensity	ARISTOTLE ISRCTN： 09351447	Sebag-Montefiore et al., ASCO meeting 2020	III 564	Control group: capecitabine-based CRT (C-CRT) treatment; experimental group: irinotecan (60mg/m2,once a week) combined with capecitabine-based CRT (IrCRT) treatment	pCR rate: IrCRT group was 20.2% and C-CRT group was 17.4% (p = 0.45)	The rate of gastrointestinal adverse events in grade 3-4 was higher with IrCRT (21%, 58/276) compared to CRT (12%, 34/283) (p = 0.004).
	CinClare NCT02605265	Zhang et al., J Clin Oncol 2020	III 356	CapRT group：capecitabine during preoperative radiotherapy + 1cycle XELOX + TME + 5cycles XELOX; capIriRT group: capecitabine and irinotecan during preoperative radiotherapy + 1cycle XELIRI + TME + 5Cycles XELOX; The dose of irinotecan are based on UGT1A1 genotype *1*1 （80 mg/m2）or *1*28 （65 mg/m2）	pCR rate：CapRT group was 15% and capIriRT group was 30% (p < 0.001)	Among the patients who received CapRT, 6% experienced grade 3-4 toxic effects, compared to 38% of patients who received CapIriRT (p <0.01).

Intensive radiotherapy	Morpheus NCT03051464	Vuong et al., Cancers 2022	II -III 40	Group A: EBRT booster dose of 9Gy/5F Group B: Adaptive brachytherapy booster dose of 30Gy/3F	cCR rate: 50 per cent in group A (n = 10/20) and 90 per cent in group B (n = 18/20)	There was no significant difference in grade 3 acute toxicity between the two groups
	OPERA NCT02505750	Sun Myint et al., J Clin Oncol 2021	III 144	Group A (standard treatment group): EBCRT (45Gy/25/5 weeks) + oral capecitabine 825mg/m2 + EBRT (9Gy/5/5 days); Group B (experimental group: EBCRT 90Gy, i.e., close radiotherapy mode, using low energy and high dose to perform a small range of targeted irradiation, once every 2 weeks, a total of 3 radiotherapy sessions.	cCR rate was observed in 44/69 (64%) in group A and 66/72 (92%) in group B at 24 weeks ($p < 0.001$)	21 (30%) patients in group A and 30 (42%) in group B had an early grade 2–3 adverse event ($p = 1{\cdot}0$)
Radiotherapy combined with immunisation for MSS LARC	Voltage-A NCT02948348	Yoshino et al., Clin Cancer Res. 2022	II 39	Group A1: 37 patients with MSS. Group A2: 5 patients with MSI-H. Treatment regimen: LCCRT + 5 cycles of Navulizumab + TME	pCR rate: 30% in group A1 (n = 11/37) and 60% in group A2 (n = 3/5)	Only mild toxicity in both groups

Radiotherapy combined with immunisation for MSS LARC	NSABP FR-2 NCT03102047	George et al., ASCO meeting 2022	II 45	45 patients with stage II/III rectal cancer（Stage III 89 %）and MSS Treatment regimen: LCCRT + 4 cycles of Duvarizumab + TME	pCR 22.2% cCR 31.1%	Side effects were consistent with both CRT and durvalumab safety profile. Most common grade 3 AEs included diarrhea, lymphopenia, and back pain. There was one grade 4 AE (elevated amylase/lipase) and no grade 5 AEs
	AVANA NCT03854799	Tortora et al., Annals of Oncol 2021	II 101	100 patients with resectable LARC (StageIII 94%) Treatment regimen: LCCRT + 6 cycles of Avelumab + TME	pCR 23%	The rate of grade 3-4 non-immune and immune-related adverse events was 8% and 4%, respectively.
	R-IMMUNE NCT03127007	Eynde et al., Annals of Oncol 2021	Ib/II 25	Treatment regimen: LCCRT + 4 cycles of Atezolizumab + TME	pCR 24%	Out of 26 patients, 151 adverse events (AEs) were reported, with 20 (13%) being grade 3-4

Radiotherapy combined with immunisation for MSS LARC	NRG-GI002 NCT02921256	George et al., JAMA Oncol 2021	II 178	Arm I (mFOLFOX6, RT, Capecitabine) Arm II (mFOLFOX6, RT, Capecitabine, Veliparib) Arm III (mFOLFOX6, RT, Capecitabine, Pembrolizumab)	pCR 31.9% cCR 13.9%	The most frequently occurring grade 3/4 adverse events were diarrhea and cytopenias
	Ave-Rec NCT03299660	Michael et al., ASCO meeting 2023	II 37	Experimental group: SCRT+6 cycles of mFOLFOX and Avelumab+TME	pCR 37.5%	A total of 10 pts had grade 3/4 AEs, with 15 G3/4 events. Only 3 pts with treatment-emergent G3 and no G4 AEs. No specific immune-related G3 AEs
	UNION NCT04928807	Zhang et al., ESMO meeting 2023	III 113	Control group: SCRT + CAPOX + TME ; experimental group: LCRT + CAM and CAPOX + TME	pCR rate：Control group was 15.3% and experimental group was 39.8% ($p < 0.001$)	No significant difference in the incidence of adverse events was seen between the two groups
	TORCH NCT04518280	Wang et al., ASCO meeting 2022	II 130	Induction group: 2cycles CAPOX and Toripalimab + SCRT + 4cycles CAPOX and Toripalimab ; consolidation group: SCRT + 6cycles CAPOX and Toripalimab	total rate of pCR: 49.2%	The only grade 3 AE was thrombocytopenia (4/11). And no grade 4 AE was observed.

Immunisation alone for MSI-H LARC	A prospective study from MSKCC NCT04165772	Cercek et al., ASCO meeting 2022	II 12	Dostarlimab every 3 weeks for 6 months + standard chemoRT+TME	pCR rate of 14 patients :100%	No serious adverse events > grade 3

Abbreviations: **LARC:** locally advanced rectal cancer; **pCR:** pathological complete remission; **cCR:** clinical complete remission; **TNT:** total neoadjuvant therapy; **LCCRT:** long-course chemoradiotherapy; **SCRT:** short-course radiotherapy; **TME:** total mesorectal excision; **RT:** raditaion therapy**CRT:** chemoradiotherapy; **EBCRT:** external beam chemoradiotherapy; **EBRT:** external beam radiotherapy; **MSS:** microsatellite stability; **MSI-H:** microSatellite instability-high; **CAPOX:** capecitabine and oxaliplatin; **FOLFOX:** 5-fluorouracil, leucovorin and oxaliplatin; **XELIRI:** capecitabine and irinotecan; **XELOX:** capecitabine and oxaliplatin; **AEs:** adverse event; **CAM:** Camrelizumab; **5-FU:** 5-fluorouracil; **NR:** not reported;