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Table 2. Primary clinical endpoint in randomised phase 2/3 trials of total neoadjuvant therapy with or without NOM option

Randomised phase 2 trials testing TNT	**Patient number**	**Treatment schedule**	**Primary clinical endpoint**
GCR-3[68]	108	Capecitabine/Oxaliplatin CRT followed by surgery vs Induction CAPOX chemotherapy followed by Capecitabine/Oxaliplatin CRT and surgery	pCR
EXPERT-C[69]	165	Induction CAPOX chemotherapy + Cetuximab followed by Capecitabine/Cetuximab CRT and surgery vs CAPOX chemotherapy followed by Capecitabine CRT and surgery	cCR and pCR
GEMCAD 1402[60]	115	Induction mFOLFOX6 chemotherapy + Aflibercept followed by Capecitabine CRT and surgery vs Induction mFOLFOX6 chemotherapy followed by Capecitabine CRT and surgery	pCR
GRECCAR4[70]	194	Induction FOLFIRINOX followed by: -Good responders: immediate surgery vs Capecitabine CRT followed by surgery; -Poor responders: Capecitabine CRT (50 Gy) followed by surgery vs Capecitabine CRT (60 Gy) followed by surgery	R0 rate
CAO/ARO/AIO-12[18]	304	Induction mFOLFOX6 chemotherapy followed by 5-FU/Oxaliplatin CRT and surgery vs 5-FU/Oxaliplatin CRT followed by consolidation mFOLFOX6 chemotherapy and surgery	pCR
OPRA (NCT02008656)	300	Induction mFOLFOX6 chemotherapy followed by 5-FU CRT and surgery/NOM vs 5-FU CRT followed by consolidation mFOLFOX6 chemotherapy and surgery/NOM	3-year DFS
NRG GI002 (NCT02921256)		Induction FOLFOX chemotherapy followed by capecitabine CRT vs induction FOLFOX chemotherapy followed by capecitabine/Veliparib CRT vs induction FOLFOX chemotherapy followed by capecitabine/Pembrolizumab CRT	NAR
Randomised phase 2/3 trials testing NOM and LE/TEM	**Patient number**	**Treatment schedule**	**Primary clinical endpoint**
Brazilian trial (NCT02052921)	150	5-FU CRT followed by observation vs 5-FU CRT followed by TME surgery after achieving cCR at 12 weeks post CRT	3-year DFS
TESAR (NCT02371304)	302	TME surgery vs LE followed by capecitabine CRT	3-year LRR
OPERA (NCT02505750)	236	Capecitabine CRT followed by EBRT boost vs Capecitabine CRT followed by brachytherapy boost (if cCR: NOM or LE; if PR: TME)	3-year organ preservation[§]
WW3 (NCT04095299)	111	Capecitabine CRT vs Capecitabine CRT with SIB (if cCR: NOM or LE; if PR: TME)	2-year organ[§] preservation
MORPHEUS (NCT03051464)	40	Capecitabine CRT followed by EBRT boost vs Capecitabine CRT followed by brachytherapy boost (if cCR: NOM; if PR: TME)	2-year organ preservation

GRECCAR12 (NCT02514278)	218	mFOLFIRINOX followed by Capecitabine CRT vs Capecitabine CRT (if good response: LE; if poor response: TME)	12-month organ preservation[$]
TESS (NCT03840239)	168	Induction CAPOX chemotherapy followed by Capecitabine/Oxaliplatin CRT vs capecitabine/oxaliplatin CRT (if cCR: NOM; if PR: LE orTEM; if poor response: TME)	Sphincter preservation (stoma absence) at 18 months
STAR TREC (phase 2 part; NCT02945566)	120	TME surgery vs Capecitabine CRT followed by NOM vs SCRT followed by NOM (if cCR: NOM; if PR: TEM; if poor response: TME)	Recruitment rate at 12 and 24 months*
TREC (ISRCTN 14422743)	-	TME surgery vs SCRT followed by TEM and NOM	Recruitment rate at 12, 18 and 24 months*
APHRODITE (ISRCTN16158514)	104	5FU or capecitabine CRT vs 5FU or Capecitabine CRT with SIB (if cCR: NOM)	cCR rate at 6 months

[§]In the OPERA trial, organ preservation is defined as follows: the rate of rectum preservation either with local excision or watch and wait strategy after neoadjuvant treatment without non-salvageable locally progressive disease at 3 years post treatment, or permanent stoma. In the WW3 trial, organ preservation is defined as follows: rectum intact, no locoregional failure, no stoma at 2 years post-treatment

[$]In the GRECCAR12 trial, organ preservation is defined as follows: Number of patients with organ preservation and absence of stoma at 1 year after surgery.

*The aim of the studies is to assess the feasibility of recruitment within the phase 2 trial. If successful, the investigators will proceed into the phase 3 trial.

All trials shown above are phase 2, except the OPERA and GRECCAR12, which are randomised phase 3 trials; the MORPHEUS is a pilot randomised trial;

The Polish II, RAPIDO and ACO/ARO/AIO-18.1 phase 3 trials that evaluate(d) the concept of TNT are summarized in Table 3.

Abbreviations: pCR, pathological complete response, 5-FU, 5-Fluorouracil; CAPOX, capecitabine/oxaliplatin; FOLFOX, 5-FU, leukovorin, oxaliplatin; FOLFIRINOX, 5-FU, leukovorin, irinotecan, oxaliplatin; CRT, chemoradiotherapy; TME, total mesorectal excision; DFS, disease-free survival; LRR; locoregional recurrence; NOM, non-operative management; LE, local excision; TEM, transanal endoscopic microsurgery; PR, partial response; SCRT, short-course radiotherapy; W&W, watch and wait; SIB, simultaneously integrated boost;