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Table 3. Primary clinical endpoint in phase 3 trials with neoadjuvant treatment of rectal cancer

<b>Phase 3 trials</b>	<b>Patient number</b>	<b>Treatment schedule</b>	<b>Primary clinical endpoint</b>
Swedish trial <sup>41</sup>	1168	Surgery with or without preoperative SCRT	5-year OS
NSABP R03 <sup>71</sup>	267	Preoperative vs postoperative 5-FU/LV CRT followed by surgery and adjuvant 5-FU/LV chemotherapy	5-year DFS and 5-year OS
Frykholm <sup>72</sup>	70	Preoperative methotrexate/5-FU/LV CRT vs RT alone followed by surgery and adjuvant chemotherapy	5-year Local recurrence
Dutch TME trial <sup>73</sup>	1861	Surgery with or without preoperative SCRT	2-years Local recurrence
CAO/ARO/AIO-94 <sup>74</sup>	823	Preoperative vs postoperative 5-FU CRT followed by surgery and adjuvant 5-FU chemotherapy	5-year OS
Polish I <sup>5</sup>	316	Preoperative 5-FU/LV CRT vs SCRT followed by surgery and adjuvant chemotherapy	Sphincter preservation
Braendengen <sup>75</sup>	207	Preoperative methotrexate/5-FU/LV CRT vs RT alone followed by surgery and adjuvant chemotherapy	5-year OS
EORTC 22921 <sup>76</sup>	1011	Preoperative 5-FU CRT vs RT alone followed by surgery and adjuvant 5-FU chemotherapy vs follow-up	5-year OS
FFCD 9203 <sup>77</sup>	762	Preoperative 5-FU CRT vs RT alone followed by surgery and adjuvant 5-FU chemotherapy	5-year OS
MRC CR07 and NCIC-CTG C016 <sup>42</sup>	1350	Preoperative SCRT and surger vs surgery followey by selective postoperative CRT (only CRM+)	3-year Local recurrence
STAR-01 <sup>78</sup>	747	Preoperative 5-FU CRT vs 5-FU/Oxaliplatin CRT followed by surgery and adjuvant chemotherapy	5-year OS
ACCORD 12/0405 PRODIGE 2 <sup>79</sup>	598	Preoperative CapecitabineCRT vs Capecitabine/Oxaliplatin CRT followed by surgery and adjuvant chemotherapy	pCR
NASBP R-04 <sup>44</sup>	1608	Preoperative Capecitabine CRT vs Capecitabine/Oxaliplatin CRT vs 5-FU CRT vs 5-FU/Oxaliplatin CRT, all followed by surgery and adjuvant chemotherapy	3-year Local recurrence
PETACC-6 <sup>80</sup>	1094	Preoperative CapecitbincCRT vs Capecitabine/Oxaliplatin CRT followed by surgery and adjuvant chemotherapy	3-year DFS
Hofheinz <sup>81</sup>	401	5-FU- vs Capecitabine preoperative induction chemotherapy and CRT followed by surgery and adjuvant chemotherapy	5-year OS
CAO/ARO/AIO-04 <sup>82</sup>	1236	Preoperative 5-FU CRT vs 5-FU/Oxaliplatin CRT followed by surgery and adjuvant chemotherapy	3-year DFS
FOWARC <sup>34</sup>	495	Preoperative 5-FU/LV CRT vs 5-FU/LV/Oxaliplatin CRT vs FOLFOX6 chemotherapy followed by surgery and adjuvant chemotherapy	3-year DFS
Stockholm III <sup>43</sup>	840	SCRT followed by surgery within 1 week vs SCRT followed by surgery after 4-8 weeks vs RT followed by surgery after 4-8 weeks	Local recurrence

Polish II <sup>32</sup>	515	SCRT and consolidation FOLFOX4 vs 5-FU/LV/Oxaliplatin CRT followed by surgery and adjuvant chemotherapy	R0 resection rate
GRECCAR-2 <sup>52</sup>	186	Preoperative CRT followed by local excision vs TME surgery	2-year Composite endpoint <sup>§</sup>
ARISTOTLE (ISRCTN09351447)	600	Preoperative Capecitabine CRT vs Capecitabine/Irinotecan CRT followed by surgery and adjuvant chemotherapy	3-year DFS
RAPIDO (NCT01558921)	920	Preoperative CRT followed by TME surgery vs SCRT followed by CAPOX (or FOLFOX) consolidation chemotherapy and TME surgery	Time to Disease-related Treatment Failure (TdrTF)
PROSPECT (NCCTG N1048/Alliance; NCT01515787)	1194	Induction FOLFOX chemotherapy followed by surgery (response>20%) or CRT and surgery (response <20%) vs CRT followed by surgery and adjuvant FOLFOX chemotherapy	Local recurrence and 3-year DFS
STAR TREC (Phase 3 part; NCT02945566)		TME surgery vs Capecitabine CRT followed by NOM vs SCRT followed by NOM (if cCR: NOM; if PR: TEM; if poor response: TME)	30-month organ preservation rate
ACO/ARO/AIO-18.1 (EudraCT: 2018-000876-14)	822	Preoperative CRT followed by consolidation FOLFOX chemotherapy and TME surgery (or NOM by cCR) vs CRT followed by TME surgery (or NOM by cCR)	3-year DFS

<sup>§</sup>The primary clinical endpoint in the GRECCAR-2 trial was a novel composite outcome of death, recurrence, morbidity, and side-effects at 2 years after surgery.

In the STAR TREC trial (phase 3 part), organ preservation is defined as follows: rectum intact, no locoregional failure, no stoma

Abbreviations: pCR, pathological complete response, 5-FU, 5-Fluorouracil; CRT, chemoradiotherapy; TME, total mesorectal excision; DFS, disease-free survival; NOM, non-operative management; LE, local excision; PR, partial response; SCRT, short-course radiotherapy; W&W, watch and wait; CRM, circumferential resection margin