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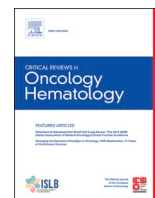
Opportunities on the horizon for the management of early colon cancer

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ABSTRACT

There is a clear unmet need to improve early colon cancer management. This review encompasses the current systemic treatment landscape and summarises novel and pivotal trials. The Immunoscore and circulating tumour DNA (ctDNA) are studied to evaluate which patients should receive no, 3, or 6 months of adjuvant treatment. Several trials also test escalating treatment strategies for non-cleared ctDNA following standard adjuvant chemotherapy. Advances made in treating patients with metastatic colon cancer are now being translated to the early colon cancer setting. Two ongoing RCTs study immune checkpoint inhibitors (ICI) in patients with microsatellite instable high (MSI-H) early colon cancer as adjuvant treatment. Neo-adjuvant treatment is being studied in several ongoing RCTs as well. The complete response rate in patients with MSI-H tumours following ICI in neoadjuvant trials has potential organ-sparing implications.

1. Introduction

Colorectal (CRC) cancer ranks third place in cancer-related deaths worldwide (GLOBOCAN website: globocan.iarc.fr., 2022). Improvement in diagnosing colon cancer at an early stage, followed by curative surgical resection, has lowered the mortality rate of patients with colon cancer (Lin et al., 2016). Moreover, adjuvant systemic treatment administered after surgical resection reduces the risk of recurrence and increases overall survival (OS).

Early studies failed to show OS benefit of single-agent therapy compared to surgery alone (Buyse et al., 1988). The addition of leucovorin (LV) to 5-fluorouracil (5-FU) as adjuvant chemotherapy improved OS and has been the standard of care since the mid-nineties. As of 2004, oxaliplatin has been added to the 5-FU/LV chemotherapy backbone (André et al., 2004). Oxaliplatin improved disease-free survival (DFS) and OS in patients with stage 3 disease, at the price of more severe and more frequent peripheral sensory neurotoxicity (André et al., 2015; Schmoll et al., 2015; Yothers et al., 2011). Since the introduction of oxaliplatin, no further DFS improvement has been made (Argiles et al., 2020; Benson et al., 2021). Currently, still, 30–50 % of the patients treated for localised colon cancer relapse and die of the disease (Sargent et al., 2009). Furthermore, while the incidence of colon cancer is declining in older adults, the incidence in individuals below the age of 50 is rising rapidly, especially in Western countries (Siegel et al., 2019).

Young age is an independent poor prognostic factor, and the disease recurs more frequently in young patients with high-risk stage 3 colon cancer than older patients despite receiving a higher adjuvant oxaliplatin-based treatment intensity (Fontana et al., 2021). Thus there is a clear unmet need to improve the management of patients with early colon cancer.

However, new opportunities that may change the management of patients with early colon cancer are on the horizon. This manuscript encompasses early colon cancer's changing epidemiology, the current systemic treatment landscape and reviews novel and pivotal trials whose results might improve outcome with a focus on systemic treatment.

2. Search strategy

We performed a comprehensive search of the literature and trial databases, including PubMed and ClinicalTrials.gov. Articles were identified using various combinations of the search terms "adjuvant", "biomarkers", "chemotherapy", "colon cancer", "colorectal cancer", "ctDNA", "drug therapy", "immune checkpoint inhibitor", "Immunoscore", "immunotherapy", neoadjuvant", "therapy". We only included articles published in English. We also identified references from relevant articles. Furthermore, we searched abstracts of all major conferences from 2017 to September 2022 (American Association for Cancer Research AACR), American Society of Clinical Oncology (ASCO) annual

meeting, ASCO Gastrointestinal Cancer Symposium, European Society of Medical Oncology (ESMO) annual meeting, ESMO World Congress on Gastrointestinal Cancer).

3. The current standard of care

The international American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) tumour-node-metastasis (TNM) staging system currently provides the best prognostic classification of early colon cancer (Brierley et al., 2016)). Five-year survival rates of patients after surgical resection alone are 99 % for stage 1, 68–83 % for stage 2, and 45–65 % for stage 3 disease (Brierley et al., 2016).

3.1. Stage 3 colon cancer

For patients with stage 3 colon cancer, adjuvant systemic therapy is generally recommended (Argiles et al., 2020; Benson et al., 2021). Adjuvant fluoropyrimidines decrease the absolute risk of death by 10–15 %, with a further 4–5% decrease when oxaliplatin is added (Knapen et al., 2020). The International Duration Evaluation of Adjuvant (IDEA) consortium, combining six individual randomised controlled trials (RCTs) within a noninferiority design, compared LV/5-FU/oxaliplatin (FOLFOX) and capecitabine/oxaliplatin (CAPOX) for 3 versus 6 months (Grothey et al., 2018). They reported a very similar 3-year DFS rate, 74.6 % (95 % CI, 73.5–75.7) in the 3-month therapy group and 75.5 % (95 % CI, 74.4–76.7) in the 6-month therapy group, but noninferiority was not shown for the intention-to-treat population. However, 3 months of treatment with CAPOX was non-inferior to 6 months. T4 versus T1–3 and N2 versus N1 subgroups were pre-specified; however, their combinations in high - pT4N1–2M0 or pT1–4N2M0 - versus low-risk subgroups were not, and its interaction test was not significant. Common terminology criteria for adverse events (CTCAE) grade 3 or higher neurotoxicity rates are lower for patients who receive 3 than 6 months of treatment (3 % versus 16 % for FOLFOX and 3 % versus 9 % for CAPOX). Based on these results, recommendations regarding adjuvant therapy were de-escalated to 3 months in the ESMO guideline and National Comprehensive Cancer Network (NCCN) guideline for patients with low-risk stage 3 colon cancer (Argiles et al., 2020; Benson et al., 2021).

3.2. Stage 2 colon cancer

The adjuvant treatment of patients with stage 2 colon cancer is controversial, with international guidelines recommending a range of options from observation to chemotherapy with single-agent or oxaliplatin combination regimens (Argiles et al., 2020; Benson et al., 2021). Recommendations are often based on the presence or absence of high-risk features. Lymph node sampling with a yield of less than 12 lymph nodes and pT4 is considered the most important high-risk features for patients with stage 2 colon cancer. A large meta-analysis states that adjuvant fluoropyrimidines decrease the absolute risk of death by ~ 5 % in stage 2 disease (Sargent et al., 2009). However, this might be an overestimation as this meta-analysis included older trials conducted between 1978 and 1999. Patients characterised as stage 2 might have been classified as stage 3 by the current standard, exemplified by the lymph node ratio (the number of positive nodes divided by total nodes harvested) in patients with stage 3 disease declined over time (Knapen et al., 2020).

4. Prognostic and predictive biomarkers for adjuvant therapy

Among patients with the same stage, the clinical outcome and the benefit of chemotherapy can be very different. Fifty percent of patients with stage 3 disease never develop recurrent disease after surgery alone and are overtreated with adjuvant therapy (Auclin et al., 2017). Adjuvant chemotherapy leads to a cure in around 20 % of patients with stage

3 disease, while 30 % still experience disease recurrence. Thus 80 % of patients are exposed to unnecessary toxicity (Auclin et al., 2017). Conversely, adjuvant chemotherapy is withheld in patients with non-high-risk stage 2 disease. Still, around 12 % of them develop recurrent disease, which might be prevented by adjuvant chemotherapy for some of them (Osterman and Glimelius, 2018). Insight into colon cancer biology has resulted in one biomarker currently used in clinical practice, namely microsatellite instability (MSI). Around 15 % of the stage 2 colon tumours are MSI-high, and these patients are at very low risk of recurrence and do not benefit from adjuvant chemotherapy (Sargent et al., 2010). For stage 3 colon cancer, MSI status is less important for adjuvant chemotherapy decision making, as MSI-high stage 3 colon cancer patients benefit from adjuvant oxaliplatin-based therapy (Cohen et al., 2021). Gene expression profiling-based molecular tumour subtyping, including the consensus molecular subgroup (CMS) classification and gene signatures such as Oncotype DX and GeneFx colon, lack predictive value for chemotherapy and are therefore not used in clinical practice (Gray et al., 2011; Guinney et al., 2015; Niedzwiecki et al., 2016; Argiles et al., 2020).

4.1. Immunoscore

Immunoscore is a digital immunohistochemistry-based tumour assay that quantifies CD3+ and CD8+ lymphocytes at the edge (invasive margin) and the core of the tumour combined into an Immunoscore. Scores range from low (0) to high (4). Immunoscore has been validated prospectively in a trial in 2500 patients with stage 1–3 colon cancer (Pages et al., 2018). In three independent datasets, patients with a high Immunoscore had the lowest risk of recurrence. Immunoscore was the strongest parameter to predict DFS and OS in multivariate analysis and surpassed the impact of the TNM stage. Another trial assessed the Immunoscore in 763 patients with stage 3 colon cancer (Mlecnik et al., 2020). Patients with a low Immunoscore had a similar DFS outcome regardless of chemotherapy treatment, clinically high-risk ($p = 0.12$) and clinically low-risk ($p = 0.83$). In contrast, patients with intermediate and high Immunoscore benefitted most from adjuvant chemotherapy (clinically low-risk: HR, 0.42; 95 % CI, 0.25–0.71; $p = 0.0011$ and clinically high-risk: HR, 0.50; 95 % CI, 0.33–0.37; $p = 0.0015$). None of the 5 patients with the highest Immunoscore 4, relapsed, even when untreated with chemotherapy. The IDEA France study, part of the IDEA consortium, studied in 1062 patients the value of Immunoscore to predict adjuvant chemotherapy benefit (Grothey et al., 2018; Pagès et al., 2020). Intermediate or high Immunoscore predicted benefit of 6 over 3 months treatment (HR 0.53; 95 % CI, 0.37–0.75; $p = 0.0004$). The 46.4 % of the patients with a low Immunoscore did not benefit from 6 over 3 months of adjuvant chemotherapy. These findings suggest that the Immunoscore might serve to select which patients should receive no, 3 or 6 months of adjuvant treatment. For further implementation in clinical practice, prospective validation in larger phase 3 trials is mandatory. The iMAGINE phase 3 trial will prospectively investigate Immunoscore for decision guidance for adjuvant chemotherapy in patients with stage 3 colon cancers (NCT04488159). In the experimental Immunoscore stratification arm, patients with Immunoscore low receive 3 months CAPOX, with Immunoscore intermediate-high 6 months FOLFOX, and with Immunoscore high get no adjuvant chemotherapy.

4.2. Circulating tumour DNA

Circulating tumour deoxyribonucleic acid (ctDNA) are fragments of DNA shed into the bloodstream by dying cancer cells. ctDNA has a very short half-life of around 2 h offering a real-time dynamic measure of tumour burden (Diehl et al., 2008). The prognostic value for recurrence of ctDNA post-surgery and post-adjuvant chemotherapy has been shown in several studies in various stages of early CRC (Tie et al., 2016; Schøler et al., 2017; Reinert et al., 2019; Tarazona et al., 2019; Naidoo et al., 2021; Parikh et al., 2021). For example, a study in 230 patients with

resected stage 2 colon cancer showed that recurrence in patients not treated with adjuvant chemotherapy was 18 times more likely in patients with detectable ctDNA post-surgery than in patients without detectable ctDNA (HR = 18; 7.9–40; p = 0.001) (Tie et al., 2016). Detectable ctDNA after adjuvant chemotherapy was also associated with an inferior recurrence-free survival (HR = 11; 1.8–68; p = 0.001)." Another study in 130 patients with stage 1–3 CRC, showed that those with detectable ctDNA after surgery were more likely to relapse than those that were ctDNA negative (HR 7.2; 95 % CI, 5.4–56.5; p < 0.001) (Reinert et al., 2019). Of the 58 patients with post-adjuvant chemotherapy ctDNA samples, all seven ctDNA-positive patients relapsed, while of the 51 patients who were ctDNA negative, seven relapsed (Schøler et al., 2017). Other trials had similar results, showing a positive predictive value of ctDNA for recurrent disease of nearly 100%. The prognostic value of ctDNA has also been demonstrated with real world data. In a retrospective analysis, ctDNA data from approximately 12,000 patients with stage 1–3 CRC was analysed. ctDNA was taken at several time windows: within 8 weeks post-surgery and prior to adjuvant chemotherapy, defined as the minimal residual disease (MRD) window, anytime post-surgery and during surveillance. Detectable ctDNA at these timepoints was associated with shorter recurrence-free survival (HR = 12.2; 5.3–27.8; p = 0.0001), (HR = 16.7; 7.4–37.4; p = 0.0001), and (HR = 25.4; 12.6–51.3; p = 0.0001), respectively (Cohen et al., 2022). Patients without detectable ctDNA during the MRD window did not benefit from adjuvant chemotherapy.

Whether ctDNA is also predictive of the benefit of standard adjuvant chemotherapy remains to be seen. A recent study in 168 patients with stage 3 colon cancer, provides some information. In 13 patients with detectable ctDNA postoperatively, samples were collected during and after adjuvant chemotherapy for up to 3 years. Only three of them (23 %) had a complete and permanent clearance of ctDNA after adjuvant chemotherapy. These three did not relapse, while the other 10 did (Henriksen et al., 2022). In a large observational study, 1365 patients with CRC stage 1–4, patients were followed with serial ctDNA assessments. In patients in whom ctDNA measurements were available at 4, and 24 weeks post-surgery, the ctDNA clearance rate was 26 % for the patients that had received adjuvant chemotherapy and 0 % for the patients that had not received adjuvant therapy (Katoka et al., 2022). Thus, although this data is observational, adjuvant chemotherapy may reduce the risk of relapse in patients with detectable ctDNA after surgery. The 618 patients with non-detectable ctDNA post-surgery and post-adjuvant chemotherapy and the 58 patients with detectable ctDNA post-surgery but non-detectable ctDNA post-adjuvant chemotherapy had an excellent prognosis, with a 6 months DFS rate of 98 % and 100 % respectively.

In a phase 2 RCT, 455 patients with stage 2 colon cancer were randomised between ctDNA guided treatment decisions and standard of care treatment decisions based on clinicopathological features (Tie et al., 2022a). Patients with detectable ctDNA postoperatively received oxaliplatin-based or fluoropyrimidine chemotherapy at the clinician's discretion. Patients who were ctDNA-negative did not receive adjuvant systemic therapy. The study met its primary endpoint, the recurrence-free survival at 2 years was 93.5 % and 92.4 % for the ctDNA guided and standard management arm respectively, which was non-inferior. This trial confirms the low risk of recurrence for patients without detectable ctDNA post-surgery. This trial does suffer from several limitations. The chosen noninferiority margin was − 8.5 % which is wide for stage 2 colon cancer where the absolute benefit of adjuvant chemotherapy is disputable. Furthermore, due to the clinicians discretion of adjuvant chemotherapy choice, in the standard management arm 90 % received fluoropyrimidine monotherapy while in the ctDNA-guided management arm 62 % received oxaliplatin based chemotherapy. This means that actually more people received oxaliplatin based chemotherapy in the ctDNA-guided management arm than in the standard management arm. Nevertheless, the authors should be applauded for this first reported prospective RCT of ctDNA-based interventional adjuvant treatment for stage 2 colon cancer. Later

presented data of this trial confirmed that ctDNA clearance can be achieved with adjuvant chemotherapy (Tie et al., 2022b). Of 38 patients, ctDNA data was available post-surgery and post-adjuvant chemotherapy. In 31 of them the ctDNA converted from detectable post-surgery to non-detectable after adjuvant chemotherapy, and in seven ctDNA remained detectable post-adjuvant chemotherapy. Two of 31 (6.5 %) patients with converted ctDNA recurred compared to five out of seven (71 %) with non-converting ctDNA (HR = 17.3; 3.3–90.2; p = < 0.001).

For ctDNA testing to guide treatment decisions in colon cancer, the used assay must be robust. Both tumour-informed and tumour-agnostic assays are being used. Tumour-informed testing was considered more sensitive but requires a patient's tumour to be sequenced in order to create a custom ctDNA test. Novel plasma-only assays improved sensitivity by combining methylation or epigenomic signatures, and the assays are expected to improve with continued advances in the field (Benhaim et al., 2021;Parikh et al., 2021).

Many ongoing trials with both escalating and de-escalating treatment strategies based on ctDNA assessment in early colon cancer (Table 1) will further define the utility of ctDNA for adjuvant systemic treatment decisions. These strategies involve administrating or withholding standard adjuvant chemotherapy based on ctDNA results. More experimental strategies are also investigated, for example, a phase 2 RCT (NCT04486378) investigates watchful waiting versus autogene cevumeran, liposomal formulated messenger RNA encoding neoantigens, in patients with detectable ctDNA after surgery. In addition, escalating treatment in patients that do not clear ctDNA with standard adjuvant chemotherapy is investigated.

5. Molecular colon cancer subgroups with (potential) therapeutic relevance in early colon cancer

Epidermal growth factor receptor (EGFR) inhibitors and vascular endothelial growth factor (VEGF) inhibitors are registered to treat patients with metastatic CRC. However, the addition of these drugs to standard adjuvant chemotherapy failed to improve DFS and OS in patients with early colon cancer compared to standard adjuvant chemotherapy (Allegra et al., 2011; Alberts et al., 2012; de Gramont et al., 2012; Kerr et al., 2016; Taieb et al., 2017). Advances in better understanding CRC biology lead to new treatment options for patients with metastatic disease, targeting specific molecular features. Encorafenib targeting BRAF combined with cetuximab is approved for patients with BRAF V600E mutated metastatic CRC by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The registration study scored a 4 on the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) (Kopetz et al., 2019). Scores of 4 and 5 are considered a meaningful clinical benefit. For the patients with advanced MSI-H CRC the immune checkpoint inhibitor (ICI) pembrolizumab was approved in 2020 by the FDA and EMA for first-line treatment. The registration study scored a 4 on the ESMO-MCBS (André et al., 2020). Nivolumab plus ipilimumab is approved by the FDA and EMA, as second line treatment (ESMO-MCBS score 3) (Overman et al., 2017; Overman et al., 2018). There are now ongoing trials to assess the value of these treatment strategies in early colon cancer. Both the ACT-3 trial (Table 1) and the FoxTROT3 trial (Table 2) incorporated BRAF targeting in patients with BRAF V600E mutated early colon cancer. ATOMIC (NCT02912559) and POLEM (NCT03827044) are ongoing phase 3 randomised trials examining adjuvant chemotherapy with or without ICI in patients with early MSI-H colon cancer. The latter also includes patients with somatic mutations in DNA polymerase ε (encoded by POLE), a rare CRC originating event leading to hypermutated tumours. ICI post-adjuvant chemotherapy with persistently detectable ctDNA in patients with MSI-high tumours is also being investigated (NCT03803553) to see if this therapy can clear ctDNA and decrease the recurrence rate. For the translation of these therapies to the early setting it is important to realise that the prevalence of targetable molecular alterations differs between

Table 1
Ongoing randomised ctDNA trials in early colon cancer.

ClinicalTrials.gov or National Registry trial identifier and trial name	Study intervention	Accrual goal	Assay	Primary outcome	Estimated completion date
Escalating trials					
NCT04089631 **CIRCULATE AIO-KRK-0217**	Patients with ctDNA+ stage 2 MSS only colon and upper rectum cancer randomised to surveillance or adjuvant chemotherapy	4812	Not-reported	DFS	June 2026
NCT04120701 **CIRCULATE PRODIGE 70**	ctDNA+ stage 2 colon and upper rectum cancer patients randomised to surveillance or adjuvant chemotherapy	1980	ddPCR	DFS	January 2028
NCT04068103 **NRG GI-005COBRA**	Patients with stage 2A colon cancer undergo active surveillance (active comparator arm) or receive adjuvant chemotherapy if ctDNA+ or surveillance if ctDNA-.	1408	Guardant LUNAR-1™	ctDNA clearance and RFS	July 2024
NL6281/NTR6455) MEDOCC-CrEATE	Patients with stage 2 colon cancer randomised to surveillance or receive adjuvant chemotherapy if ctDNA+ and surveillance If ctDNA-.	1320	PGDxeliotm	Recurrence rate at 2 years	January 2022
NCT03803553 **ACT-3**	Patients with ctDNA+ stage 3 CRC after standard adjuvant chemotherapy randomised to surveillance and escalation of adjuvant treatment based on biological subgroups: FOLFIRI (MSS/BRAF wild-type), encorafenib/binimetinib/cetuximab (BRAF mutant) or nivolumab (MSI-high)	500	Guardant LUNAR-1™	DFS and ctDNA clearance	February 2023
ACTRN-12615000381583 DYNAMIC II	Patients with stage 2 colon or rectal cancer randomised to clinician determined management without knowledge of ctDNA results or receive adjuvant chemotherapy if ctDNA+ and surveillance if ctDNA-	450	Safe-SeqS	RFS	August 2024
UMIN000039205 ALTAIR	Patients with stage 2, 3 or stage 4 no evidence of disease ctDNA+ after standard adjuvant chemotherapy will be randomised between surveillance and escalation of treatment with trifluridine/tipiracil	240	Signatera™	DFS	2030
NCT04486378	Patients with ctDNA+ high risk stage 2 or stage 3 colon cancer randomised to adjuvant chemotherapy and autogene cevumeran or adjuvant chemotherapy and watchful waiting	201	Not-reported	DFS	July 2027
Escalate/de-escalate trials					
NCT05174169 **NRG GI-008 CIRCULATE-US**	Patients with ctDNA- T1-3N1 stage 3 colon cancer are randomised between adjuvant chemotherapy or surveillance but re-esclation to chemotherapy if ctDNA becomes + during follow-up. Patients that are ctDNA+ will be randomised between standard doublet adjuvant chemotherapy and mFOLFIRINOX.	1912	Signatera™	DFS	2030
ACTRN-12617001566325 DYNAMIC-III	Patients with stage 3 colon or rectal cancer randomised between clinician determined management or receive an escalated adjuvant chemotherapy regimen when ctDNA+ or de-escalated regimen when ctDNA-	1000	Safe-SeqS	ctDNA-: RFS non-inferiority ctDNA+: RFS superiority	April 2024
NCT04259944 **PEGASUS**	Patients with stage 3 and high-risk stage 2 disease receive oxaliplatin containing doublet adjuvant chemotherapy if ctDNA+ and monotherapy if ctDNA- but escalation to a doublet if later ctDNA+. After adjuvant treatment, treatment will be escalated or de-escalated based on ctDNA as follows: ctDNA+/+: FOLFIRI for 6 months or until radiological progression or toxicity; ctDNA-/+: CAPOX for 6 months or until radiological progression or toxicity. If after 3 months ctDNA+: switch to FOLFIRI. ctDNA+/-: de-escalate treatment to capecitabine for 3 months. If after 3 months ctDNA+: switch to FOLFIRI. ctDNA-/-: surveillance, if positive ctDNA during surveillance switch to CAPOX.	140	Guardant LUNAR-1™	Number of post-surgery and post-adjuvant false-negative cases after a double ctDNA-negative detection	July 2024
De-escalating trials					
UMIN000039205 **VEGA**	Patients with high-risk stage 2, low-risk stage 3 ctDNA- colon cancer randomised to standard of care adjuvant chemotherapy and surveillance (patients enrol in ALTAIR study if ctDNA becomes + at 3 months)	1240	Signatera™	DFS Non-inferiority	2030
NCT04050345 **TRACC**	Patients with high-risk stage 2 and 3 CRC randomised between standard of care adjuvant chemotherapy or standard adjuvant chemotherapy when ctDNA+ and de-escalation of adjuvant chemotherapy if ctDNA- but re-escalation if ctDNA becomes +	1000	NGS-based 22-gene colorectal panel	DFS	December 2024

BRAF, B-Raf, and v-Raf murine sarcoma viral oncogene homologue B; CAPOX, capecitabine, and oxaliplatin; CRC, colorectal cancer; ctDNA, circulating tumour deoxyribonucleic acid; ddPCR, digital droplet polymerase chain reaction; DFS, disease-free survival; FOLFIRI, fluoro-uracil and irinotecan; FOLFIRINOX, fluoro-uracil, irinotecan, and oxaliplatin; MSI-H, microsatellite instable-high; MSS, microsatellite stable; NGS, next-generation sequencing; RFS, recurrence-free survival;

Table 2

Neoadjuvant systemic therapy trials in early colon cancer.

ClinicalTrials.gov or national registry trial identifier and trial name	Study intervention	Accrual goal	Phase	Primary endpoint	Estimated completion date
Neoadjuvant chemotherapy					
NCT03125980	Patients with locally advanced colon cancer randomised between standard of care upfront surgery followed by CAPOX x8 or neoadjuvant CAPOX x4 followed by surgery followed by CAPOX x4	1370	Phase 3	3-year DFS	May 2027
NCT03426904	Patients with locally advanced colon randomised between standard of care upfront surgery followed by FOLFOX x 12 or neoadjuvant FOLFOX x4 followed by surgery followed by adjuvant FOLFOX x8	560	Phase 3	RFS	February 2026
NCT01918527	Patients with locally advanced colon cancer randomised between standard of care upfront surgery followed by CAPOX x4–8 or neoadjuvant CAPOX x3 followed by surgery followed by adjuvant chemotherapy if indicated based on pathology.	250	Phase 3	2-year DFS	February 2025
NCT04188158 **ELECLA**	Locally advanced colon cancer patients randomised between standard of care upfront surgery followed by FOLFOX x12 or neoadjuvant FOLFOX ± cetuximab x4 followed by surgery followed by FOLFOX ± cetuximab x8	238	Phase 2	2-year DFS	March 2024
NCT03484195	Patients with locally advanced colon cancer receive neoadjuvant FOLFOXIRI x4	30	Phase 2	The rate of tumour downstaging to stage 0 and stage I	Originally anticipated October 2021; however no data presented or published yet
No identifier yet FOxTROT 2	Patients at higher age or frail with locally advanced MSS colon cancer randomised between standard of care upfront surgery or neoadjuvant dose-adapted FOLFOX followed by surgery.	?	Phase 3	3-year DFS	2029
No identifier yet FOxTROT 3	Young and fit patients with locally advanced MSS colon cancer randomised between standard of care upfront surgery or neoadjuvant 6 weeks mFOLFOXIRI or encorafenib/cetuximab if BRAF V600E mutated, followed by surgery	?	Phase 3	TRG	2029
Neoadjuvant immune checkpoint inhibitors					
NCT04231526	Patients with locally advanced colon cancer receive neoadjuvant pembrolizumab x2 followed by surgery	46	Phase 2	Feasibility	March 2025
NCT03985891	Patients with locally advanced colon cancer are randomised between neoadjuvant FOLFOX x6 or neoadjuvant FOLFOX + toripalimab x6	40	Phase 1/2	pCR rate rCR rate ORR rate	June 2026

CAPOX, capecitabine and oxaliplatin; DFS, disease-free survival; FOLFOX, fluoro-uracil and oxaliplatin; FOLFIRINOX, fluoro-uracil, irinotecan and oxaliplatin; NGS, next-generation sequencing; mFOLFOXIRI, modified fluoro-uracil, irinotecan and oxaliplatin; MSS, microsatellite stable; RFS, recurrence-free survival; TRS, tumour regression grade.

early-stage and advanced-stage disease (Fig. 1). For example, MSI-H prevalence is higher in early-stage ($\sim$ 15 %) than in the advanced stage ($\sim$ 5 %). Therapeutic success against other CRC molecular subtypes in the metastatic setting might be an opportunity for the early

colon cancer setting as well. Examples include epidermal growth factor receptor 2 (HER2), gene fusions including those involving neurotrophic receptor tyrosine kinase 1 *(NTRK1), NTRK2, NTRK3*, anaplastic lymphoma kinase *(ALK)*, rearrangement during transfection (RET), and
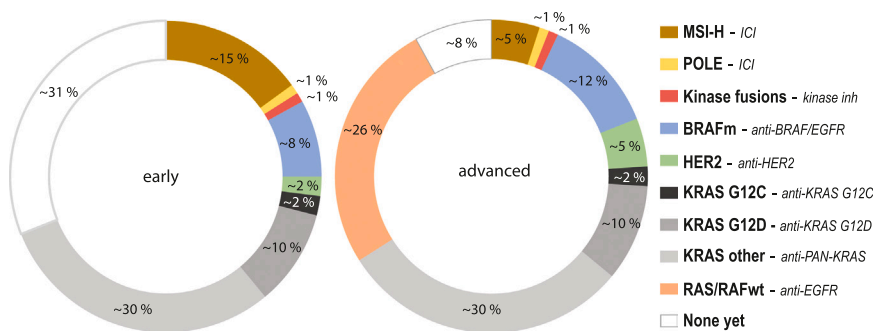

Fig. 1. Actionable molecular colon cancer subgroups with (potential) therapeutic relevance in early colon cancer. The prevalence of targetable molecular alterations in colon cancer differs between early-stage and advanced stage. The prevalence of targetable mutations is shown for early-stage on the left and advanced stage on the right. **MSI-H:** The prevalence of MSI-H in metastatic CRC is $\sim$ 5 %, while the prevalence in early CRC is $\sim$ 15 % (Alberts et al., 2012; Allegra et al., 2011). **POLE:** The prevalence of POLE mutations is < 1 % in metastatic CRC and $\sim$ 1 % in early CRC (André et al., 2004; Andre et al., 2015). **Kinase fusions:** The prevalence of oncogenic driving gene fusions (NTRK, ALK, RET, ROS1) is $\sim$ 1 % for patients with metastatic and early CRC (André et al., 2020). Oncogenic driving gene fusions are enriched in MSI-H BRAF/KRASwt tumours. In 15 % of these tumours

fusions are present (André et al., 2020). **BRAF-V600E:** The prevalence of BRAF V600E mutations in metastatic CRC is $\sim$ 12 %, while the prevalence in early CRC is $\sim$ 8 % (Argiles et al., 2020; Auclin et al., 2017). **HER2:** The prevalence of HER2 amplification in metastatic CRC is 5–6 % and in early CRC around 2 % (Benhaim et al., 2021; Benson et al., 2021; Brierley et al., 2016). **KRAS G12C:** The prevalence of KRAS G12C mutations in metastatic CRC is 2–4 % and in early CRC $\sim$ 2 % (Blank et al., 2018; Buyse et al., 1988). **RAS/RAFwt:** EGFR inhibitors registered to treat patients with metastatic CRC, improve overall survival only in patients with RAS/RAF wt tumours ($\sim$ 27 %) (Cercek et al., 2022). The addition of these drugs to standard adjuvant chemotherapy, also in RAS/RAF wt tumours, failed to improve survival in patients with early colon cancer compared to standard adjuvant chemotherapy. ACT, adjuvant chemotherapy; ALK, anaplastic lymphoma kinase; ctDNA, circulating tumour deoxyribonucleic acid; BRAF, v-Raf murine sarcoma viral oncogene homologue B; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; INH, inhibitor; KRAS, Kirsten rat sarcoma virus; ORR, overall response rate; NTRK, neurotrophic receptor tyrosine kinase; RAF rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RET, rearrangement during transfection; WT, wild type.

c-ros oncogene 1 (*ROS1)* and KRAS G12C. However, no trials are ongoing to investigate these in the early colon cancer setting. Furthermore, the main limitation of the development of these studies are that these alterations are infrequent (Fig. 1).

6. Neoadjuvant strategies in early colon cancer

The administration of neoadjuvant ICI, compared to adjuvant ICI, results in the activation of more tumour-specific T cells due to the presence of more tumour neoantigens (Blank et al., 2018; O'Donnell et al., 2019). Therefore, testing neoadjuvant ICI is of interest in patients with colon cancer.

6.1. Neoadjuvant immune checkpoint inhibitors in MSI-High colon cancer

In a randomised phase 2 trial in 34 patients with early MSI-high CRC of which 28 had colon cancer, half of them received the PD-1 antibody toripalimab plus celecoxib and the other half toripalimab monotherapy. Six cycles were administered before surgery. Thereafter all patients underwent surgery without treatment-related surgical delays. Fifteen out of 17 patients (88 %) in the toripalimab plus celecoxib and 11 out of 17 (65 %) in the toripalimab group had a pathological complete response. All patients were alive and free of recurrence at data cut-off at a median follow-up of 14.9 months (Hu et al., 2021). In the NICHE trial, nivolumab and ipilimumab were given to patients with MSI-high tumours and to patients with MSS early colon cancer (Chalabi et al., 2020). Patients received a short neoadjuvant regimen with ipilimumab (day 1) and nivolumab (days 1 and 15). Patients with MSS tumours were additionally randomly assigned to also receive celecoxib 200 mg daily until the day before surgery or no additional treatment. The intervention was safe, and there were no delays in surgery. All 20 patients with MSI-high tumours had a pathologic response, of which 60 % complete. At a median follow-up of 9 months, all patients with MSI-high tumours were alive and without disease recurrence. In the NICHE 2 trial, 112 patients with MSI-high early colon cancer were treated with the same short neoadjuvant regimen with ipilimumab (day 1) and nivolumab (days 1 and 15). Treatment was safe and all patients underwent surgery. Three patients experienced delay in surgery. 106/107 patients had a pathologic response and 72/107 had a pathologic complete response. (Chalabi et al., 2022). Neoadjuvant ICI therapy for patients with locally advanced MSI-high early colon cancer could become the standard of care if more extensive studies and follow-up confirm these initial data. Suppose the correlation of clinical and pathological complete response and a decreased recurrence risk is validated in these more extensive trials. In that case, early MSI-high colon cancer might even become a surgery-free disease for some patients. This idea is supported by data in rectal cancer. In a phase 2 trial, the PD-1 antibody dostarlimab was given for 6 months to 13 patients with locally advanced MSI-H rectal cancer. All patients achieved clinical complete response – based on previously established criteria defined as endoscopic complete response and a complete response based on a pelvic MRI - and have not required chemoradiotherapy or surgery (Cercek et al., 2022).

6.2. Neoadjuvant systemic treatment in MSS colon cancer

Around 85 % of patients with locally advanced colon cancer have MSS tumours. Neo-adjuvant systemic therapy is of interest to them as well. In the NICHE trial, 27 % of patients with MSS tumours had a pathological response of which 13 % were complete (Chalabi et al., 2020). This contrasts to the efficacy of ICI in advanced colon MSS tumours, with a 0 % (0/18) response to the PD-1 inhibitor pembrolizumab (Le et al., 2015). Neo-adjuvant ICI for early colon cancer should be further explored. Neo-adjuvant chemotherapy for MSS early colon cancer has also been investigated. The FOxTROT phase 3 RCT in 1053 patients with early colon cancer investigated 3 cycles of neo-adjuvant FOLFOX, followed by surgery and 9 cycles adjuvant FOLFOX versus

standard of care surgery followed by adjuvant chemotherapy (Seymour and Morton, 2019). Neo-adjuvant chemotherapy was safe and well-tolerated. After two years, the rate of relapse or persistent disease between the 2 study arms was non-significant at 14 % for peri-operative chemotherapy versus 18 % for adjuvant chemotherapy (HR 0.77, *p* = 0.11). The 20.2 % of patients with MSI-high tumours had with 7 % a lower pathological response rate than the 23 % with MSS tumours. Similarly, reductions in recurrence at two years were primarily seen in MSS tumours (RR = 0.72, 0.52–1.00), and much less in MSI-high tumours (RR = 0.94, 0.43–2.07). Importantly, pathological tumour response was closely related to recurrence risk, with 0 % recurrence in patients with pathological complete response. The maturation of this trial will provide information on OS. The OPTICAL phase 3 RCT in 752 patients with early colon cancer investigated 3 months of neo-adjuvant oxaliplatin based chemotherapy followed by surgery and 3 months adjuvant oxaliplatin based chemotherapy versus standard of care surgery followed by adjuvant chemotherapy (Hu et al., 2022). Neo-adjuvant chemotherapy was safe and well-tolerated. Primary endpoint DFS was non-significantly different with a 3-year DFS rate of 78.7 % versus 76.6 % (HR = 0.83, 0.60–1.15, *p* = 0.138). Secondary endpoint OS was significantly different with a 3-year OS rate of 94.9 % versus 88.6 % (HR = 0.47, 0.25–0.87; *p* = 0025). Furthermore, neo-adjuvant chemotherapy induced a 7 % pCR. Several ongoing trials are evaluating the role of neoadjuvant systemic therapy in early colon cancer (Table 2).

7. Conclusions and future directions

After many years of paucity, there are now many ongoing trials with novel treatment strategies for patients with early colon cancer. Prospective trials are ongoing to better define how Immunoscore and ctDNA will guide clinical decision making. Advances made in treating patients with metastatic colon cancer are now being translated to the early colon cancer setting, most prominently ICI therapy with 2 ongoing phase 3 adjuvant trials. The complete response rate in patients with MSI-H tumours following ICI in neoadjuvant trials has potential organ-sparing implications. All these trials might lead to a more biology-based treatment approach, better results, and escalating treatment when necessary and de-escalating treatment when possible.

CRediT authorship contribution statement

Daan G. Knapen: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Jacco J. de Haan**: Conceptualization, Writing – review & editing. **Elisabeth G. E. de Vries**: Conceptualization, Methodology, Writing – review & editing, Supervision. **Rudolf S.N. Fehrmann**: Conceptualization, Methodology, Writing – review & editing. **Derk Jan A. de Groot**: Conceptualization, Methodology, Writing – review & editing, Supervision.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2023.103918.

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