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Rewriting the Playbook: Neoadjuvant and Adjuvant Immunotherapy in dMMR Colon Cancer

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Introduction: Understanding dMMR Colon Cancer

Deficient mismatch repair (dMMR) is a molecular subtype of colorectal cancer (CRC) defined by the loss of function of one or more of the four key DNA mismatch repair (MMR) proteins: MLH1, PMS2, MSH2, and MSH6. This deficiency can be identified either by immunohistochemistry (IHC), which detects loss of protein expression, or by PCR and next-generation sequencing assays that detect microsatellite instability-high (MSI-H) status. The two designations are used interchangeably in clinical practice, as their functional consequence is equivalent: a hypermutated tumour genome that produces a high burden of neoantigens, conferring immunogenicity.

dMMR tumours arise through two primary pathways. The majority, approximately 85%, are sporadic and result from somatic hypermethylation of the *MLH1* promoter, frequently co-occurring with a *BRAF* V600E mutation. The remaining 15% arise in the context of Lynch syndrome, an

autosomal dominant hereditary condition caused by germline pathogenic variants in one of the four MMR genes. Universal MMR testing is now standard practice for all newly diagnosed CRC cases and is embedded in both Canadian and international guidelines.[1]

From an epidemiological standpoint, the prevalence of dMMR varies by disease stage. Population-based studies and meta-analyses show that dMMR is present in approximately 20% of stage II colon cancers and 12% of stage III cases.[2] The prognostic and predictive value of dMMR in CRC have been well reported, with the strongest evidence coming from two separate pooled individual patient data analyses of the Adjuvant Colon Cancer Endpoint (ACCENT) database.[2,3] Briefly, adjuvant fluoropyrimidine (FP)–based chemotherapy has not shown a clear benefit and is generally not recommended in stage II dMMR colon cancer. In contrast, three to six months of oxaliplatin-based adjuvant chemotherapy is recommended for stage III dMMR colon cancer based on improved overall survival (OS) compared to FP alone (hazard ratio [HR]: 0.52; 95% confidence interval [CI]: 0.28-0.93). Despite optimal treatment, up to 40% of patients with dMMR colon cancer will eventually relapse, highlighting a significant unmet need and the limitations of current treatment approaches for this patient subgroup.

Failure to repair mismatch errors leads to the accumulation of frameshift mutations and the generation of several abnormal tumour-specific peptides that trigger a host antitumour immune response. Tumours evolve over time under the selective pressure of the immune system and eventually escape immune surveillance through various mechanisms that promote self-tolerance.[4] The genomic instability characteristic of dMMR tumours also confers decreased sensitivity to chemotherapy and, most importantly, exquisite sensitivity to immune checkpoint inhibitors

Trial	Treatment	Phase	Population	pCR / cCR	Survival
NICHE-2[6,16]	Nivolumab + Ipilimumab (1 cycle)	II	Stage II-III dMMR colon cancer	pCR 67–68% MPR 95%	DFS 100% at 3 years
NICHE-3[7]	Nivolumab + Relatlimab (2 cycles)	II	cT3-4/N+ dMMR colon cancer	pCR 68% MPR 92%	DFS 98% (median f/u 8 months)
RESET-C[8]	Pembrolizumab Single dose	II	Stage I–III dMMR colon cancer	pCR 44% (67% stage I/II; 33% stage III), MPR 57%	DFS 96% (median f/u† 18.4 months)
IMHOTEP[9]	Pembrolizumab (1 year)	II	cT3-4/N+ dMMR colorectal cancer	pCR 53.8% (68% with 2 cycles)	DFS 93.1% at 2 years
Cercek *et al.*[11]	Dostarlimab (6 months) (NOM intended)	II	Stage I-III dMMR solid tumors	cCR 82% (100% rectal, 65% non-rectal)	RFS 92% at 2 years
NEOPRISM[12]	Pembrolizumab (9 weeks)	II	cT3-4/N+ dMMR colorectal cancer	pCR 59%	RFS 100% (median f/u 32.9 months)
UNICORN[13]	Botensilimab +/- Balstilimab (1 cycle)	II	Locally advanced pMMR or dMMR colon cancer (cT3-4, N0-2)	BOT: pCR 29% BOT+BAL: pCR 93% (dMMR)	Not reported

Table 1. Key Outcomes of Neoadjuvant Immunotherapy Trials in dMMR Colon Cancer; *courtesy of Abla Alj, MD, Melina Boutin, MD*

Abbreviations: BAT: balstilimab; **BOT:** botensilimab; **cCR:** clinical complete response; **DFS:** disease-free survival; **dMMR†:** deficient mismatch repair; **f/u:** follow up; **MPR:** major pathological response; **NOM:** non-operative management; **pCR:** pathological complete response; **RFS:** recurrence-free survival.

(ICIs). The recognition of these unique key characteristics has led to the development of several clinical trials incorporating ICIs in the adjuvant and neoadjuvant settings.

Adjuvant Immunotherapy: The ATOMIC Trial

While neoadjuvant strategies have generated substantial interest, most patients with dMMR colon cancer still present in the post-operative setting, highlighting the importance of adjuvant therapy trials.

The ATOMIC trial was a multicentre, randomized phase III study that enrolled 712 patients with surgically resected stage III dMMR colon cancer across more than 300 sites between 2017 and 2023.[5] Patients were randomized 1:1 to receive either six months of standard mFOLFOX6 (leucovorin, fluorouracil, and oxaliplatin) alone (n=357) or mFOLFOX6 combined with atezolizumab (anti-programmed cell death ligand 1 [PD-L1] ICI, 840 mg intravenous [IV] every 2 weeks) for 12 cycles, followed by atezolizumab monotherapy for 13 additional cycles—totaling about one year of ICI exposure (n=355). The primary endpoint was disease-free survival (DFS).

At a median follow-up of 37.2 months, three-year DFS was 86.4% in the atezolizumab arm versus 76.6% in the mFOLFOX6-alone arm (HR: 0.50; 95% CI: 0.35–0.72; p<0.0001), corresponding to a 50% reduction in the risk of recurrence or death. The benefit was consistent across all pre-specified subgroups, including patients over 70 years of age and both low- and high-risk disease strata. The safety profile was consistent with the known toxicities of both regimens: treatment-related grade ≥3 adverse events occurred in 71.7% of the atezolizumab arm versus 62.1% of the mFOLFOX6 arm, grade ≥3 immune-related adverse events were rare and manageable. OS data were not yet mature at the time of analysis.

ATOMIC represents the first prospective, randomized phase III trial to evaluate immunotherapy in the adjuvant setting for dMMR colon cancer. The 10.1 percentage-point improvement in 3-year DFS is clinically meaningful and establishes atezolizumab plus mFOLFOX6 followed by atezolizumab maintenance as a standard of care for resected stage III dMMR colon cancer, pending regulatory approval. Even though ATOMIC is an important step forward, the field has since moved towards chemotherapy-free neoadjuvant immunotherapy approaches. This raises questions about treatment duration for both chemotherapy and immunotherapy, whether chemotherapy is necessary at all, and how adjuvant ICIs compare with neoadjuvant ICIs.

Neoadjuvant Immunotherapy: Current Evidence

The documented activity of ICIs in the metastatic setting has led to the hypothesis that these agents could be even more active when applied in the pre-operative setting, when the immune microenvironment is less disrupted. Preclinical and clinical evidence across tumour sites has shown that ICIs are more effective at priming immune cells to induce a response when the tumour is still in place. Also, locoregional lymph nodes appear to play an important role in antigen presentation and the generation and expansion of specific antitumour effector lymphoid cells in animal models, further supporting the rationale for a neoadjuvant, chemo-free approach.[4] This rationale has driven the current wave of neoadjuvant and perioperative clinical trials **(Table 1)**.

The NICHE program has been central to this evidence base. NICHE-2, a phase II study, enrolled 115 patients with locally advanced (stage I to III, predominantly cT3–T4 and/or node-positive) dMMR colon cancer who received a brief neoadjuvant regimen: one dose of the ICI ipilimumab (anti-cytotoxic T lymphocyte-associated protein 4 [CTLA-4]; 1 mg/kg, Day 1) and two doses of the ICI nivolumab (anti-programmed cell death protein 1 [PD-1]; 3 mg/kg, Days 1 and 15), followed by surgery within six weeks. The authors reported a pathological response rate of 98%, with 95% of patients achieving a major pathological response (MPR, defined as ≤10% residual viable tumour), and 68% achieving pathological complete response (pCR, ypT0N0). Grade 3–4 immune-related adverse events occurred in 4% of patients, and 98% of patients underwent timely surgery, meeting the safety co-primary endpoint.[6]

Three-year DFS data from NICHE-2 were subsequently reported, with a median follow-up of 60.4 months.[16] The 3-year DFS rate was 100%, surpassing the pre-specified success threshold of 93%, with no recurrence observed in any patient. These survival outcomes compare favourably with historical data for stage III dMMR colon cancer, where recurrence rates approach 40%.[3]

An alternative combination was evaluated in NICHE-3: nivolumab was paired with the anti-LAG-3 ICI relatlimab and administered in two four-week cycles to 59 patients with locally advanced dMMR colon cancer. Pathological responses were observed in 97% of participants, with MPR rates of 92% and pCR rates of 68%. Grade 3–4 immune-related adverse events occurred in 10% of patients. All patients achieved R0 resection, with a median time from immunotherapy to surgery of 7.6 weeks. These results support anti-LAG-3 combinations as a potentially comparable alternative to anti-CTLA-4 regimens, though cross-trial comparisons should be interpreted with caution.[7]

The recently published RESET-C study was designed to investigate the efficacy, safety, and endoscopic response of neoadjuvant single-cycle pembrolizumab (anti-PD-1) in 85 patients with localized dMMR colon cancer who were scheduled for curative-intent surgery. The pCR rate was 44%, with higher rates in stage I-II than stage III (67% vs. 33%, odds ratio: 3.1; 95% CI: 1.2-8.1; p=0.02). When compared to a histopathology reference, endoscopy showed a sensitivity of 77%, specificity of 93%, positive predictive value of 90%, negative predictive value of 83%, and overall accuracy of 86% for predicting pCR.[8]

The IMHOTEP trial evaluated an innovative perioperative strategy with pembrolizumab. Patients with localized resectable dMMR/MSI-H cancers across multiple tumour types were enrolled, including a CRC cohort of 87 patients. Patients received pembrolizumab 400 mg IV every 6 weeks for 1 year; the first 1 or 2 doses were administered preoperatively. The trial met its primary endpoint, with a pCR rate of 53.8% (95% CI: 42.8–64.7%). Of note, the pCR rate increased with the number of neoadjuvant cycles received—47.1% with one cycle versus 68.0% with two cycles—suggesting a dose-response relationship. At a median follow-up of 24.5 months, the two-year DFS was 93.1%: one patient experienced disease progression after one cycle, 3 patients had disease recurrence at 4, 24, and 24 months, and one patient died of a non-cancer-related cause. IMHOTEP is the first study to show a dose-dependent effect, suggesting that additional cycles may enrich pathological responses, but this may come at the cost of delaying surgical resection.[9] The ongoing phase III AZUR-2 trial is designed to provide randomized evidence comparing a perioperative ICI with dostarlimab (anti-PD-1) to the standard of care. Canadian sites are participating in AZUR-2; results are not anticipated before 2028–2029.[10]

Is Surgery Still Required?

The excellent response rates and outcomes demonstrated with short courses of immunotherapy across dMMR gastrointestinal cancers have paved the way for organ preservation.

Building on their experience with dostarlimab in dMMR rectal cancer, Cercek *et al*. have published results of their expanded cohorts of rectal and non-rectal dMMR solid tumours, including 33 patients with colon cancer. Six months of neoadjuvant dostarlimab yielded a complete clinical response (cCR) in 82% of patients who completed treatment, including 100% in rectal cancer and 65% in non-rectal tumours. Of the 84 patients who achieved a cCR, 82 elected to forgo surgery without loss of surgical eligibility, and the two-year recurrence-free survival (RFS) rate reached 92%. Clinical response was determined by imaging and endoscopy whenever feasible; patients were monitored with the same modalities and with circulating tumor DNA (ctDNA). The median time to cCR was 6.2 months, and ctDNA clearance correlated strongly with clinical response. These results extend the organ-preservation concept beyond rectal cancer and suggest that prolonged neoadjuvant PD-1 blockade may ultimately spare surgery in a significant proportion of dMMR patients.[11]

One of the key caveats with non-operative management (NOM) in colon cancer is the lack of validated criteria to define complete response. Conventional cross-sectional imaging has well-recognized limitations in this context and correlated poorly with response in the NICHE-2 trial.[6] Endoscopic assessment of clinical response is routinely used in rectal cancer but not yet standardized in colon cancer and requires a full colonoscopy. Molecular monitoring with ctDNA appears promising, yet not sensitive enough on its own. In NICHE-2[16], presurgical ctDNA demonstrated a high specificity of 93% (95% CI 83-97) for detecting residual disease but low sensitivity (35%, 95% CI 19-55), with corresponding positive and negative predictive value of 69% (95% CI 41-89) and 75% (95% CI 64-84), respectively.

Controversies and Unanswered Questions

Despite the progress outlined above, important questions remain. The first concerns optimal treatment sequencing and patient selection for neoadjuvant approaches. Non-randomized NICHE-2 and UNICORN trial data demonstrated the highest pCR rates and 3-year DFS of 100% with a well-tolerated, only two-week course of neoadjuvant ICI alone, making this regimen most appealing for locally advanced (cT3-T4 or N+) dMMR colon cancer. In the metastatic setting, dual ICI is more effective than a single agent.[14] Although it is plausible that dual ICI would achieve higher efficacy at the earlier stage as well, patients treated with anti-PD1 monotherapy also achieve excellent outcomes, especially when treated at earlier stages or in those with non-bulky tumours. However, patients with dMMR colon cancer presenting at an earlier stage can be cured with surgery alone, without the need for neoadjuvant or adjuvant therapy. Patients undergoing surgery who are subsequently diagnosed with stage III disease should still be treated with 3 to 6 months of oxaliplatin-based adjuvant chemotherapy with the addition of atezolizumab per ATOMIC, when available in Canada. Implementing neoadjuvant treatment for locally advanced colon cancer requires a shift in patients' trajectories, timely assessment of MMR status, and increased awareness and communication with gastroenterologists and surgeons.

A second area of interest is the feasibility of organ preservation. Whether surgery could be safely omitted in a selected subset of patients with clinical or molecular complete response is a hypothesis that warrants prospective evaluation. The available evidence suggests a few useful points to consider when contemplating NOM: higher and quicker response rates with dual ICI,[6,7,13] deepening of responses over time with single ICI with a small risk of primary resistance,[9] a median time to cCR of 6 months with anti-PD1 monotherapy,[11] lower rates of pCR with T4 tumours,[8,15] and the need for a multimodal assessment and monitoring of response with endoscopy and ctDNA rather than imaging alone.[6,8,9,11,16] The current data are encouraging but limited by the short follow-up, small number of patients and lack of availability of routine ctDNA monitoring. A confirmatory randomized trial would be required for NOM to become standard of care in colon cancer, given that surgery has no severe complications or effect on quality of life, unlike surgery for rectal or gastro-esophageal cancers. At present, this approach should be reserved for surgically unfit patients following multidisciplinary discussion.

Finally, the identification of predictive biomarkers beyond MMR status itself remains an active area of investigation. Preliminary data from the NICHE-2 trial suggest that Lynch syndrome–associated tumours may have higher pCR rates, and that specific MMR protein loss may carry differential prognostic weight. Tumour mutational burden, *BRAF* mutation status, and on-treatment ctDNA kinetics are among the candidate biomarkers being explored. Prospective validation of these markers will be necessary before they can guide treatment decisions.

Translating Evidence into Canadian Clinical Practice

For Canadian medical oncologists, the evolving evidence has several practical implications. Universal MMR/MSI testing at the time of CRC diagnosis is the standard of care and should be reflexive—both to guide treatment decisions and to enable appropriate hereditary cancer counselling and family cascade testing, when Lynch syndrome is identified.

The management of dMMR colon cancer is undergoing a meaningful shift. For those with newly diagnosed, locally advanced dMMR colon cancer, neoadjuvant ICI with nivolumab and ipilimumab is now supported by phase II data with three-year DFS outcomes,[6,16] while ATOMIC established for the first time that adjuvant ICI improves DFS in the post-operative setting.[5] Referral to AZUR-2 or similar trials should be considered whenever possible. Coordinated multidisciplinary care among oncologists, surgeons, and pathologists is essential for optimal staging, surgical planning, and pathological assessment post-neoadjuvant therapy. Results from ongoing randomized trials, along with translational analyses from completed studies, will be required to clarify the optimal treatment sequence, the role of chemotherapy de-escalation, and the potential for organ preservation in selected patients.

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