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- In the subgroup of PD-L1 ≥1 patients, OS events for OPDIVO + YERVOY + platinum-doublet chemotherapy were 105/203 vs. 139/204 for platinum-doublet alone (HR 0.64[‡] [95% CI: 0.50, 0.82]); median OS was 15.8 months vs. 10.9 months

OPDIVO Safety Information[1]

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Severe/fatal immune-mediated adverse reactions (imARs): OPDIVO as monotherapy or in combination with YERVOY (ipilimumab) can cause severe and fatal immune-mediated adverse reactions, including pneumonitis, interstitial lung disease, encephalitis, myocarditis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and autoimmune hemolytic anemia. Immune-mediated adverse reactions may involve any organ system. Onset may occur during treatment or months after the last dose. Early diagnosis and appropriate management are essential to minimize potential life-threatening complications. Monitor patients for signs and symptoms of imARs and appropriately manage with treatment modifications. Permanently discontinue for any severe imARs that recur and for any life-threatening imARs.

Administration: Administer OPDIVO under the supervision of physicians experienced in the treatment of cancer.

Allogeneic hematopoietic stem cell transplantation (HSCT): Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host disease (GVHD) and transplant-related mortality. Complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grades 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic venoocclusive disease (VOD), and other immune-mediated adverse reactions, and intervene promptly.

Multiple myeloma: Increased mortality in patients with multiple myeloma [not an approved indication] when OPDIVO is added to a thalidomide analogue and dexamethasone. Treatment of patients with multiple myeloma with a PD-1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when OPDIVO was administered in combination with YERVOY vs. OPDIVO alone
- Severe cases of these imARs have been observed, including fatal cases. Monitor patients for signs and symptoms of:
  - Cardiac adverse events and pulmonary embolism with combination therapy
  - Endocrinopathies, including hypothyroidism, hyperthyroidism, hypoparathyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus, and diabetic ketoacidosis
  - Diarrhea, additional symptoms of colitis, and cytomegalovirus (CMV) infection/reactivation
  - Hepatotoxicity, including hepatitis
  - Pneumonitis or interstitial lung disease
  - Nephrotoxicity, including nephritis and renal failure
  - Rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Encephalitis
  - Aplastic anemia
  - Myelitis (including transverse myelitis)
  - Autoimmune hemolytic anemia
  - Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
  - Other imARs, including solid organ transplant rejection and rapid-onset and severe graft-versus-host disease (GVHD)
- Infusion reaction
- Patients on controlled sodium diet
- Caution when driving or operating a vehicle or potentially dangerous machinery
- Haemophagocytic lymphohistiocytosis (HLH)
- Effective contraception in women of reproductive potential
- Pregnancy and nursing women
- Has not been studied in patients with moderate or severe hepatic or severe renal impairment

For more information:

Please consult the OPDIVO Product Monograph at www.bms.com/assets/bms/ca/documents/productmonograph/OPDIVO_EN_PM.pdf for important information relating to adverse reactions, drug interactions, and dosing, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

YERVOY Safety Information[2]

Clinical use:

Efficacy and safety not established in pediatric patients.

Contraindication:

In patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life threatening.

Most serious warnings and precautions:

Severe/fatal immune-mediated adverse reactions (imARs): YERVOY as monotherapy or in combination with OPDIVO (nivolumab) can cause severe/fatal imARs, including enterocolitis, intestinal perforation, hepatitis, dermatitis (incl. toxic epidermal necrolysis), Stevens-Johnson syndrome, neuropathy, endocrinopathy, pneumonitis, interstitial lung disease, myocarditis, encephalitis, myasthenia gravis, autoimmune hemolytic anemia and other organ system toxicities. Most occurred during the induction period; onset months after the last dose has been reported. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Monitor patients for signs and symptoms suggestive of imARs. Permanently discontinue treatment for any severe imAR reaction that recurs and for any life-threatening imAR.

Consult the OPDIVO (nivolumab) Product Monograph prior to initiation of YERVOY in combination with OPDIVO.

Administration: Administer YERVOY under the supervision of physicians experienced in the treatment of cancer.

Other relevant warnings and precautions:

- imARs have occurred at higher frequencies when YERVOY was administered in combination with OPDIVO vs. YERVOY alone
- Patients who have had a severe or life-threatening skin adverse reaction on a prior cancer immune stimulatory therapy
- Severe cases of these imARs have been observed, including fatal cases. Monitor for signs/symptoms of:
  - Gastrointestinal adverse reactions
  - Hepatic adverse reactions
  - Pulmonary adverse reactions
  - Renal adverse reactions
  - Skin adverse reactions
  - Encephalitis
  - Neuropathies
  - Endocrinopathies, including diabetes mellitus (including fulminant type 1 diabetes), and diabetic ketoacidosis
- Other imARs including ocular events
- Haemophagocytic lymphohistiocytosis (HLH)
- Vogt-Koyanagi-Harada syndrome
- Serous retinal detachment
- Graft-versus-host disease (GVHD)
- Solid organ transplant rejection in the post-marketing setting
- Infusion reaction
- Patients on immunosuppressive therapy for life-threatening disease or condition
- Autoimmune hemolytic anemia
- Myotoxicity (myositis, myocarditis, and rhabdomyolysis)
- Patients on controlled sodium diet
- Concurrent administration with vemurafenib
- Caution when driving or operating machinery
- Patient counselling information: imARs and fatigue
- Not studied in patients with hepatic impairment
- Not studied in patients with renal impairment
- Pregnancy and nursing women
- Effective contraception in women of reproductive potential
- Close monitoring required: liver function tests, thyroid function test, electrolytes, any signs of imARs

For more information:

Please consult the YERVOY Product Monograph at www.bms.com/assets/bms/ca/documents/productmonograph/YERVOY_EN_PM.pdf for important information relating to adverse reactions, management of imARs, drug interactions, and dosing information, which have not been discussed in this piece.

The Product Monograph is also available by calling us at: 1-866-463-6267.

CI: confidence interval; HR: hazard ratio; mNSCLC: metastatic non-small-cell lung cancer; OS: overall survival; PD-L1: programmed death-ligand 1.

* CheckMate 9LA: a randomized, multicenter, open-label trial in patients with previously untreated metastatic or recurrent NSCLC with no EGFR or ALK tumour aberrations. Patients (N=719) were randomized (1:1) to OPDIVO 360 mg administered intravenously over 30 minutes every 3 weeks in combination with YERVOY 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-doublet chemotherapy administered every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles.

† Stratified log-rank *p*-value.

‡ Unstratified hazard ratio.

References: 1. OPDIVO Product Monograph. Bristol-Myers Squibb Canada. **2.** YERVOY Product Monograph. Bristol-Myers Squibb Canada. **3.** Paz-Ares L, Ciuleanu T-E, Cobo M, *et al.* First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy in patient with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncology.* 2021;22:198-211.

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Beyond Chemotherapy - The Role of Aspirin in Resected Colorectal Cancer

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Colon cancer is the fourth most commonly diagnosed cancer, the third leading cause of death, and accounts for approximately 11% of all new cancer diagnoses in Canada.[1] Advancements in adjuvant chemotherapy have translated into clinically meaningful improvements in survival after surgical resection.[2,3,4] However, three-year disease-free survival (DFS) still remains at approximately 75% for patients with stage III colon cancer treated with oxaliplatin-based chemotherapy, underscoring the need for further therapeutic advancements in adjuvant colon cancer.

There is mounting evidence that aspirin (ASA) holds clinical utility in the management of colorectal cancer.[5,6,7] Mechanistically, ASA is proposed to exert anti-tumour effects on colon cancer primarily through cyclooxygenase-2 (COX-2)-dependent and independent mechanisms.[6] ASA inhibits COX-2, an enzyme

that is overexpressed in the majority of colorectal adenocarcinomas. COX-2 leads to increased production of prostaglandin E2 (PGE2) and subsequent activation of the phosphatidylinositol 3-kinase (PI3K)-mammalian target of rapamycin (mTOR) signalling pathways, facilitating increased colorectal carcinogenesis. Inhibition of COX-2 is thought to decrease PGE2 production and inhibit PI3K signalling.[8] ASA has also been shown to inhibit mTOR (a downstream effector of the PI3K pathway) signalling through AMPK in colorectal cancer (CRC) cells, leading to autophagy and enhanced cancer cell clearance.[9] Extra-tumorally, ASA may limit metastasis by inhibiting platelet activation through COX enzymes, proposed to enhance immune clearance of metastasizing cells by suppressing platelet-derived thromboxane A2 and restoring T cell–mediated anti-tumour activity **(Figure 1)**.[10]

In the context of cancer prevention, ASA has been previously investigated. A meta-analysis of 51 randomized controlled trials suggested that ASA reduced CRC incidence relative to placebo.[11] However, ASA remains not currently recommended for primary prevention of CRC in the general population due to variable outcomes in certain subgroups (eg, older adults), the risk of adverse events, and the duration of therapy required (U.S. Preventive Services Task Force). The strongest evidence supporting the use of ASA in chemoprevention is from patients with Lynch syndrome. Lynch syndrome is an autosomal dominant hereditary cancer syndrome caused by germline alterations that lead to loss of function variants in one or more of several key DNA mismatch repair (MMR) genes, culminating in a dysfunctional MMR pathway. In the CAPP2 study, treatment with ASA at 600 mg per day for two years significantly reduced the incidence of CRC compared with placebo (9% vs. 13%; hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0·34–0·91; p=0.019) after 10 years of follow-up.[12] In a per-protocol analysis among those who took ASA for at least two years, the HR was 0.56 (95% CI: 0.34-0.91; p=0.91). Further research is needed to determine the optimal dose of ASA for patients with Lynch syndrome. The American Gastroenterological Association recommends offering ASA to patients with Lynch syndrome for cancer prevention (Conditional recommendation).[13]

Several studies have explored the utility of adjuvant ASA in resected CRC, with the greatest benefit observed in patients with PI3K pathway abnormalities.[14-16] More recently, ALASCCA is perhaps the most paradigm-changing prospective clinical trial. This study evaluated the effect of adjuvant ASA on recurrence and survival in patients with resected CRC harbouring somatic alterations in the PI3K pathway.[17] Eligible patients had stage I–III rectal cancer and stage II–III colon

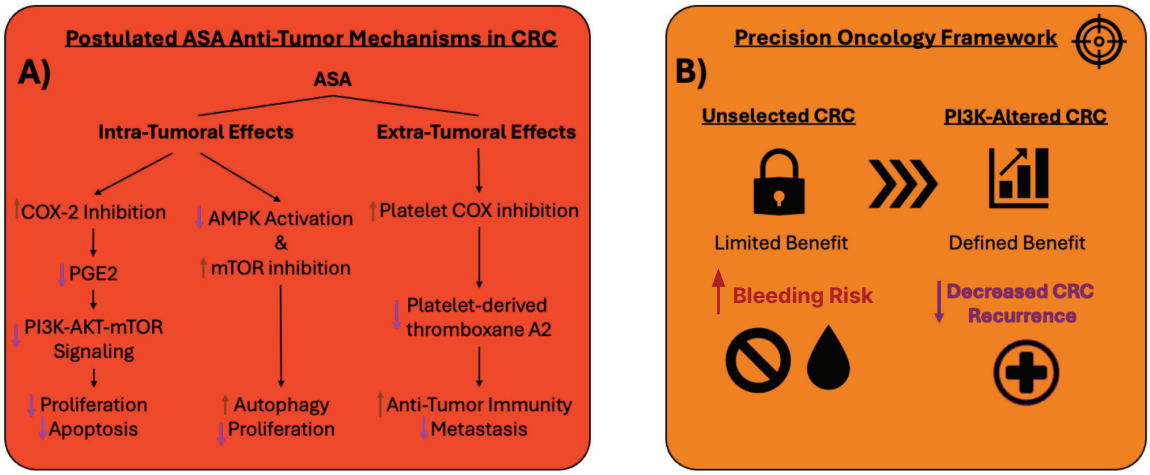

Figure 1. A) Selection of proposed intra- and extra-tumoral mechanisms of anti-tumor activity due to ASA in CRC onocogenesis. B) Importance of biomarker-driven personalization of patient selection in maximizing benefit in CRC risk reduction, specific to those individuals with actionable PI3K mutation pathway alterations; *courtesy of Scott W. Strum, MD, MSc, FRCPC, Patricia A.Tang, MD*

Abbreviations: ASA: aspirin; **CRC:** colorectal cancer; **COX-2:** cyclooxygenase-2; **mTOR:** mammalian target of rapamycin; **PGE2:** prostaglandin E2; **PI3K:** phosphatidylinositol 3-kinases.

cancer, and had either pre-specified PI3K catalytic subunit alpha hotspot mutations in exon 9 or 20 (Group A), or moderate- to high-impact somatic variants in *PIK3CA, PIK3R1*, or *PTEN* (Group B). Patients were randomized 1:1 to receive ASA 160 mg orally once daily or a placebo for three years. The estimated three-year cumulative incidence of recurrence was significantly lower with ASA compared with placebo in both molecular subgroups: 7.7% vs. 14.1% in Group A (HR: 0.49; 95% CI: 0.24–0.98; p=0.04) and 7.7% vs. 16.8% in Group B (HR: 0.42; 95% CI: 0.21–0.83). The three-year DFS favoured ASA in both Group A (88.5% vs. 81.4%; HR: 0.61) and in Group B (89.1% vs. 78.7%; HR: 0.51). Severe adverse events occurred in 16.8% of ASA-treated patients versus 11.6% with placebo; they were most commonly postoperative complications, thromboembolic events, and infections, whereas non-severe events were primarily hematologic and gastrointestinal. The number needed to treat to prevent one recurrence ranged from 6 in stage III rectal cancer to 42 in stage II colon cancer, supporting a favourable risk–benefit profile for ASA in molecularly-selected patients. This trial has supported its use in clinical practice for this subpopulation and has already been implemented into international guidelines.[18]

In contrast to the strongly positive results from ALASCCA, SAKK 41/13 was a phase III, prospective, randomized, double-blind, placebo-controlled, multi-centre trial evaluating adjuvant ASA in patients with R0-resected stage II or III colon cancer.[19] Patients with centrally confirmed activating *PIK3CA* mutations in exon 9 or 20 were randomized in a 2:1 ratio to receive ASA (100 mg daily) or placebo for three years, independent of decisions regarding adjuvant chemotherapy. Of 1,040 patients screened, 180 (17.3%) had *PIK3CA*-mutated colon cancer, and 112 were ultimately randomized. Baseline characteristics included 45.9% stage II and 54.1% stage III disease, and 63.2%–70.3% received adjuvant chemotherapy. The study did not meet its primary endpoint. Although DFS was numerically better in the ASA group, the 3-year DFS rates were 88.3% with ASA and 82.4% with placebo, with an unstratified hazard ratio of 0.57 (90% CI: 0.27–1.22; p=0.11). Compared with the positive results of ALASCCA, SAKK 41/13 evaluated a narrower range of *PIK3CA* mutations, used a lower ASA dose, excluded rectal cancer, and was underpowered due to early closure. These factors may have contributed to the lack of statistically significant results.

Important insights can also be gleaned from trials involving adjuvant ASA in molecularly unselected populations. For example, the ASCOLT trial was a prospective randomized, placebo-controlled study evaluating adjuvant ASA in patients with resected CRC.[20] Eligible patients included those with Dukes' C or high-risk Dukes' B colon cancer and Dukes' B or C rectal cancer who had completed standard adjuvant therapy. Patients were randomized 1:1 to receive either 200mg of ASA daily or placebo for 3 years. Among 1,550 patients in the modified intention-to-treat population, five-year DFS was 77.0% with ASA and 74.8% with placebo (HR: 0.91; 95% CI: 0.73–1.13; p=0.38), resulting in no statistical improvement in DFS. In the ASAC phase III clinical trial enrolling patients with CRC after radical treatment of liver metastases, they were randomized to three years of adjuvant ASA 160 mg once daily vs placebo.[21] Similarly, this trial was also negative, as ASA did not improve DFS (HR for recurrence or death 1.08 [95·44% CI 0.85–1.38]; p=0.58). Importantly, ASA was actually associated with lower overall survival (OS) than placebo (OS 76% with ASA vs 85% with placebo at 36 months [HR for death 1·64 (95% CI 1.01–2.65); p=0.045]), and more serious adverse events. Lastly, in yet another randomized phase III study, the EPISODE-III clinical trial demonstrated that 3 years of adjuvant low-dose ASA of 100mg once daily did not significantly improve DFS in an unselected R0-resected stage III adenocarcinoma from the cecum to upper rectum population: three-year DFS was 75.4% with placebo and 78.8% with ASA (HR 0.84, 95% CI 0.65–1.09; one-sided p=0.0987).[22] Results from studies such as these strongly suggest that for molecularly unselected patients, the use of ASA may not only be not beneficial, but may in fact be harmful.

In an effort to enhance the identification patients who may benefit from adjuvant ASA outside of PI3K testing, circulating tumour DNA (ctDNA) has also been evaluated. The presence of ctDNA after surgery is known to be a reasonable prognostic marker, although it's predictive value has remained more variable.[23] ctDNA was evaluated in CALBG/SWOG 80702, a phase III trial of patients with stage III colon cancer who were treated with adjuvant celecoxib (a selective COX-2 inhibitor) in addition to adjuvant chemotherapy.[24] In a post-hoc analysis, among patients with post-operative ctDNA positivity, celecoxib was associated with improved DFS (adjusted HR: 0.61; 95% CI: 0.42-0.89) and overall survival (adjusted HR: 0.62; 95% CI: 0.40-0.96) compared to

placebo. These findings persisted after stratifying for *PIK3CA* mutation status. Conversely, no such difference was observed in patients with negative post-operative ctDNA results. Therefore, ctDNA may help complement or further refine the selection of patients who may benefit from adjuvant COX-inhibitor-based therapies. The results of several trials incorporating ctDNA are pending, aiming to clarify how to integrate ctDNA in routine clinical practice (reviewed in[23]).

While ASA has shown strong promise in reducing recurrence in pre-specified populations, it carries an inherent risk profile. ASA is an irreversible inhibitor of COX enzymes, which play important roles in modulating inflammation and platelet function. ASA has been studied in large populations outside of cancer, with a well-established safety profile. In a meta-analysis of 13 trials (n=164,225) assessing the efficacy of ASA in the primary prevention of cardiovascular events, the use of ASA (at most dose levels between 75-100 mg/day) was associated with an increased rate of major bleeding (HR: 1.43; 95% CI: 1.30-1.56); number needed to harm 210) compared with no ASA.[25] This included intracranial hemorrhage and gastrointestinal bleeding. In the Physician's Health Study (n= 22,071) assessing 325 mg ASA every other day versus placebo, the relative risk of ulcer in the ASA group was 1.22 (169 for ASA vs. 138 for placebo; 95 % CI: 0.98 to 1.53; P = 0.08), and the relative risk of requiring a blood transfusion was 1.71.[26] In the ALASCCA trial, non-severe adverse events occurred in 43.4% of patients who received ASA and in 35.4% of patients who received placebo, and the most common events were hematologic and gastrointestinal. Four patients had a grade 5 serious adverse event in the ASA arm (1.3%), with one death considered potentially related to ASA use. ASA use should be avoided, or used with great caution, in patients with coagulopathies, such as hemophilia, peptic ulcer disease, or gastrointestinal bleeding, *G6PD* deficiency, uncontrolled hypertension, ASA-induced asthma/bronchospasm, and severe hepatic or renal dysfunction. In ALASCCA, patients with these comorbidities were largely excluded. The risks should always be discussed when counselling patients prior to initiating ASA, to provide context for the clinically meaningful DFS benefit in appropriately selected patients.

Overall, ASA has been shown to be highly effective in reducing recurrences in patients with resected stage I–III rectal cancer and stage II–III colon cancer, who have activating *PI3K* mutations, which encompasses up to 37% of patients in this demographic.[17] A personalized, precision oncology-based approach is important in deciding which patients will benefit most from adjuvant ASA, which is best supported by a dose of ASA 160 mg PO daily for three years. The benefits from treatment generally outweigh the adverse effects of ASA, especially in high-risk patient populations, such as stage III colon and rectal cancer, with a number needed to treat of 9 (95% CI: 6-18) and 6 (95% CI: 4-13), respectively.[17] Obtaining sequencing data in a timely, cost-effective fashion and ensuring that laboratory workflows can accommodate it is of utmost importance.

Future directions include optimizing ASA dosing and duration of therapy, as well as determining its benefit in molecular subpopulations such as those with microsatellite instability-high/deficient MMR disease, where immunotherapy has emerged as a cornerstone of treatment.[27] Further research on the role of adjuvant ASA will require refinement of biomarkers, particularly for PI3K and ctDNA subpopulations, and assessment of the biological mechanisms underpinning its clinical benefit. The CHALLENGE trial demonstrated the benefit of a structured exercise program after adjuvant chemotherapy in stage II-III colon cancer compared to health education material;[28] whether ASA has an additive benefit to a structured exercise program remains to be determined.

In conclusion, emerging data support adjuvant ASA as one of the first biomarker-directed, low-cost therapeutic strategies in CRC, with the greatest benefit observed in tumours harbouring PI3K pathway alterations. Molecular profiling remains the greatest barrier to implementing this advancement on a more global scale. ASA is considered safe and effective, has already been adopted into international guidelines, and should be considered an existing standard of care in this patient population.

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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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Advancing Precision Medicine for Breast and Ovarian Cancer Patients Through Mainstream Genetic Testing: A Pilot Program in Saskatchewan

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Abstract

Mainstream genetic testing integrates germline analysis directly into oncology care, streamlining access and reducing reliance on genetics referrals. This pilot program evaluated the implementation of a mainstream testing model for patients with breast or ovarian cancer in Saskatchewan from February 2024 to April 2025. Eligible patients were offered testing by oncology and surgical teams at two provincial cancer centres. Clinicians received training on eligibility, consent, and counselling procedures. Mainstreaming reduced the average time from diagnosis to results from 737 to 201 days, representing a 3.7-fold improvement in turnaround time. These findings demonstrate that mainstream genetic testing is feasible, scalable, and effective within a publicly funded Canadian healthcare system, supporting national efforts to expand routine oncology-led genetic testing for improved access, equity, and patient care for hereditary breast and ovarian cancer.

Introduction

Breast cancer is the most common cancer in Canada after non-melanoma skin cancer.[1] Individuals with germline BRCA variants face a significantly elevated risk of developing breast, ovarian, and other cancers.[2,3] Approximately 13% of Canadians will be diagnosed with breast cancer in their lifetime; however, for those with *BRCA* variants, this risk increases up to 72% by age 80.[2] Timely identification of pathogenic or likely pathogenetic variants is critical, as it informs treatment decisions and enables preventive strategies for patients and their families.[4] Mainstreaming models of care are increasingly adopted across Canadian health systems to meet growing demand for genetic testing amid a stable genetics workforce. Mainstream genetic testing integrates testing into routine oncology care, bypassing traditional referrals to genetics services **(Figure 1)**.[5–8] A recent pan-Canadian framework describes mainstreaming as "*the shifting of all or part of the clinical genetic testing process to clinicians outside of the genetics service to facilitate patient access to genetic testing.*"[8] This approach aims to improve accessibility, reduce delays, and optimize resource use.[9] The primary objective of this pilot program was to implement mainstream genetic testing for people with breast and ovarian cancer in Saskatchewan.

Methods

Study Design

A pilot program of mainstreaming genetic testing was implemented at the Saskatoon Cancer Centre in Saskatoon and the Allan Blair Cancer Centre in Regina to assess its impact on reducing cancer genetic testing access wait times. The program was reviewed and approved by the University of Saskatchewan's Research Ethics Board, the Saskatchewan Cancer Agency, and the Saskatchewan Health Authority. Clinicians who were involved in the program (breast surgeons, gynecologic oncologists, and medical oncologists) received education and training on mainstreaming, eligibility criteria, informed consent, and genetic testing protocols. All patients provided their informed consent prior to participating in the study.

Eligibility Criteria

The target population of this study included individuals with breast cancer in the province of Saskatchewan. Patients were eligible for mainstream genetic testing if they had a personal history of breast cancer, including triple-negative breast cancer (TNBC) diagnosis age ≤60 years, male breast cancer, breast cancer diagnosis age ≤35 years, bilateral breast cancer with at least one diagnosis age ≤50 years; strong family history of breast cancer; or met criteria for companion drug access for olaparib. These criteria were used to identify patients at high risk of harbouring pathogenic or likely pathogenic *BRCA* variants. Eligible patients who met genetic testing criteria were offered enrollment in the program. Patients diagnosed prior to February 2024 and on the waitlist for genetic testing were also eligible for mainstreaming.

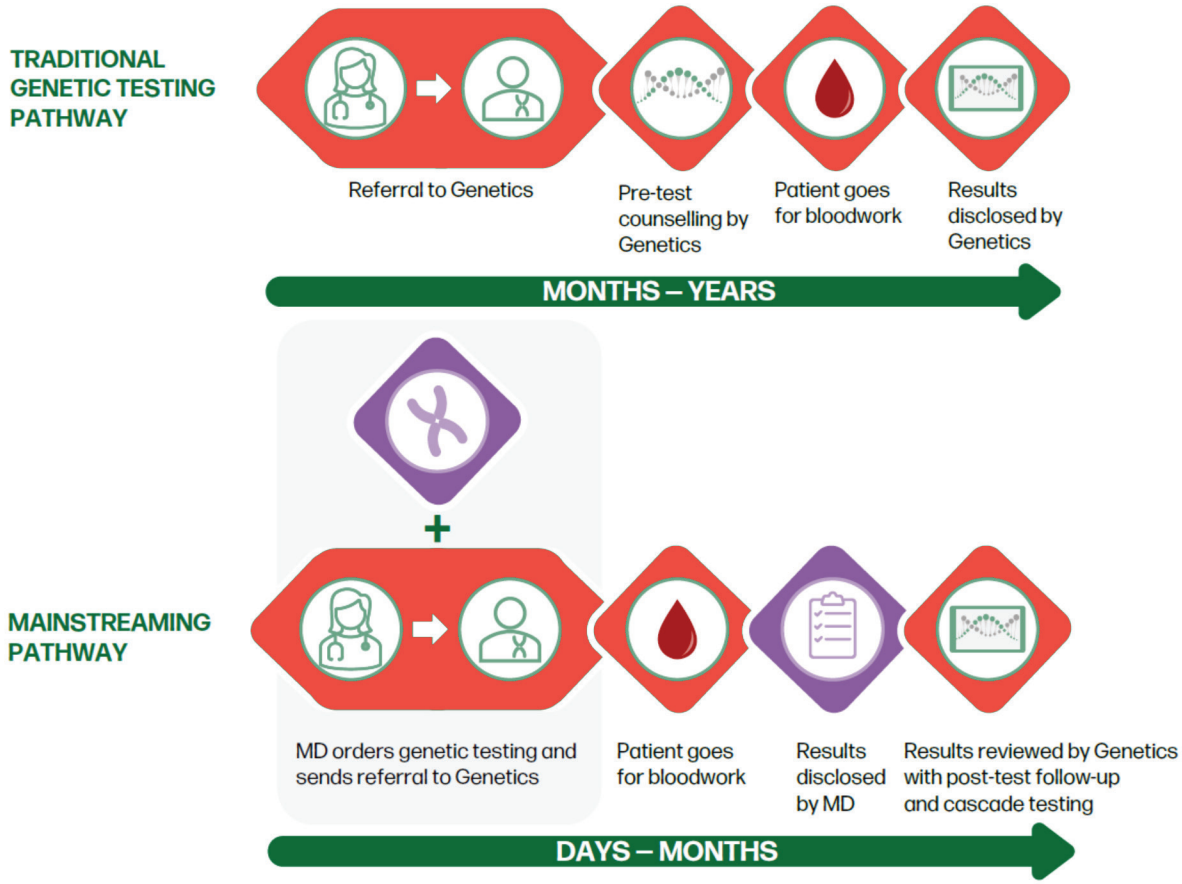

Figure 1. Traditional and mainstream genetic testing pathways. In a traditional genetic testing pathway, eligible patients are referred to Medical Genetics, undergo pre-test counselling, obtain bloodwork for testing, and then undergo post-test counselling. In a mainstream genetic testing pathway, pre-test genetic counselling is performed by non-genetic healthcare professionals, thereby making genetic testing more accessible to all eligible patients who might benefit from it; *courtesy of the Canadian Association of Genetic Counsellors (CAGC), adapted with permission.*[10]

Higher-risk patients, according to eligibility criteria, were defined as individuals for whom genetic testing could result in an immediate change in medical management (e.g., surgical planning or limited survivability) or who had characteristics associated with hereditary cancers (e.g., TNBC, male breast cancer, age <35). All other patients met testing criteria primarily based on personal or family history.

Study Procedures

Informed consent was requested by the ordering physician. Participants who consented to data collection in the pilot program and were eligible for genetic testing automatically received a lab requisition and provided blood samples, which were sent to the Roy Romanow Provincial Laboratory (RRPL) in Regina.

Genetic testing was conducted at the RRPL in accordance with the American College of Medical Genetics and Genomics (ACMG)[11] and ClinGen[12] guidelines, as well as gene-specific recommendations and standards for interpretation of sequence variations. Next-generation sequencing was performed to target the coding regions of genes associated with hereditary cancers. Multiplex ligation-dependent probe amplification was used to detect copy number variants across all 13 genes in the expanded breast/ovarian cancer testing panel (*ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*).

Genetic test results were provided within 6 to 8 weeks. Patients with a positive genetic result (clinically significant variant or variant of uncertain significance [VUS]) received an automatic referral to the Medical Genetics department at the Royal University Hospital (RUH) in Saskatoon.

Data Analysis

We collected and analyzed data from the Saskatchewan Cancer Agency electronic records pre- and post-mainstreaming. Pre- and post-implementation metrics assessed included ordering providers (medical oncologists vs. surgeons), region of testing (Saskatoon vs.

Clinical characteristic	Patients with genetic variants n=50
Age, average	53 years
Gender	
Female	50 (100%)
Male	0
Family history of cancer	
Breast	11 (22%)
Ovarian	0
Both	2 (4%)
Genetic variants	
BRCA1/2 or VUS	16 (32%)
BRCA1	6 (12%)
BRCA2	3 (6%)
VUS	7 (14%)
Other (*ATM, PALB2, PTEN, BRIP1, PMS2*)	34 (68%)
Surgery*	
Bilateral salpingo-oophorectomy	2 (4%)
Bilateral mastectomy	5 (10%)

Table 1. Clinical characteristics of all patients identified with a genetic variant through mainstream genetic testing; *courtesy of Mita Manna, MD, FRCPC.*

*Two women underwent bilateral salpingo-oophorectomy and bilateral mastectomy; both carried a germline *BRCA1* variant. Among the three additional women who underwent a bilateral mastectomy, two carried *BRCA1* variants, and one carried a *BRCA2* variant.

Abbreviations: VUS: variant of uncertain significance

Regina), time from sample collection to receipt of results, lab turnaround times, and indications for testing.

Results

Between February 2024 and April 2025, 348 patients met eligibility criteria for mainstreaming genetic testing. Of these, 132 patients consented to data collection, 109 completed testing, and results were available for 97 patients. The testing uptake rate was 82.6%. In total, 90 patients were enrolled at the Saskatoon Cancer Centre in Saskatoon and 42 at the Allan Blair Cancer Centre in Regina. Genetic tests were ordered by medical oncologists (n=71) and surgeons (n=61). Among 97 evaluable patients, 67% (65/97) had hormone receptor-positive human epidermal growth factor receptor 2-negative (HR+/HER2-) cancer, 21% (20/97) had TNBC, and 12% (12/97) had hormone receptor-negative HER2-positive (ER-PR-HER2+) cancer.

We examined the clinical characteristics of patients who underwent mainstream genetic testing and were identified as carriers of a genetic variant **(Table 1)**. Fifty patients (52%) had a genetic variant linked to breast cancer. Of these patients, 16 had germline pathogenic or likely pathogenic variants classified as *BRCA1/2* or a VUS. Of the six women with *BRCA1* variants, two underwent bilateral mastectomy, and two had both a bilateral mastectomy and bilateral salpingo-oophorectomy. One of the three women with a *BRCA2* variant underwent a bilateral mastectomy.

Among the women with an identified genetic variant (n=16), seven had TNBC, including four (25%) with a germline *BRCA1* variant, one (6%) with a *BRCA2* variant, and two (13%) with a VUS. Among those with an identified genetic variant and HR+/HER2- breast cancer, two (13%) had a *BRCA1* variant, two (13%) had a *BRCA2* variant, and four (25%) had a VUS. A single patient with HR-/HER2+ breast cancer was found to have a VUS.

Mainstream Testing Turnaround Time

Mainstream genetic testing markedly reduced the time from diagnosis to receipt of genetic testing results from 737 days to 201 days **(Figure 2)**, representing a 3.7-fold reduction in turnaround time. Among patients considered at higher risk based on eligibility criteria, the mean turnaround time decreased from 770 to 90 days with mainstream genetic testing. The time from receipt of test results to genetic counselling also decreased from 54 to 51 days, reducing the total time from diagnosis to counselling from 791 to 252 days.

Discussion

Improved Access Through Mainstreaming

This pilot study assessed the implementation of mainstream genetic testing for patients with breast and ovarian cancer across Saskatchewan, beginning in February 2024. Over the 15-month study period, this initiative demonstrated that a mainstreaming approach substantially reduced turnaround times compared with the traditional genetic referral pathway.

The most notable outcome of mainstreaming was a marked reduction in time from diagnosis to receipt of genetic results. With mainstreaming, turnaround time decreased 3.7-fold, from over two years (737 days) to approximately 201 days, and to 90 days for those classified as higher risk based on eligibility criteria. These reductions are clinically meaningful, as timely access to genetic test results can directly influence surgical planning, systemic therapy selection (e.g., eligibility for poly (ADP-ribose) polymerase [PARP] inhibitors), and cascade testing for at-risk relatives.[13]

The results achieved in our program align with Canadian and international evidence supporting a mainstreaming approach.[5,7,14–18] A systematic review of 15 studies across various cancers (ovarian, breast, endometrial, and prostate cancer) found that the quality of genetic care was maintained with mainstreaming, test results were typically disclosed within 3 to 6 weeks of the testing referral, and turnaround times were consistently shorter with the mainstream approach.[17]

In the Canadian setting, an observational study from British Columbia found that among 149 patients with a personal history of breast and ovarian cancer, oncology clinic-based testing significantly reduced the time from date of referral to the return of test results, from 403 to 191 days.[18] In Alberta, a provincial mainstreaming initiative reported an average of 2.7 months from provider appointment to result disclosure, with a laboratory turnaround of 2.1 months.[5] Our results in Saskatchewan are therefore consistent with these provincial experiences, indicating that mainstream genetic testing can be effectively implemented across diverse Canadian healthcare systems.

Internationally, evidence similarly demonstrated significantly shorter turnaround times and higher testing uptake with mainstream genetic testing.[14–16] The GENE-SMART study, a large, national study in the Netherlands spanning a 6-year period, found that the uptake of genetic testing among patients with breast cancer was 2.5x higher with mainstreaming than with direct referral to genetics.[15] In Australia, mainstream genetic testing improved patient access to testing and reduced pressure on genetic counselling services.[14] In that setting, test results impacted treatment decisions for most (88.6%) patients with a detected pathogenic variant.

Collectively, these data demonstrate that mainstreaming minimizes the need for pre-test genetics consultations without compromising quality, enabling genetic specialists to focus on patients with positive or complex results. The present study confirms that similar outcomes are achievable in the Canadian healthcare context, particularly when supported by provincial funding and institutional commitment.

Canadian Consensus Recommendations and Mainstreaming Framework

A recent pan-Canadian expert working group (comprising medical oncologists, a geneticist, a surgical oncologist, and a genetic counsellor) recommended reflexive and broad germline testing at the time of initial cancer assessment for patients with breast cancer.[9] This recommendation aligns with our findings and underscores the clinical importance of mainstreaming to improve timely access to hereditary risk information and personalized treatment planning. Another pan-Canadian expert group comprising medical geneticists, medical genetics resident physicians, a laboratory geneticist, and a genetic counsellor developed a national conceptual mainstreaming framework comprising four models for different testing scenarios across the diagnostic care

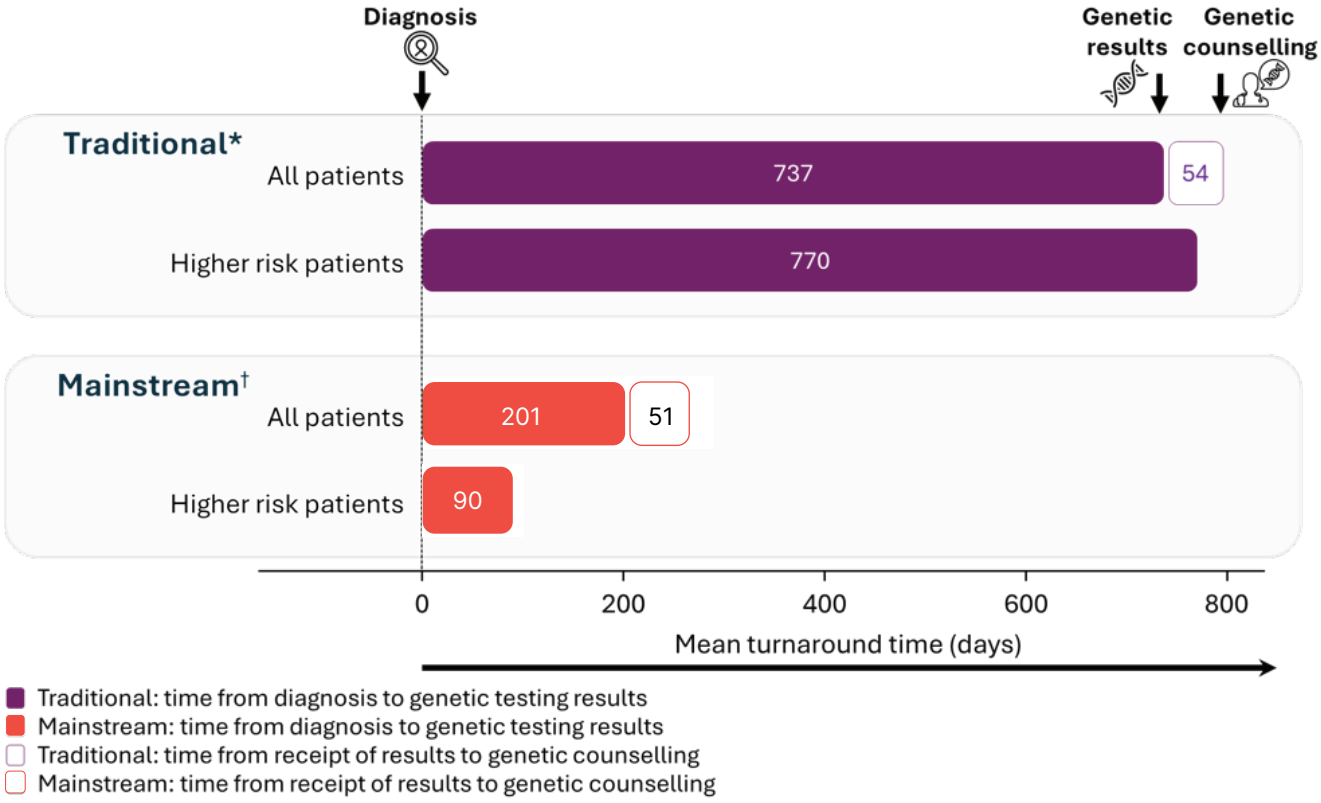

Figure 2. Mean time from diagnosis to genetic testing results and genetic counselling with traditional and mainstream genetic testing pathways. Compared with the traditional approach, mainstream genetic testing resulted in a time from diagnosis to genetic results and counselling that was more than 3x shorter. Solid bars indicate mean time to genetic results; white bars indicate mean time to genetic counselling; *courtesy of Mita Manna, MD, FRCPC*.
* Representative of the process where patients are referred to a genetic testing specialist prior to testing.
† All patients were diagnosed after 2023.

pathway.[8] Our implementation aligns with the "to-result" model outlined in the framework, in which oncology clinicians identify eligible patients, obtain consent, provide pre-test counselling, and order testing, while the genetics service provides result disclosure and follow-up support.

Challenges and Opportunities

Barriers to mainstream genetic testing include inadequate knowledge among referring healthcare professionals, a lack of system infrastructure, and limited human and financial resources.[17] In addition, patients of lower socioeconomic status remain less likely to receive genetic testing, even under a mainstream approach, highlighting a persistent gap in equity.[15] Sustained educational initiatives to improve genomic literacy and competency among non-genetic clinicians, and collaboration across disciplines, are essential to effectively implement mainstream genetic testing. Broader adoption of mainstreaming requires a national structured care program with defined workflows, roles, and responsibilities across oncology, genetics, and laboratory teams.[8,9] Further, there is room for improvement to bring Canada closer to the international average of 3 to 6 weeks from diagnosis to disclosure of test results.[17]

Limitations

This pilot study has several limitations. First, the sample size was modest, and data were collected from two tertiary cancer centres in Saskatchewan, which may limit generalizability to other jurisdictions or community-based settings. Second, as a program evaluation, outcomes such as patient satisfaction, recall of genetic information, and long-term behavioural or psychosocial impact were not assessed. Finally, as highlighted in the national conceptual framework for mainstreaming genetic testing, variability in clinician expertise, infrastructure, and inter-professional coordination across health systems may influence the scalability and sustainability of this model.[8]

Future Directions

Future directions for this work include expanding provincial eligibility criteria for genetic testing to improve access for patients who may benefit the most from testing. Specifically, broadening the criteria to include all patients diagnosed with TNBC and HR+ breast cancer at age 50 or younger would align with evolving evidence supporting the clinical utility of early genetic testing in these populations.[19] Integrating the support of cancer specialist nurses, particularly in underserved regions, may contribute to the sustainability and expansion of mainstreaming programs.[20] For example, one study showed that with the support of breast cancer coordinators, expanding testing to patients with early breast cancer treated in a community setting was feasible without increasing the burden on genetic specialists.[21] Additionally, reducing wait times for genetic consultations and prioritizing referrals for patients with identified pathogenic or likely pathogenic variants could facilitate more timely and informed treatment decision-making, particularly for patients whose management may be impacted by genetic findings. Together, these efforts will continue to advance the integration of genetic testing into routine breast and ovarian cancer care.

Summary

Our results demonstrate the feasibility and effectiveness of mainstreaming genetic testing for breast cancer within a provincial healthcare system. In Saskatchewan, this approach has markedly reduced wait times from more than 2 years to 90 days for those considered higher risk based on eligibility criteria, enabling more timely access to genetic information and facilitating treatment decisions. Mainstreaming is now the provincially funded standard of care, reflecting its established value in advancing precision oncology. Aligned with national recommendations,[9] this model supports broader implementation to improve access and outcomes in hereditary breast cancer care. Continued success of the program at the provincial and national levels will require coordinated strategies that address workforce capacity, provider training, patient education, and system-level communication. Structured care pathways will be essential to ensure long-term program sustainability and equitable access to mainstream genetic testing.

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Management of Extrapulmonary Small Cell Carcinomas

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Introduction

Extrapulmonary small cell cancer (EPSCC) is a rare entity, accounting for approximately 2.5 to 5% of small-cell carcinomas.[1,2] EPSCC primarily occurs in patients aged 50 years and older. Despite the variety of primary sites, it is frequently associated with smoking and excessive alcohol consumption[2], although the association with tobacco may not be as strong as with small-cell lung cancer (SCLC). As presented in Table 1, its most frequent primary sites are the female reproductive organs, the gastrointestinal and genitourinary tracts, and head and neck.[3-5]

Site	*Percentage*
Esophagus	18%
Other GI (stomach, colorectal, pancreas, hepatobiliary)	15-22%
Genito urinary	15%
Prostate	7%
Gynecological (mainly cervix)	17%
Breast	10%
Head and neck	11%

Table 1 : Distribution of extra-pulmonary small cell carcinoma per primary site[4,5]

Two main hypotheses have been proposed to explain the physiopathology of the disease. The first hypothesis is that it develops from a multipotent stem cell that differentiates towards a neuroendocrine phenotype. The alternate hypothesis is that it develops from a later-stage event in non-neuroendocrine carcinomas.[2]

In both lung and extrapulmonary sites, genetic alterations in *TP53* and *RB1* are present in nearly all cases.[6,7] Other genetic alterations appear to be more site-specific, such as *TERT* promoter mutations in the bladder and *ERG* rearrangements in the prostate.[8] Interestingly, these mutations are also found in cancers of more common histologies of the same organs, such as urothelial carcinoma and adenocarcinoma.

Recently, there has been renewed interest in Delta-like Ligand 3 (DLL3) expression in the context of small-cell neoplasms, including EPSCC. DLL3 is responsible for inhibition of NOTCH, a tumour suppressor. DLL3 is expressed in 85% and highly expressed in 68% of small-cell lung cancers (SCLCs), making it a target of great interest in several current bispecific T-cell engager trials.[6] Limited data on DLL3 expression exist for EPSCC, but the available data suggest comparable expression.[9-11]

Analogous to SCLC, the clinical course of EPSCC is aggressive, with a median overall survival (OS) of 1.4 to 3.5 years for localized disease and 8 to 12 months in the metastatic setting.[3,12] Due to its aggressive growth pattern, about 50% of cases present with metastases at initial diagnosis.[2] Incidence of brain metastases in EPSCC appears to be lower than in SCLC. It is seen in approximately 6% for all primary sites combined, but around 16-19% for prostate and up to 41% for head and neck.[13]

General Management

For localized disease, a combination of chemotherapy and radiotherapy is often recommended based on retrospective data, case reports, and extrapolation from SCLC.[13] Surgery can also be an option when anatomically feasible in early-stage disease, usually with consideration of adjuvant chemotherapy. There are, however, no randomized or prospective studies supporting these approaches.

The preferred chemotherapy regimen is based on SCLC experience and typically consists of a doublet of a platinum-based agent (either carboplatin or cisplatin) plus etoposide. This

strategy yields promising overall response rates (ORR), but responses are often short-lived.[14-16] For subsequent lines, options are also frequently extrapolated from lung disease, with topotecan as the most frequent second-line treatment despite a very modest efficacy in EPSCC.[17]

In case of treatment-refractory disease, the ipilimumab and nivolumab immune checkpoint inhibitor combination has demonstrated promising activity in high-grade neuroendocrine neoplasms and, if available, can be considered regardless of mismatch repair (MMR) status based on late-line basket trials.[18,19]

While single-agent immunotherapy has changed the management of SCLC over the last few years in both localized and metastatic disease, registrational phase III trials did not include extrapulmonary primary tumours.[20-22] There are very few data on single-agent immunotherapy in early lines of therapy for EPSCC, mainly consisting of case reports, so its place in EPSCC treatment remains unclear.[23-25] A notable exception is Merkel cell carcinoma, a high-grade neuroendocrine carcinoma of the skin, which is usually considered a separate entity to EPSCC and will not be discussed here.

Data on prophylactic cranial irradiation in EPSCC are retrospective in nature, and its role is probably limited. Some experts recommend discussing prophylactic pancranial irradiation for head and neck (except larynx) and prostate primaries, due to higher rates of brain metastases in case series with these primary sites.[26,27]

While the treatment principles above provide a top-line review of the recommended management of EPSCC, disease-site-specific data, including potential therapeutic options, exist and will be discussed below.

Site Specificities

Gastropancreatic

For localized gastropancreatic tumours, neoadjuvant chemotherapy may be offered to facilitate surgery and improve OS compared with upfront surgery.[28-30] Adjuvant treatment may also be appropriate, either with chemotherapy alone or in combination with radiation. The preferred chemotherapy regimen is 4 to 6 cycles of platinum and etoposide. When surgery is not possible, chemoradiation is the primary treatment option.[31]

For metastatic disease, the same chemotherapy backbone of a platinum agent and etoposide is favoured, but cisplatin-irinotecan and alternatives used in gastrointestinal adenocarcinomas, such as FOLFOX (folinic acid, fluorouracil, and oxaliplatin)and FOLFIRINOX (folinic acid, fluorouracil, oxaliplatin and irinotecan), have also been studied.[32-35] There is limited data on the use of immunotherapy in this setting. Although its primary endpoint was not met, the NICE-NEC phase II study demonstrated favourable outcomes with the addition of nivolumab to the chemotherapy regimen and with maintenance immunotherapy for a year in treatment-naïve patients with advanced grade 3 neuroendocrine neoplasms. After a median follow-up of 30 months, the median progression-free survival (PFS) and OS were 6 and 14 months, respectively, with an ORR of 57% and 38% of patients alive at 2 years of follow-up.[36] More data will likely be needed before changing official treatment recommendations.

Second-line treatment depends on tumour characteristics. In cases of deficient MMR/high microsatellite instability (dMMR/MSI-H), representing about 5% of cases, immunotherapy is prioritized, whether with pembrolizumab or dostarlimab.[37,38]

Data support tumour-agnostic treatment with dabrafenib and trametinib in patients with tumours harbouring *BRAF* V600 mutations[39], with selpercatinib in the presence of a *RET* fusion[40], and with larotrectinib, entrectinib, or repotrectinib in the presence of *NTRK* fusions.[41,42] However, use of tyrosine kinase inhibitors (TKI) in high-grade neuroendocrine carcinomas is controversial. It remains unclear whether such alterations, considered driver mutations in most settings, act as such in the setting of small-cell carcinoma. It has been shown that *EGFR*-mutant non-small cell lung cancer (NSCLC) that transforms to small-cell lung cancer loses EGFR protein expression and thus becomes resistant to EGFR TKIs.[43] Despite this, at least one case report suggests potential activity of BRAF inhibition in SCLC[44], and digestive neuroendocrine carcinomas were not excluded from most tumour-agnostic trials. As such, after the use of available cytotoxic chemotherapy regimens, use of TKIs in the presence of an activating mutation can be considered.

For patients without an actionable mutation, if the disease progresses within 6 months of the first-line regimen, alternative first-line options listed above can be used. Other options include

FOLFIRI (folinic acid, fluorouracil, and irinotecan) and temodal with or without capecitabine[45,46], or, as noted above, topotecan in an SCLC-inspired approach. If the disease progresses more than 6 months after a platinum agent and etoposide, rechallenge with the same regimen is recommended.[32]

Bladder and Upper Urinary Tract

Small-cell carcinoma of the bladder represents less than 1% of bladder and upper urinary tract cancers.[47] The standard approach for localized disease involves neoadjuvant chemotherapy, which improves OS compared with the adjuvant approach.[48,49] The preferred regimen is cisplatin and etoposide, but carboplatin and etoposide can be used in cases of cisplatin ineligibility. A regimen of cisplatin-etoposide alternating with doxorubicin and ifosfamide was studied in a prospective phase II study, but the added benefit of this approach remains unknown in the absence of comparative studies.[48-50] After the initial systemic approach, either consolidation radiotherapy, chemoradiation, or radical cystectomy can be performed with similar outcomes depending on the patients' preferences and comorbidities.[51,52]

For patients undergoing upfront surgery, adjuvant chemotherapy consisting of 4 to 6 cycles of a platinum agent and etoposide can be offered, as it has suggested to improve OS in retrospective data.[53] There is no established role for immunotherapy in the adjuvant setting, as the CheckMate-274 trial with adjuvant nivolumab did not include small-cell histology.[54]

Metastatic disease is managed globally as SCLC, with cisplatin and etoposide as the standard first-line treatment.[50] Later-line options studied in this setting include topotecan, lurbinectedin, nivolumab plus ipilimumab, or monoimmunotherapy.[55-60]

Prostate

Primary small-cell carcinoma of the prostate is a rare entity, whereas small-cell transformation in the setting of pretreated, metastatic castration-resistant prostate cancer is observed slightly more often. It should be suspected in the setting of disease progression with very low or negative prostate-specific antigen (PSA) levels, especially if a neuroendocrine component was described in initial prostate biopsies. The recommended first-line treatment is the combination of a platinum-based agent (cisplatin or carboplatin) with etoposide. Addition of carboplatin to taxanes used in prostate adenocarcinoma (docetaxel or cabazitaxel) can also be considered.[61]

Cervix

Small cell tumours of the cervix account for approximately 2% of cervical cancers.[62] The disease tends to be bulkier and presents at a higher stage than standard cervical cancer.[63] Tumours <4 cm can be approached surgically upfront with adjuvant treatments, whereas tumours >4 cm receive chemoradiotherapy, potentially followed by surgery depending on the response. The benefit of surgery after chemoradiation remains unclear. The preferred chemotherapy regimen is 4 cycles of a platinum-based agent and etoposide.[64]

For metastatic disease, the standard approach of combining a platinum-based agent with etoposide also applies.[64] For recurrent disease, a combination of topotecan, paclitaxel, and bevacizumab demonstrated encouraging activity in this difficult-to-treat setting and may be considered for fit patients who can tolerate the toxicity.[65]

Unknown Primary

Unknown primary small cell tumours are a very rare entity. For high-grade undifferentiated tumours of unknown primary origin, platinum and etoposide are recommended, with an ORR of around 70%, similar to that in primary NECs.[66,67] The phase II NICE-NEC trial with nivolumab, discussed above, included 6 patients with EPSCC of unknown primary.[36] Considering the relative frequency of SCLC compared with other primary sites of small cell carcinoma, if no convincing site of origin is found, many clinicians will approach this type of disease as they would SCLC.

MiNENs

Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) are a rare and aggressive cancer type characterized by the presence of distinct neuroendocrine and non-neuroendocrine components within the same tumour. According to the World Health Organization (WHO) classification, each component must constitute at least 30% of the tumour to be classified as MiNEN.[68] The most frequent non-neuroendocrine and endocrine components are adenocarcinoma and carcinoma, respectively. The general guideline is to treat the most aggressive component in the tumour, namely neuroendocrine carcinoma,

regardless of its percentage within the tumour.[69] A combination of platinum and etoposide is the most often used regimen, but approaching the disease like a digestive neoplasm with FOLFOX (folinic acid, fluorouracil, and oxaliplatin) or FOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) is also feasible in selected patients.[70,71]

DLL3-Targeted Therapy

With the emergence of DLL3-targeted therapy such as tarlatamab in SCLC, there is excitement about whether the practice-changing benefits of these therapies could translate to the setting of EPSCC. Fortunately, there is a growing body of phase I and II data on the role of DLL3-specific therapies (mostly bispecific T-cell engagers) in EPSCC across multiple tumour sites. The ORR ranges from 20% to 56%, and the disease control rate is up to 75%, depending on DLL3 expression level, tumour site, and drug used.[9,72-77] The DLL3 expression level seems to correlate with response to these therapies. Responses appear to be durable, with a median duration of approximately 6 to 12 months. The safety profile of such molecules, including a risk of cytokine release syndrome (CRS), is generally low-grade and manageable. Grade 3 CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) are rare and concordant with known SCLC literature. Based on these emerging data, experts recommend utilization of DLL3-directed therapy in refractory EPSCC after chemotherapy if such therapies are available. Clinicians should still use caution in directly extrapolating results of large, phase 3 clinical trials in SCLC to the EPSCC population as larger trials and retrospective series are expected.

Specifically for tarlatamab in prostate EPSCC, a phase 1b trial has shown an ORR of 22.2% and PFS of 27.7% at 6 months for DLL3-positive (IHC >=1 %) tumors. Interestingly, and in contrast to what is observed in SCLC, the ORR for DLL3-negative tumors was 0%.[78]

As for antibody-drug conjugates (ADCs) targeting DLL3, there is a paucity of data regarding EPSCC. While development of this drug has since been terminated, rovalpituzumab tesirine (Rova-T), one of such ADCs with a pyrrolobenzodiazepine (PBD) payload, has shown an ORR of 17% in DLL3-positive tumors (50% or more DLL3+ cells).[79] More recently, ABBV-706, an ADC targeting SEZ6 with a topoisomerase-1 payload, has shown in a phase 1 including SCLC and EPSCC an ORR of 43.8%.[80]

There is currently no published data for other molecules proved to be active in SCLC, such as risvutatug-rezetecan and tambotatub-pelitecan.

Conclusion

In summary, EPSCC is an aggressive entity that shares some clinical and molecular characteristics with the more frequent and better-known SCLC, but also has some significant nuances. While tumour-site-specific management exists for some primary sites, first-line systemic therapy typically consists of platinum-based chemotherapy plus etoposide. The role of immunotherapy and prophylactic whole-brain radiation remains unclear across different primary sites. DLL3-targeted therapies are currently being studied prospectively in this setting and may offer significant benefits to patients with EPSCC in the near future. It is expected that other promising therapies for SCLC, including antibody-drug conjugates, will also be further investigated in the context of EPSCC in the next few years.

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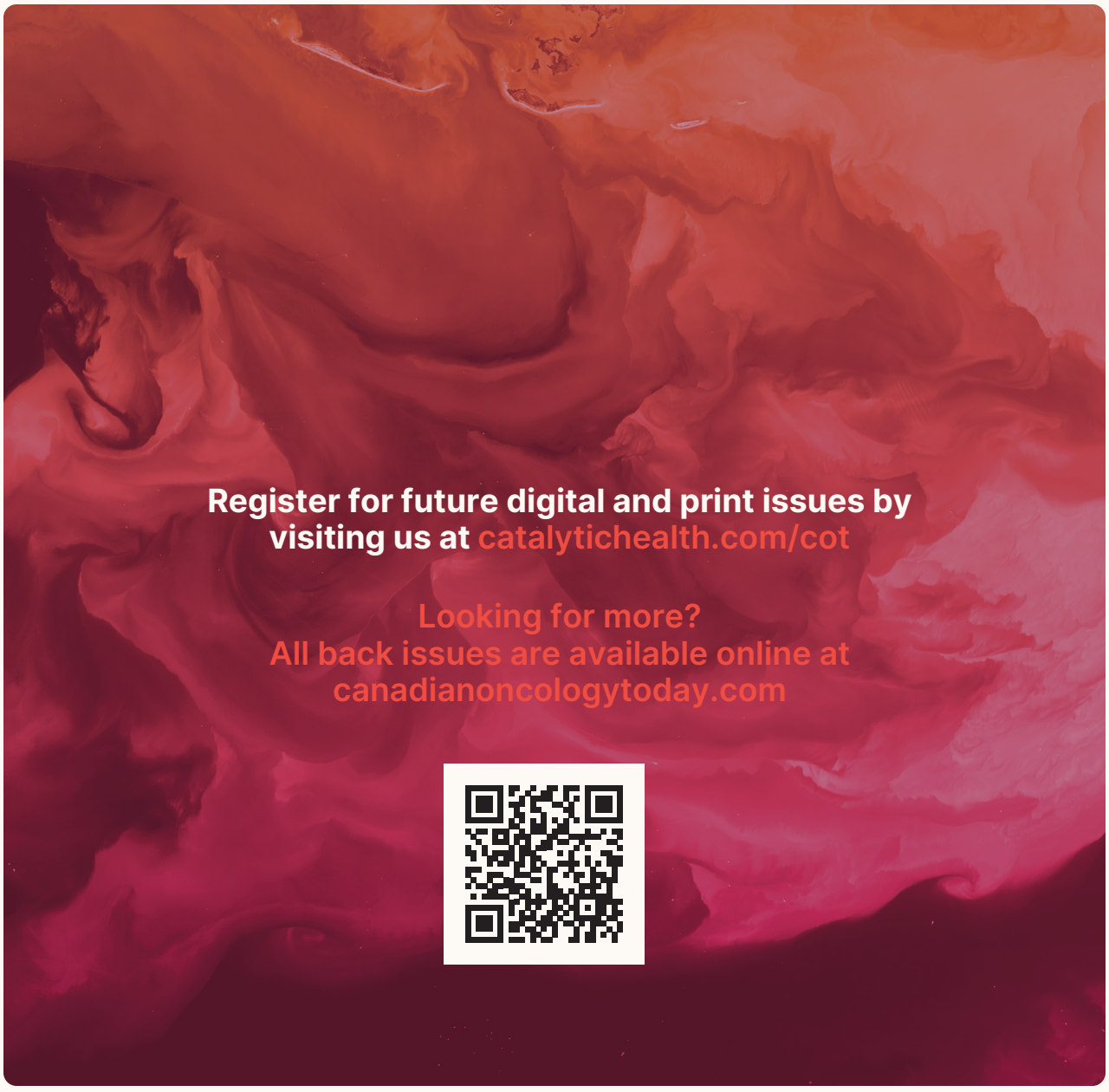
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