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A network approach to developing immuno-oncology combinations in Canada

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ABSTRACT

Immune checkpoint inhibitors have revolutionized care for many cancer indications, with considerable effort now being focused on increasing the rate, depth, and duration of patient response. One strategy is to combine immune strategies (for example, CTLA-4 and PD-1/L1–directed agents) to harness additive or synergistic efficacy while minimizing toxicity. Despite encouraging results with such combinations in multiple tumour types, numerous clinical challenges remain, including a lack of biomarkers that reliably predict outcome, the emergence of therapeutic resistance, and optimal management of immune-related toxicities. Furthermore, the selection of ideal combinations from the myriad of immune, systemic, and locoregional therapies has yet to be determined. A longitudinal network-based approach could offer advantages in addressing those critical questions, including long-term follow-up of patients beyond individual trials.

The molecular cancer registry Personalize My Treatment, managed by the Networks of Centres of Excellence nonprofit organization Exactis Innovation, is uniquely positioned to accelerate Canadian immuno-oncology (IO) research efforts throughout its national network of cancer sites. To gain deeper insight into how a pan-Canadian network could advance research in IO combinations, Exactis invited preeminent clinical and scientific advisors from across Canada to a roundtable event in November 2017. The present white paper captures the expert advice provided: leverage longitudinal patient data collection; facilitate network collaboration and assay harmonization; synergize with existing initiatives, networks, and biobanks; and develop an IO combination trial based on Canadian discoveries.

Key Words Immuno-oncology, biobanking, molecular profiling, precision oncology, molecular cancer registries, cancer networks

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BACKGROUND

Immunotherapy results in a strong, durable response in some cancer patients, but most patients do not respond because of intrinsic or acquired resistance[1,2]. Immuno-oncology (IO) therapeutics are now being explored in combination with a number of other interventions to simultaneously target non-overlapping oncogenic and immune mechanisms, and to synergistically increase the rate, depth, and duration of patient response. In multiple cancers, administering additional therapy with IO has been shown to increase patient benefit[3–6], with several combinations already having been approved by the U.S. Food and Drug Administration and Health Canada. Driven by those successes, combination studies to evaluate IO in combination with radiotherapy, chemotherapy, targeted therapy, and other IO therapy have opened at an astounding rate. A recent analysis reported the launch of 469 anti–PD-1/L1 combination trials in 2017 alone, representing an expected enrolment of more than 50,000 patients[7].

However, although IO has launched us forward, many questions are unanswered. Humanized animal models being lacking, the dynamic interplay between the immune system and IO therapies used alone or in combination remains incompletely understood. Despite significant efforts, predictive biomarkers are suboptimal, which complicates efforts to improve patient selection and monitor pharmacodynamic response. An understanding of how using IO in combinations can overcome therapeutic resistance is in the beginning stages, but the sheer number

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of potential therapies, combinations, and administration regimens precludes testing all options for financial and ethical reasons. Moreover, although the enthusiasm for IO has resulted in progress, efforts have also been described as fragmented and uncoordinated, with considerable duplication of studies with similar scientific questions[7]. It has been suggested that, despite insufficient or weak scientific rationale, many IO combinations have entered trials in an attempt to "see what sticks"[8]. To advance the field, appeals have been made to develop IO combinations rationally and strategically, with increased collaboration and alignment between stakeholders[9,10].

In Canada specifically, IO development has unique advantages and challenges. Because cancer care in the publicly funded Canadian health care system might be more uniform than in multi-payer or hybrid systems[11,12], the medical histories of patients at trial enrolment might be less variable in Canada than elsewhere. Lower or delayed rates of approval and reimbursement of cancer therapies[13–15] might motivate more Canadian patients to enrol on trials as their only means of accessing innovative therapies. Furthermore, the collaborative approach of many Canadian oncologists offers strong potential for building an IO network. Nonetheless, the dispersion of the Canadian population across a large landmass constitutes a distinct barrier to clinical research, because distant centres might not have access to cutting-edge trials, and trials could struggle to recruit patients with low-prevalence biomarkers.

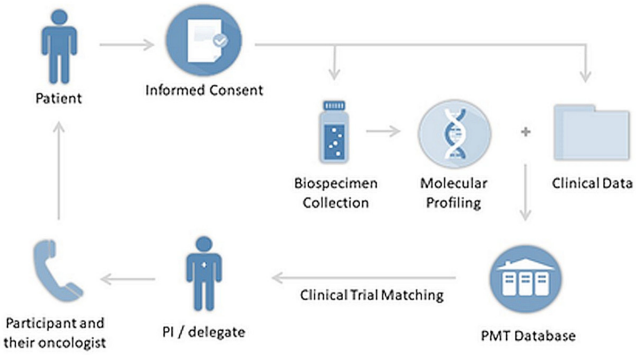

FIGURE 1 Workflow for the Personalize My Treatment (PMT) initiative. This pan-Canadian initiative aims to facilitate the recruitment and matching of patients to clinical trials of innovative personalized therapies, including immunotherapies. Patients are recruited to PMT by their cancer care institution, where they consent to have their clinical and molecular data collected, to have their samples profiled, and to be contacted if they become eligible for a trial based on their clinical profile and the molecular characteristics of their cancer. Patient data are stored in a centralized digital biobank. Through this single portal, patients across the country can be identified, selected for biomarker profiling, contacted, and matched to clinical trials. Patient recruitment focuses on cancers of clinical research interest that represent a high unmet need. In addition to the network of participating cancer centres, a federated group of labs uses various platforms to provide standardized and flexible analysis of patient samples for determination of eligibility for clinical trials.

ROUNDTABLE EVENT ON IO COMBINATIONS

In light of the research advantages and challenges, leading Canadian scientists and clinicians were invited to a roundtable event in November 2017. The event was managed by Exactis Innovation, a Networks of Centres of Excellence nonprofit organization that hosts a molecular cancer registry at a network of cancer centres across Canada ("Personalize My Treatment," Figure 1). With strong motivation to encourage IO research in Canada, Exactis requested guidance from the roundtable participants about leveraging its national network to advance the development of IO combinations. The advice and insights provided are captured in the subsections that follow.

Facilitate Standardization

The tumour immune response can be variable, with a variety of mechanisms underlying immune escape in inflamed compared with non-inflamed tumours[16,17], evidence of intra-patient and intra-tumour immune heterogeneity[18,19], and inconsistent response to IO in various cancer types and patients. Tailoring therapy to appropriate histologic, molecular, and immune characteristics of tumours is therefore essential, but reliable markers for patient selection have been elusive. Microsatellite instability combined with high mismatch repair deficiency has been identified as a strong predictive biomarker for anti–PD-1 therapy, but is rare. Mutational burden looks promising as a biomarker of response no matter the cancer type, although the optimal cut-off for predictive validity in blood compared with tumour and the appropriate integration with other biomarkers such as PD-L1 expression remain to be described[20–24]. Biomarker discovery is likely to become more challenging in the future, because each therapeutic combination might have a unique set of biologic indicators, and studies will increasingly compare those combinations with IO monotherapy as the standard of care. Beyond increasing the response rate, identifying appropriate candidates for a particular IO combination would spare unnecessary cost and toxicity for patients for whom monotherapy might be sufficient. Moreover, biomarkers predictive of severe toxicity are crucial as IO moves into the curative setting.

A major challenge in biomarker discovery is the lack of standardization of sample collection and analysis in clinical research. Each trial generates a set of samples that are unique in their timing of collection, tumour type, processing, and so on, from which data are generated for targets ranging from immunity to proteomics to epigenomics. Those inconsistent datasets, coupled with assay variability, have hampered large-scale multi-study comparisons of IO biomarkers[25]. To address the inconsistency, a national network could identify a set of promising IO biomarkers to be included in all trials, develop resources to harmonize sample collection and analysis, and provide support for integration of those tasks. Such broad alignment of processes and research targets would allow for cross-trial analysis and, potentially, improvements in the data reproducibility issues historically seen with IO. A large-scale network could also facilitate discovery and validation of blood-based biomarkers, allowing patients to be profiled using techniques that are less invasive and more economical than tissue biopsy. A major academic–industry collaboration with a similar goal is in development in the United States under

the umbrella of the U.S. "Cancer Moonshot" (Partnership for Accelerating Cancer Therapies)[26]. Although the goal should not be to replicate the efforts of the U.S. Partnership, complementary avenues for standardizing biomarker discovery in Canada should be explored.

Beyond biomarkers, a network is essential for standardizing disease assessment and establishing consensus concerning measurement of clinically meaningful benefit with IO. In the clinical setting, response can take longer with IO therapies than with cytotoxics, and pseudoprogression can be mistaken for progression of disease[27,28]. Response criteria specific to immunotherapies—the immune-related response criteria[29] and the Response Evaluation Criteria in Solid Tumors for immunotherapeutics[30]—have been devised, but remain to be validated in various cancer subtypes, and in particular, where dynamic responses to combinations of IO and non-IO interventions are seen. For the time being, there continues to be variability in how responses are measured in different clinical trials[30]. As the clinical settings in which IO is administered diversify (for example, neoadjuvant, adjuvant, metastatic, recurrent disease), early surrogate efficacy endpoints have to be identified and validated for each setting[31].

Collaborate with Other Networks

Cross-Canada standardization would be of greatest benefit if harmonized with existing databases, biobanks, and networks. Fostering synergistic collaborations with national players such as CellCAN, the Canadian Tissue Repository Network, the Canadian Cancer Immunotherapy Consortium, the Canadian Cancer Trials Group, BioCanRx, the Terry Fox Research Institute, and other indication-specific networks would best facilitate alignment of data, samples, and trials. Rather than everyone working in a silo, collaboration could promote process improvement, quality control, biomarker standardization, exploitation of unused data, cross-trial comparisons, and analyses of increasingly complex data despite shrinking research budgets[32]. Pooling resources (databases and bioinformatics capabilities, for instance) and exchanging knowledge (standard operating procedures, standards, tools, and so on) would build on past accomplishments and best advance IO research in the country as a whole.

Leverage Longitudinal Collection of Samples and Data

Data from trials are normally limited to the duration of the study, but data and samples from a longitudinal initiative can be collected throughout a patient's disease trajectory. That unique situation provides the potential for real-world data to inform pharmaco-epidemiology, patterns of care, long-term toxicity, and clinical outcomes (especially as they relate to biomarker expression)[33–35]. With respect to IO specifically, longitudinal retrospective analyses have the potential to describe the comparative efficacy of therapeutic sequencing, acquisition of IO resistance, or the evolution of immunogenicity over time, among other topics. Integration of information from medical records and from pharmacy, insurance, and health care databases would be particularly valuable in Canada, given variability in the adoption rate and data format of the electronic medical record across the country[36,37].

Lead an Innovative IO Combination Trial

A network of Canadian cancer centres could be the catalyst for a Canadian combination IO trial. Coordinated patient screening would allow for recruitment of patients with an immune profile, mutation, or tumour type that otherwise might be too rare to be of interest. In addition, collaboration across the network could enable the construction of a large-scale adaptive platform trial for IO combinations. A master protocol that permits the addition and removal of IO combinations according to early signals of efficacy would make testing new combinations more efficient and would streamline trial start-up and management through shared logistics, data collection, quality control, and oversight[38,39]. As the rapid pace of IO development drives evolution in the standard of care, an adaptable trial design of that kind could also provide greater flexibility to update corresponding control arms in consequence.

A number of strong strategies for designing a rational IO combination were discussed. The importance of targeting multiple non-redundant steps of the cancer–immunity cycle[40] to induce synergistic efficacy, overcome resistance, and minimize overlapping toxicity was highlighted[16]. For example, targeting antigen release, antigen presentation, and T-cell recognition of cancer cells by administering anti–PD-1 therapy with intratumoural injection of an oncolytic virus producing granulocyte macrophage colony–stimulating factor (specifically, talimogene laherparepvec) resulted in an impressive response rate of 62% in advanced melanoma, with several patients experiencing complete response despite very low intratumoural CD8-positive T-cell density at baseline[41]. Combinations targeting secreted immunosuppressive factors (for example, cytokines), immunosuppressive enzymes (for example, CD73), stromal components that limit T-cell invasion, or cells with immunosuppressive function could all be promising targets to overcome the non-inflamed tumour microenvironment[42–44]. As an example, early evidence suggests that dual inhibition of PD-1 and IDO1 might be very active, with an overall response rate similar to that seen with combined ipilimumab and nivolumab, but with a better toxicity profile[45,46]. Another proposed strategy would combine systemic and local modalities to sidestep the toxicity of multiple systemic IO therapies. Locoregional radiotherapy or cryothermal ablation can enhance the antitumour immune response through tumour cell death, antigen release, production of cytokines, and so on, with the potential for systemic response beyond the site of damage (abscopal effect)[47–49]. A number of clinical trials combining those locoregional therapies with checkpoint inhibition are ongoing, with results anticipated soon.

Several ideas were also put forward to address outstanding clinical knowledge gaps. Following on from the positive outcomes seen in advanced, metastatic, and recurrent disease, a number of trials are now exploring checkpoint inhibitors in early-stage and locally advanced disease, with the first U.S. Food and Drug Administration approval for a PD-1/L1 inhibitor in the adjuvant setting having occurred in late 2017. Appropriate monotherapy and combination regimens in the neoadjuvant and adjuvant settings should be explored, keeping in mind the much lower threshold for acceptable long-term toxicity in the curative setting. Furthermore, very little evidence

has been developed concerning the optimal duration of therapy for patients who have responded to IO in various disease settings and whether re-challenge (for example, after toxicity) can be beneficial.

Focus on Canada

Beyond answering relevant scientific or clinical questions, the attendees felt that any research conducted under the umbrella of a national initiative would ideally address challenges or leverage advantages that are uniquely Canadian. Given Canada's dispersed population, a collaborative network of cancer centres is key to recruiting sufficient patients with low-prevalence biomarkers and to facilitating better access to trials (and drugs not yet reimbursed) for patients at regional centres. Given the widespread use of checkpoint inhibitors in cancer care and clinical trials in the United States, Canadian centres could soon be important for patient recruitment, especially for patients naïve to IO. A Canadian network that comprises scientists and clinicians alike offers the potential to foster homegrown IO research and to shepherd innovations into clinical trials. Finally, a national initiative offers significant potential to better understand Canadian health care by comparing drugs with the local standard of care, by providing insights into Canadian medical practices, by assessing biomarker prevalence in Canada, or by informing patient outcomes.

A NETWORK APPROACH TO DEVELOPING IO COMBINATIONS

The constructive discussions at the IO roundtable event serve as a fitting example of cross-Canada collaboration driving innovation in oncology. With a strong network of cancer care sites across Canada and more than 3600 patients consented into Personalize My Treatment (Appendix A), Exactis is now exploring adoption of some of the insightful strategies highlighted during the roundtable (Figure 2). Regardless of the specific approach chosen, leveraging the strengths of a network that spans the country will be key to driving direct benefits for Canadians with cancer.

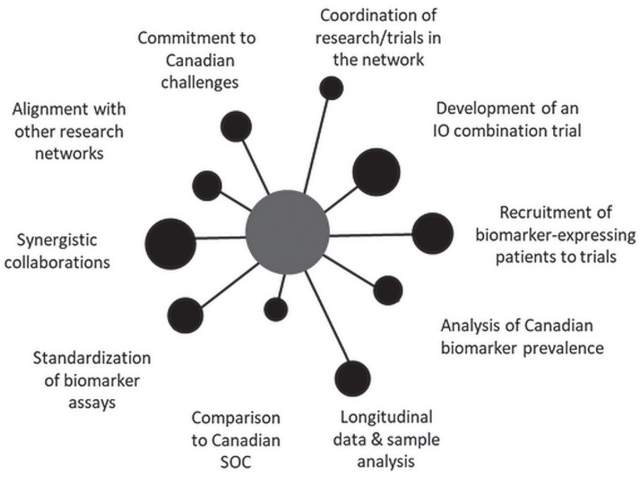

FIGURE 2 Potential strategies to leverage a pan-Canadian network for immuno-oncology (IO) combinations. SOC = standard of care.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests outside the submitted work: VH is an employee of Exactis Innovation; RF is the CEO of Exactis Innovation; GB has received research funding from several pharmaceutical companies and is the CMO of Exactis Innovation; PKC has received fees as an advisory board member for Bristol–Myers Squibb, Merck, AstraZeneca, Pfizer, and Roche; HLM has received fees as an advisory board member for Merck, Spectrums, Syndax Pharmaceuticals, OBI Pharma, Calithera, Roche, Lilly, Peregrine, TapImmune, Amgen, Puma, Pfizer, and Immunomedics, and has received research funding from Bristol–Myers Squibb, MedImmune, Ziopharm, Eli Lilly, and Merck; TMP has received advisory board member fees from Bristol–Myers Squibb, Merck, and Incyte, and a grant from Roche; RS has received honoraria from Pfizer, and honoraria or advisory board fees from Boehringer Ingelheim, AstraZeneca, Roche, Lundbeck, Bristol–Myers Squibb, Merck, AbbVie, and Takeda; MFS has received honoraria from Amgen; JS is a permanent member of the scientific advisory board of Surface Oncology and owns stock in Surface Oncology; DJS has received honoraria or consulting or advisory board fees from Roche, Boehringer Ingelheim, Novartis, Merck, AstraZeneca, Bristol–Myers Squibb, and Exactis, and scientific writing or clinical trials support from Boehringer Ingelheim, AstraZeneca, Novartis, Bristol–Myers Squibb, and Celgene; SV has received fees as an advisory board member for Amgen, Lilly, AstraZeneca, Novartis, Pfizer, and Roche, and is the co-founder and medical director of OncologyEducation.com (uncompensated). BM, DM, and SSS have no conflicts of interest to disclose.

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APPENDIX A: PERSONALIZE MY TREATMENT STATUS AND HOW TO GET IN TOUCH

As of early 2019, Personalize My Treatment (PMT) was active at 11 major hospital centres across Canada, with more than 3600 participants consented. Visit https://www.exactis.ca/ for the current status of the PMT network and participant recruitment.

- As an oncologist at a Canadian hospital, how can i be involved in PMT?
  Contact Exactis Innovation directly at https://www.exactis.ca/.
- As a Canadian cancer patient, how can I sign up for PMT?

Cancer patients at hospitals where PMT is active can ask their oncologist about participating in PMT (for a list of active locations, visit https://www.exactis.ca/). Your oncologist can determine whether you would be a candidate for PMT and can tell you more about what your participation would involve. Exactis Innovation cannot offer advice on how to treat your cancer; speak to your oncologist about your best treatment options. Sample profiling and clinical trial matching are not guaranteed for all patients.