A network approach to developing immuno-oncology combinations in Canada

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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. It has been suggested that, despite insufficient or weak scientific rationale, many IO combinations have entered trials in an attempt to “see what sticks.” To advance the field, appeals have been made to develop IO combinations rationally and strategically, with increased collaboration and alignment between stakeholders.

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, 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 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.

**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, evidence of intra-patient and intra-tumour immune heterogeneity, 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. 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. 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)38. 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 disease27,28. Response criteria specific to immunotherapies—the immune-related response criteria29 and the Response Evaluation Criteria in Solid Tumors for immunotherapeutics30—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 trials30. 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 setting31.

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 budgets32. 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 country36,37.

Lead an Innovative IO Combination Trial

A network of Canadian cancer centers 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 tumor 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 oversight38,39. 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 cycle40 to induce synergistic efficacy, overcome resistance, and minimize overlapping toxicity was highlighted41. For example, targeting antigen release, antigen presentation, and T-cell recognition of cancer cells by administering anti–PD-1 therapy with intratumoral 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 intratumoral CD8-positive T-cell density at baseline42. 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 tumor microenvironment43–45. As an example, early evidence suggests that dual inhibition of PD-1 and mOri might be very active, with an overall response rate similar to that seen with combined ipilimumab and nivolumab, but with a better toxicity profile46,47. 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 antitumor immune response through tumor cell death, antigen release, production of cytokines, and so on, with the potential for systemic response beyond the site of damage (abscopal effect)48–49. 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 become 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 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.

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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 CEO of Exactis Innovation; PK 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, 20i Pharma, Calithera, Roche, Lilly, Pergrine, TaptImmune, Amgen, Puma, Pfizer, and Immunomedics, and has received research funding from Bristol–Myers Squibb, MedImmune, Zopharm, 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.